Journal of Health Policy & Outcomes Research

Opening Issue 1/2012

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 1

From the Editors

As previously announced, and in reference to the findings of the General Assembly of the Polish Society of Pharmacoeconomics and interest from other academic bodies the first issue of he international scientific journal "Journal of Health Policy & Outcomes Research (JHPOR)" is presented. in this issue you can see the problems of Health Policy in Poland, Hungary, Russia and Slovakia. Most of the works of foreign authors is thematically linked to the lectures presented at the Ninth Conference of the PTFE (ISPOR Poland Chapter). On the pages of this issue we begin a discussion of the assumptions and the various aspects of a new reimbursement law in Poland introduced in May 2011. This hot topic will be discussed many times in subsequent editions of the journal. Several articles are devoted to analyzing the cost effectiveness of drugs, and are important to Polish studies. Since the beginning of a letter to each issue, the article called "PTFE-Corner " is entered which will monitor and record the activity of members of PTFE - individual activities, activities of the sections, members' participation in conferences and meetings.

We encourage all potential contributors to publish in the fields of pharmacoeconomics, outcomes research and health policy.

Best regards,

Karina Jahnz - Różyk & Joanna Lis

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 2-6
DOI: 10.7365/JHPOR.2012.1.1

The European Medicines Agency

Prof. Tadeusz Płusa, MD, Ph.D.
Military Institute of Medicine in Warsaw, Department of Internal Diseases, Pneumonology and Allergology, Central Clinical Hospital of the Ministry of National Defence

Key words: EMA, role, structure

The European Medicines Agency (EMA) is a decentralised body of the European Union, located in London (figure 1 and 2). Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

The role and tasks of EMA

The Agency is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines. Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency.

Figure 1. The main building of EMA in London 7 Westferry Circus.

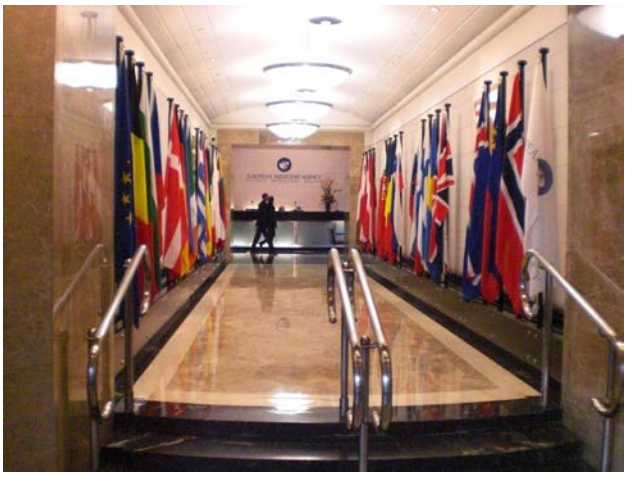

Figure 2. The main entrance into EMA in London.

All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. For medicines that do not fall under any of the above-mentioned categories, companies can submit an application for a centralised marketing authorisation to the Agency, provided the medicine constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health.

The Agency constantly monitors the safety of medicines through a pharmacovigilance network, and takes appropriate actions if adverse

drug reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised. For veterinary medicines, the Agency has the responsibility to establish safe limits for medicinal residues in food of animal origin.

The Agency also plays a role in stimulating innovation and research in the pharmaceutical sector. The Agency gives scientific advice and other assistance to companies for the development of new medicines. It publishes guideliness on quality-, safety- and efficacy-testing requirements.

Six scientific committees, composed of members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work. The Agency works with a network of over 4,500 "European experts who serve as members of the Agency's scientific committees, working parties or scientific assessment teams. These experts are made available to the Agency by the national competent authorities of the EU and EFTA states.

The Agency can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralised EU agencies. The Agency works closely with its European partners to build the best possible regulatory system for medicines for Europe and protect the health of its citizens.

In view of the continuing globalisation of the pharmaceutical sector, the Agency works to forge close ties with partner organisations around the world, including the World Health Organization and the regulatory authorities of non-European nations. The Agency is continually involved in a wide range of cooperation activities with its international partners, designed to foster the timely exchange of regulatory and scientific expertise and development of best practices in the regulatory field.

The Agency is also involved in referral or arbitration procedures relating to medicines that are approved or under consideration by Member States in non-centralised authorisation procedures.

Structure of EMA

The organization cart of the European Medicines Agency is presented in figure 3.

The scientific evaluation of medicines in the European Union

The Agency is involved in the scientific evaluation of the hundreds of medicines that fall within the scope of the centralised procedure. However, thousands of other medicines that do not fall within this scope are marketed in the European Union either in individual Member States, in accordance with their national authorisation procedures, or in multiple Member States through the decentralised or mutual-recognition procedures. The Agency only becomes involved in the asse-

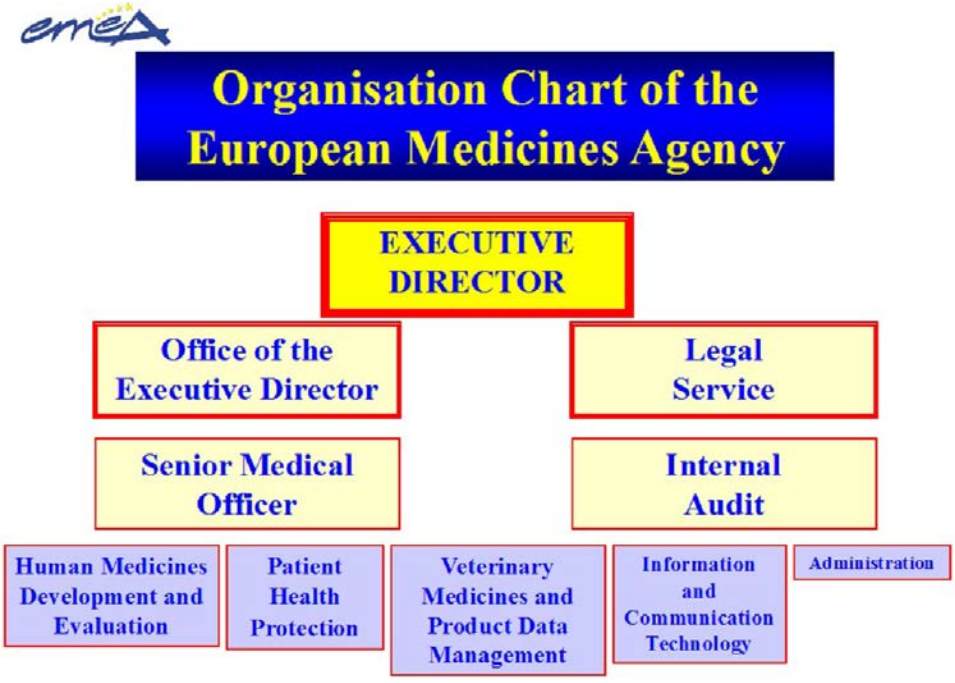

Figure 3. The main elements of EMA.

sment of such medicines when they have been referred to the Agency due to a disagreement between two or more Member States about the authorisation or use of the medicine, or due to some other issue that requires resolution in the interest of protecting public health.

The Agency does not research or develop medicines, nor does it operate laboratories on its premises or elsewhere for such work. Research and development work on medicines is carried out by pharmaceutical companies or other medicines developers themselves, who then submit the findings and test results for their products to the Agency for evaluation.

Management Board

The Agency is governed by an independent Management Board. The Management Board consists of 35 members, who are appointed to act in the public interest and do not represent any government, organisation or sector. The Board sets the Agency's budget, approves the annual work programme and is responsible for ensuring that the Agency works effectively and co-operates successfully with partner organisations across the EU and beyond. All Board members are required to make an annual declaration of any direct or indirect interests they have in the pharmaceutical industry. The Agency publishes these declarations of interest online.

The Management Board is an integral governance body of the Agency. It has a supervisory role with general responsibility for budgetary and planning matters, the appointment of the Executive Director and the monitoring of the Agency's performance. The Board's operational tasks are very broad, ranging from adopting legally binding implementing rules, to setting strategic directions for scientific networks, to reporting on the use of European Union (EU) contributions for the Agency's activities:

It has legally enforceable rule-making authority for implementation of certain parts of the fee regulation, with the implementing rules being adopted and published as decisions of the Board. The Board also adopts the Agency's financial regulation and its implementing rules, which are binding texts for the Agency, the Board and the Executive Director.

It has a key role to play in the process whereby the EU budgetary authority gives discharge to the Executive Director for the Agency's budget. The Board conducts an analysis and assessment of the Executive Director's annual activity report, which is part of the package of controls and reports that lead to the discharge of the budget. The Board also gives its opinion on the Agency's annual accounts.

It has close ties with the Agency's accounting officer, who is appointed by the Board, and with the internal auditor, who reports to the Board and to the Executive Director on audit findings. It is consulted on the rules of procedure of some of the Agency's scientific committees, and on their membership. It is responsible for adopting the implementing provisions necessary for the practical application of the rules and regulations applicable to officials and other staff of the European Communities.

The members of the Management Board are appointed on the basis of their expertise in management and, if appropriate, experience in the field of human or veterinary medicines. They are selected to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise, and the broadest possible geographical spread within the EU.

The Management Board has 35 members:

-One representative of each of the 27 Member States;

-Two representatives of the European Commission;

-Two representatives of the European Parliament;

-Two representatives of patients' organisations;

-One representative of doctors' organisations;

-One representative of veterinarians' organisations.

-In addition to the members, the Management Board also has one observer each from Iceland, Liechtenstein and Norway;

Executive Director

Photo 1. Guido Rosi Executive Director

The Agency is headed by an Executive Director and has a secretariat of approximately 530 full-time staff. The Management Board is the supervisory body of the Agency, responsible, in particular, for budgetary matters. The Executive Director is the legal representative of the

European Medicines Agency. He is responsible for all operational matters, staffing issues and drawing up the annual work programme.

The Agency's Executive Director is Guido Rosi (Photo 1.) who holds a degree in medicine and surgery, with specialisation in internal medicine, allergology and clinical immunology from the University of Rome. From 1978 to 1990, he worked as a physician in hospital, research and private practice. He worked from 1990 to 2008 in research at the Institute for Experimental Medicine of the National Research Council in Rome, directing the molecular medicine section from 2002 to 2005 and the Tor Vegata section from 2005 to 2008. He was made full professor of microbiology at the University of Rome "Tor Vegata" in 2008. From 2008 to 2011, Prof. Rasi was Director-General of the Italian Medicines Agency and a member of the European Medicines Agency's Management Board. He joined the Agency as Executive Director on 16 November 2011.

The Agency's Deputy Executive Director is Andreas Pott, who also serves as the Agency's Head of Administration.

Agency 's staff

The Agency's staff is responsible for the administrative and procedural aspects of EU law related to the evaluation and safety-monitoring of medicines in the EU. All Agency staff are required to make an annual declaration of any direct or indirect interests they have in the pharmaceutical industry.

Scientific committees

The Agency's six scientific committees are made up of independent professionals nominated by Member States from a pool of over 4,500 European experts. The committees are responsible for the scientific evaluation of marketing-authorisation application dossiers submitted by pharmaceutical companies, as well as for providing opinions on referrals and other issues impacting on public health, at the request of the Member States, the European Commission or the European Parliament. All committee members are required to make an annual declaration of any direct or indirect interests they have in the pharmaceutical industry. The Agency publishes these declarations of interest online.

Scientific evaluation on applications from pharmaceutical companies is carried out by six Scientific Committees (table 1). These Committees normally meet on a monthly basis and are comprised of members nominated by the Member States. Assessments are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC). These processes ensure that medicines have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace.

Table 1. Scientific Committees of EMA.

Committees of EMA	Abbreviations
Committee for Medical Products for Human Use	CHMP
Committee for Medicinal Products for Veterinary Use	CVMP
Committee for Orphan Medicinal Products	COMP
Committee for Herbal Medicinal Products	HMPC
Paediatric Committee	PDCO
Committee for Advanced Therapies	CAT

The Agency's scientific committees are not responsible for establishing ethical codes of conduct relating to the research or development of medicines, or for evaluating applications based on ethical considerations. Issues relating to ethics are established through legislation and directives set by the European Parliament, based on proposals from the European Commission, which in turn is advised by the European Group on Ethics in Science and New Technologies. As part of the initial administrative evaluation of the dossier of a marketing-authorisation application, the Agency's role is to ensure that previously determined standards and regulations have been implemented.

The Agency works with a number of international organisations and standardisation initiatives (figure 4 and 5).

Figure 4.

Figure 5.

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 7-11
DOI: 10.7365/JHPOR.2012.1.2

Drug Policy – what is it in Poland and UE

Wojciech Giermaziak
Departament of Drug Policy and Pharmacy, Ministry of Health

Abstract

Demographic situation – growth population of people advanced in years, greater detestability of illnesses connected with better diagnostic methods and partial covering of the costs of medicines from the public funds what causes the growth of financial expenditure for the protection of health. Considering the payment possibility of the public payer, which is obligated to finance health care services, decisions to be taken in this field must be based on clear specific requirements and defined and verified information. A proper state body which is authorized to create the structured and conscious drug policy should take planned operations aiming at rationalization of budgetary expenditure and furthermore the supply of safe, effective and cheap drugs to patients.

Keywords: drugs, drug policy, health policy, pharmacoeconomics, financing health care services, refund

Each country reaching a basic level of society's civilization, especially nowadays, deals with the problem of appropriate planning and the balancing of public expenses. A very significant part in every state budget is allocated for public health expenditure. Moreover, constant public debates, proper for the state and global economies, implying legislative changes are held. Meanwhile, apart from the used systemic solutions, the dynamic growth of health spending is observed in nearly every country in the world. 9% of GDP on average is spent on this area in Europe. Poland is ranked one of the last countries in the EU with the expenditure, depending on the assumed calculation method, ca 4.5% of GDP including private spending for this aim – up to 6.5% of GDP [2, 8].

It is worth reminding the important relevant value of GDP per capita, which ranks Poland 23rd in the European Union, which shows the efforts in creating a government policy to ensure citizens' health security. Expectations and health needs of the society are significantly higher than the national budget, which is the an unavoidable consequence of the argument that spending on health care budget will consistently grow.

It is estimated that by 2020 the European Union countries will have spent approximately 16% of GDP on health care. This value seems to be a natural consequence of health changes that occur in an aging society and moreover the indicated level of 30-35% of GDP, which will have to be spent before 2050, raises serious concerns because it is difficult to achieve a well-balanced budget, even in a wealthy society where such a huge part of it will be spent only in one area of the economy. Such an increase in the expenditure is, as I previously mentioned, determined above all by the growing health needs of an aging population. It is worth remembering that the average age reached in populations of developed societies, over the last century, increased by more than a third in analogy to the nineteenth century. However the growing cost of health care system is equally important but the biggest dynamics of spending is observed in the drug economy [1].

From 1997 to 2007, the worldwide sales of drugs increased by 150%. In Poland from 2004 to 2009, the spending for the reimbursement increased from the 6 billion 118 million PLN to 8 billion 213 million PLN. Considering that the statistically consumption of drugs grows rapidly among the people after 56 years of age, it has become a clear need for a rational drug policy. What is the rational management of drugs defined as a drug policy? The drug policy is comprehensive, organizational and it constitutes legal measures by which one of the main tasks of the Minister of Health is executed. The Ministry of Health is constitutionally responsible for the whole public health in the majority of European countries among others for guaranteeing the safe and effective access to drugs to citizens while implementing systemic process of reducing the patient's copayment in the share of the medical treatment [7].

This is a multidisciplinary operation by the Government and its shape is influenced not only by both the Ministry of Finance and the Ministry of Treasury, but it is also a key health department and whole orientations of socio-political, which it has government and parliament performance in the period of the state power.

There are some mechanisms and instruments which allow for rational development of drug policy. At the central level, the main role of the policies of the Minister of Health and central units subordinated to him is to market medicinal products and to make decisions regarding the rate of prices and subsidies for reimbursement. Even if there is no change in the reimbursement system, the increase of expenditure on drugs will still be observed, because of the dominant factors in this area and demographic as well as pharmacoeconomic indicators. The phenomenon of drug spending growth is thus not the main and the only factor determining the dynamics of health spending [6, 10].

Pharmaceuticals is a sector of the economy where, as in no other, due to the progress of sciences and engineering, introducing new molecules of medicinal products, the latest engineering technologies, the most effective ways of treating diseases that have recently been a death sentence or a long-term illness. The number of introduced innovative drugs is huge. Thanks to innovation in the pharmaceutical industry there is the progress and more effective option to treat complex diseases. However considering what this "innovation" is how to measure or rate it in the sense of public expenditure [6, 9]. At the conference of Health Ministers of European countries titled Innovation and Solidarity on Pharmaceuticals, which took place in early September 2010, the Director General of EMA, Thomas Lönngren, tried to define innovation in the pharmaceutical sector. He pointed out that the medicinal product may be considered as innovative if it meets the following criteria:

1. represents a real therapeutic value for the individual or to society,

2. shows the actual therapeutic value,

3. presents an economic value,

4. is relatively more effective than existing drugs in terms of effectiveness, efficiency and safety. He pointed out that "new and approved is not necessarily a new and improved".

Meanwhile, it is estimated that in fact innovation, according to the abovementioned definition is less than 5% of recently developed drugs. The other 95% of medicinal products has a slightly higher clinical efficacy of existing drugs, slightly greater safety, different dosage forms or do not show an advantage over existing ones, except for a consistent difference in price [4,6].

Interesting information was presented by Professor Garattini. The professor used the example of the breast cancer therapy. The median 5-year survival rate in the seventies was 68%, in recent years (2000-2007) this grew to 81%. Accordingly, in the case of colorectal cancer there was an increase from 58% to 69%. The median monthly cost of therapy in the seventies was $ 64, in 2007 it reached $ 6559. So 13% and 11% increase in the effectiveness of therapy represented more than 1000% increase in its costs [6, 5]. The task for each country becomes on the one hand, encouraging innovation, implementing the latest technology in the production and use, on the other hand, which is essential to the drug policy of any State rationalizing expenditure. The above data show how difficult this task is and that it does not generate only positive results in every case.

In the context of limited funds, especially when we deal with such precious common wealth as health every zloty a dollar or euro should be spent in a rational and purposeful way in order the positive effect to cover as much of society as possible with the smallest allocation of national income. The instrument that allows the operation of this type is pharmacoeconomics, the field that came into being relatively recently and which is defined as a scientific discipline, dedicated to comparing the value of medicinal products and medicinal therapy. It is a subdiscipline of the "Health Economics" with its meaning interepreted as the economics of health. Pharmacoeconomics evaluates the cost and effectiveness of a drug technology, which consists of price, performance and Quality-Adjusted Life Year (QALY), which corresponds to the improved quality of life. The beginning of pharmacoeconomics was the formation in 1996 of the English agency called NICE which is accountable for the issue of recommendations that helped to rationalize the financing of selected therapies. The activity was also noticed by other countries which began to create their own agencies.

In Poland, by order of the Minster of Health as of 1 September 2005 on the establishment of the Agency for Health Technology Assessment (AHTA), the agency was founded whose purpose was to help the Ministry of Health in the rationalization of public spending on drug technologies. Its position was not clearly defined. It functioned as a budgetary unit and recommendations issued by it were not binding. As a result of reforms introduced by the new government, the Agency was empowered by the act as of 25 June 2009 amending the act on healthcare services financed from public funds and the act on Prices (Journal of Laws of 2009 no. 118, item 989) and became an important element of the reimbursement system . The aim of the Agency is to perform tasks related to the assessment of health care benefits in the scope of:

a) making recommendations on: the qualifications to provide health care as a guarantee benefit, specifying or changing the level or method of financing as a guaranteed benefit, removing the provision of health care from the list of guaranteed benefits,

b) preparing reports on the evaluation of health care services excluding however reports on the evaluation of a drug or medical device,

c) development of the assessment reports on the evaluation of health care services,

d) development, verification, collection, sharing and dissemination of information on the methodology of evaluation of medical technologies and medical technologies developed in the Republic of Poland and other countries,

e) issuing opinions on health programs.

Currently, most clinical trials and analyses of medicinal products are based on comparing a drug to a placebo. However globally calls for comparative testing of drugs i.e. head-to-head research, which provides best information on their effectiveness and allows to answer the question which drug is better. In such studies the rules under which they are carried out are most important At the Selling Sickness conference held in Amsterdam from 8 - 10 October 2010 was attended by the representatives of the pharmaceutical industry and governmental agencies responsible for regulatory and legislative rationalizing the government expenditure on drugs. They pointed out that the medicinal product should be compared with the best available drug in its group and only if this analysis falls in its favor entering the product into the list of reimbursed drugs should be considered. All stakeholders in the pharmaceutical market acknowledge the need for such a solution. Only after complementing the system with this type of study, one can speak of the effective evidence-based medicine. In Italy, the mechanism created by Professor Garattini successfully works it is called the Garattini tax. Pharmaceutical companies have been charged with 5% of tax on marketing expenditure This money is spent on independent head-to-head research. The introduction of similar solutions is envisaged in Poland.

The Minister of Health with the information provided by the Agency for Health Technology Assessment decides which of society health needs are the priority and which drugs will be covered the reimbursement system, and which are excluded from it. After the completion of price negotiations with pharmaceutical companies, the Minister of Health announces the drug to be entered into the list of reimbursed drugs by reimbursement regulations.

Establishing the price of the reimbursed medicinal product is another important issue requiring careful analysis of the market in comparison to actual needs of the society. It was mentioned that the increase in spending on drugs is the most important factor determining the dynamics of growth of expenditure on the health care. Professor Erik Shokkaert from the University of Leuven shows that spending on innovative medicines accounts for half the growth of health spending in the general government budget regarding the amounts allocated for this purpose. At the same time he draws attention to the unique mechanism of pricing these products. Because, the price is created during bilateral negotiations between a responsible entity and the government, it is extremely important to this process that it is not governed by any economic mechanisms, but primarly by the health needs of citizens. Moreover, the authorities of the State, as a rule, are not able to refer to costs and prices submitted by a company in the form imposed by the company's internal standards of pricing policies.

It is therefore extremely important who and how negotiates. Depending on the negotiating skills of its officials the State may lose or gain hundreds of millions. We are proud of the achievements in this area, as drug prices in Poland are among the lowest in Europe, which has been the result of the activities of the Ministry of Health in recent years.

Of course, the important factor is that our country is almost a market of 40 million people what is taken into account by any pharmaceutical company.

Undertaking reasoned decisions and appropriate establishing of reimbursement prices creates budgetary expenditure on reimbursed drugs. However, this does not cover the subject of reducing the patient's copayment. In Poland, the reimbursement of more than 3700 medicinal products, which are grouped in 417 active ingredients, until the introduction of the Reimbursement Act with its 310 limited groups. Thus doctors had and still have quite a substantial flexibility in deciding which drugs with the same indication to prescribe. The great majority of reimbursed drugs are generic, which are much cheaper than original drugs. System of subsidies for drugs is based on the structures of limited groups, which include drugs with similar therapeutic effect. The level of subsidy of the drugs is determined by the level of payment specified in the relevant list of the Minister of Health and the level of the cheapest drug in the group. So if a patient chooses a more expensive drug he or she pays the portion which is not subject to the reimbursement from the budget of the public payer, i.e. the National Health Fund, increased by the difference in price between the purchased and the cheapest drug. Article 38 paragraph 4 of the Act of 27 August 2004 on health services financed from public funds (Journal of Laws no. 164 item 1027 as amended imposes the an obligation on pharmacy to inform the patients about the possibility of replacement of the prescribed drug with a cheaper substitute. In practice, patients are not informed of this possibility and the law is not observed due to the system of retail margins, which discourages pharmacists and retailer owners from "pro-patient". Behavior the value of retail margin is a fixed percentage, the difference between the wholesale price and retail price, thus the higher a retail price the higher a margin.

The value of the pharmacy market in 2009 amounted to almost 26 billion PLN (according to IMS PharmaExpert and IMS Poland), including the market of reimbursed products which accounts for slightly more than 11 billion PLN. The value of generic medicines market according to the Polish Association of Pharmaceutical Industry Employers accounted for about 65% with its highest rate in Europe. According to these estimates, the public payer saves approximately 7 billion PLN each year due to such a high consumption of generic medicines. At the European Union level, at the aforementioned conference on Innovation and Solidarity on Pharmaceuticals this need was acknowledged, stating that a change in market structure will bring huge savings, which will help to fund more valuable innovative medicines.

Poland, with regard to sales of innovative medicines, has one of the worst positions in Europe, only with Bulgaria, Lithuania and Latvia ahead, which was presented at the conference by Bruno Flamiona from EMA. The Ministry of Health proposes to introduce a fixed margin calculated on the basis of the price of the drug, which is the basis of the limit in the group limited. The aims of the procedure is to stop a pharmacist from offering more expensive medicines, at least in comparison to the reimbursed drugs. This should further increase the share of generics in the market and result in savings for the payer. This approach is beneficial to all stakeholders in the pharmaceutical market, because if the National Health Fund makes savings the reimbursement of medicinal products, this money may be spent on innovative products and introduction of new therapies, which will increase therapeutic possibilities for patients.

It is also important how the dialogue with pharmaceutical companies is conducted. Before 2007, the dialogue with responsible entities was conducted by the department of health in a chaotic, if not incidental, manner, On 19 February 2008, the procedure for cooperation with companies was established for the first time. This procedure requires the subject of the meeting to be defined and the right representation of the company. The time of appointment is scheduled in advance, provided that the subject of the meeting must be presented no later than 5 days before the meeting. Meetings are recorded and minuted. Each meeting is attended by at least three representatives of the Ministry. Employees of the Ministry may not accept any documents and items and all correspondence is addressed via official channels, ie.., with the participation of the Central Registry of the Ministry. The adopted solutions structure the dialogue between the private and public sectors and introduce clear rules of conduct. The above mentioned procedure is positively evaluated in Europe by many countries e.g. France trying to develop similar solutions. It should be noted that the discussed procedure corresponds with the 89/105/EEC Direc-

tive of 21 December 1988 regarding the transparency of measures regulating the pricing of medicinal products for human use and extend the scope of national health insurance systems (Journal of Laws 1989 L 40, p.8), hereinafter referred as the Directive of transparency. The described situation, entered into on 01.01.2012 i.e. the date of entry into force of the Act of reimbursement, which radically changed the Polish pharmaceutical market, while preserving and clarifying of the existing solutions.

To conclude, the main objectives presented above, and state drug policies are intended to reduce drug prices and rationalize expenditure allocated for health care. Conducting a planned, rational drug policy in the management of the state budget is a relatively new concept. The planned effort to achieve the objective should be pursued in a systematic way, in an open dialogue with all stakeholders in the pharmaceutical market. The origins of the creation of the conscious, organized drug policy are the effects of work of recent years, exemplified by the harmonization of medicinal products, the establishment of the Agency for Health Technology Assessment and undertaking specific actions by the Minister of Health. Calculating costs of reimbursement shall not be understood as an attempt to limit the availability of medicines to patients. The drug policy is to transform the money spent into the best possible therapeutic effect for the patient. The rationalization of expenditure is to increase the availability of different therapies to patients resulting in the announced amendments to the list of the reimbursed drugs which introduces more new products owing to the savings brought by the activity of the Ministry of Health.

The aim of the policy is also to reduce a patient's copayment, which in October 2010 fell to the level of 31.1%. The creation of the coherent system of drug policy creates huge opportunities for the overall health of the society, the state budget and the health safety of an individual patient. Conducting independent comparative testing of drugs that will result in reasonable recommendations is the first step and the basis on which the system should operate. The next step is to conduct effective price negotiations with the entities responsible and take rational reimbursement decisions based on evidence of cost-effectiveness, which is possible if the decision maker has appropriate actual data. At this stage, there is a necessity to organize and define the relationship of administration and responsible entity more precisely. After the completion of that process a need for the efficient functioning of the mechanism for encouraging greater consumption of cheaper drugs with the same therapeutic effect remains.

The above mentioned activities involve the implementation of Art 68 of the Polish Constitution, which formulates the general principle of state policy by which everyone, regardless of their financial situation, has the right to healthcare. However, to perform the task while respecting the expectations of patients, demanding the application of modern, often the most expensive treatment which assures high performance and high safety applied at the same time of therapy, there was a need for a rational drug policy, based on the efficient management of expenses and costs. The crowning achievement of the State's activity in this area is the enforcement , of the Act on reimbursement of medicines foodstuffs for particular nutritional and medical devices, commonly known as Reimbursement Act on 1 January2012, which clearly regulates the market, while maintaining appropriate balance between the manufacturer, distributors and the State tax payer, while maintaining compliance with the applicable procedures of the EU Transparency Directive and the Polish patient's constitutional right to access to the latest drug technology in the healthcare system.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 12-14
DOI: 10.7365/JHPOR.2012.1.3

Some thoughts regarding reimbursement act of 12 may 2011

Jacek Spławiński
Professor emeritus at National Medicines Institute

Health care costs and drug reimbursement are tightly intertwined. For more than decades healthcare costs have grown faster than our national economy. Constant cost growth threatens politicians and undermines the existence of the publicly funded National Public Fund (NHF). It is not surprising then, that the Polish Ministry of Health has decided to introduce a new bill regarding drug reimbursement, called " Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices" effective from 1 January 2012.

The project was not discussed with the medical community and was riddled with loopholes, limits, exclusions, and is full of ambiguous clauses. In addition, in the first version of the bill, articles 48 and 129b defined the penalty, for physicians and pharmacists, respectively, on top of the refund for undue reimbursements paid by the Fund including statutory interest counted from the date of the refund. These penalties were due in several cases, especially when the prescription was: incompatible with the beneficiary's rights; not justified by medical documentation; and in conflict with the registered indications. The act generously waived the penalty when the prescription was forged: "The provision of ... shall not apply in the case where the prescription ... has been counterfeited..." (sic !). Following the announcement of the act in the end of 2011, the Supreme Medical Chamber started a nationwide protest of doctors together with pharmacists that forced the legislators to promptly amend the act in January 2012. Although penalties for physicians have been lifted some ambiguous clauses still remained in the act.

The purpose of this commentary is to discuss the most sensitive articles of the act in the hope that this may help future legislators. The comments represent the author's personal opinion and do not necessarily reflect the viewpoint of the Polish Pharmacoeconomical Society. The former Minister of Health accused all protesters of criticism based on bad will making this work sensitive to the unjustified accusation of ties with the pharmaceutical industry (see below: conflict of interest).

The law is written on 40 pages and contains 86 articles. It starts with the definitions which are severely limited. There is an absence of important terms relating to reimbursement policy such as: "clinical efficacy", "practical efficacy", "rationalization analysis" (i.e. analysis indicating the source of funds for a drug to be reimbursed – see below). In addition, certain definitions are far from accurate – for example, generic is: "...a medicine containing the same active ingredient and having the same indications and the same route of administration in the absence of differences in pharmaceutical form".

The bill begins with a puzzle: "...The total reimbursement budget is no more than 17% of the total public funds assigned for to guaranteed benefits in the Fund's financial plan" (art. 3). Why 17% ? In 2010 the NHF spent 19 % on drugs, which indicates a heavy cut of 2% on drugs reimbursement for the year 2012. No explanation is provided regarding the 17% figure, and without a definite mathematical approach it is difficult to understand the steps that will be taken when the NHF will exceed the 17% threshold. The act specifically addresses this issue: "... the amount in excess shall be assigned to the given limit group...The applicant... return to the Fund an amount which is proportionate to the share of the reimbursement costs of the drug..". However the calculation for payback due to overspending is highly sophisticated – the appropriate formulae are: KZi = Siunorm*KP*G*0.5;

Sinorm = Si/∑Si and Si = G2i/∑g2i * C2i/C2L.

In Chapter 3, Article 10.3 contains a definition stating the lists of drugs excluded from the reimbursement, represents the highest level of inaccuracy: "...The following cannot be reimbursed: a medicine ... in clinical conditions in which it is possible to effectively replace that medicine...by changing the patient's lifestyle". On one hand this clause implies that physicians are likely to treat patients who do not required treatment; on the other hand it allows the cashier of the Fund to deny reimbursement in case of, for example, conditions such as type 2 diabetes where a strict diet and exercise are the best treatment options. As everybody knows the population of type 2 diabetics is enormous and therefore cost savings for the Fund may be significant. Such an article raises the suspicion that the law opens an "umbrella" for the Fund and not for the patient contrary to government announcements.

However, the umbrella does not cover the Ministry of Health as several own goals are apparent. Here is the most important (article 33): "The minister responsible for health ... shall revoke ... the reimbursement decision for a drug... in the case of finding the absence of the declared therapeutic efficacy".

The entire act is dumb on the subject of an assessment regarding a lack of therapeutic efficacy. It is not a subject that one should slide over. The Pharmaceutical Law contains an extensive list of conditions regarding the efficacy of a drug which must be fulfilled by the applicant in order to register a given indication. None is listed for the administrators to revoke the reimbursement for a given drug. It is not mentioned who is responsible for such assessment. In the Polish version of the act there is a hint that it is the Minister himself/herself. Neither is the administrative way to appeal against such decisions indicated.

The reimbursement could also be denied by administrative decision, when the obligation of the annual volume of supplies by producers is not met. In this case, it is not only the pharmaceutical manufacturers that feel the repercussions, but patients are punished as well.

Article 12 describes the intentions of the Minister of Health: "In the view of the need to obtain the best possible health effects within the framework of the available public funds ... the Minister... issues ... reimbursement decision and the decision setting the official sales price with consideration given to the following criteria". One criterion and perhaps the most important one is point no 4: "the clinical and practical efficacy". The point is that conjunction "and" is used. In that case, if it is used in the same manner as logic or mathematics, both conditions (clinical efficacy and practical efficacy) must be fulfilled in order to secure reimbursement. However, "and" could be also used as the grammatical conjunction, similarly it is used in everyday day language, novels or fairy-tales. It is difficult to accept the idea that the new law is a fairy-tale however either way - the statement in criterion no 4 is ambiguous.

Assuming that in the act "clinical efficacy" is "efficacy" and "practical efficacy" describes "effectiveness" the problems connected with the application for reimbursement become apparent, as efficacy and effectiveness must be shown together. Dura lex, sed lex. It won't be easy, for an applicant, a candidate for reimbursement, to demonstrate both efficacy and effectiveness at the same time. It is quite possible that latter condition could be fulfilled but only by a small number of candidates. The difference between these two, efficacy and effectiveness could be best exemplified by the Black's et al alendronate study (Black et al.: Randomised trial of effect of alendronate on risk of fracture... Lancet 1996;348:1535). In this study, 2027 women (aged 55-81) randomly received placebo or alendronate for 36 months with two inclusion criteria: low bone mineral density and vertebral fracture. However, the exclusion criteria are of interest. These were: peptic ulcer disease (bleeding or 2> ulcers in last 5 yrs), dyspepsia, abnormal renal function, major medical problem precluding participation for 3 years, severe malabsorption, uncontrolled hypertension, myocardial infarction, unstable angina, disturbed thyroid or parathyroid function and the use of hormone replacement therapy. In other words, only exceptionally healthy women received the studied drug. The chances that one can meet such women in the practice are like 1 to 508 since 2,027 women were recruited among 1 030 000 questioned (see Black et al.). There was no comparison between the population used to establish efficacy and the population likely to be met in clinical practice and therefore solely efficacy and not effectiveness was shown.

Finally, the most ambiguous article is number 28, clause 7, point b in which so-called "rationalization analysis" is required by the Ministry of Health

to justify application for reimbursement. When the addition of a particular drug to the reimbursement list would increase the total reimbursement costs, the applicant is obliged to provide the solution that will result in a release of public funds which will compensate for the increased total reimbursement costs. The idea is fantastic for the National Health Fund, as it will ensure there is a fixed budget on reimbursement, and perhaps this may explain the mysterious 17% figure discussed earlier.

In summary, the new act as explained in the introduction was extremely needed and there are many articles in the new act that represent solid knowledge and real help for patients and physicians. However, if the new law is expected to change the pharmaceutical market, making it more friendly to patients and pharmaceutical producers, many articles require further discussion and clarification.

(I appreciate the help of Adam Plich, M.Sc. Conflict of interest: none).

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 15-20
DOI: 10.7365/JHPOR.2012.1.4

Implications of economic crisis on health care decision-making in Hungary: An opportunity to change?

Zoltán Kaló MD MSc PhD
Health Economics Research Centre, Eötvös Loránd University, Budapest, Hungary, Syreon Research Institute, Budapest, Hungary

Imre Boncz MD MSc PhD
University of Pécs, Hungary

András Inotai PharmD PhD
Syreon Research Institute, Budapest, Hungary

Abstract

Background: Evidence base and transparency of decision making are most critical issues to improve health care in middle income countries. Capacity building of health economics and incorporation of health technology assessment into the pricing and reimbursement of pharmaceuticals happened earlier in Hungary than in neighbourhood Central Eastern European countries. The aim of this paper is to explore the implications of economic crisis on macro level health care decision making in Hungary.

Methods: The pricing and reimbursement process of new health technologies was reviewed to assess the transparency of decision-making and the availability of objective and verifiable criteria for reimbursement. In addition, a longitudinal analysis of public health care and pharmaceutical expenditures was conducted in Hungary between 1993 and 2011.

Results: Health policy and major reimbursement decisions are still not fully transparent and made without objective and verifiable criteria in Hungary. The Hungarian National Health Insurance Fund had continuous deficit since its foundation between 1993-2006. During this period the actual public pharmaceutical spending was higher than the planned budget. The highest overspending percentage ((actual – planned)/planned) was observed in parliamentary election years, 21.5% in 1994, 32.1% in 1998, 36.6% in 2002 and 30.4% in 2006. Since 2007 serious cost containment measures have been implemented.

Conclusion: There is still room to enforce the cost-effectiveness criterion in pricing and reimbursement decisions, as it improves the allocative efficiency of scarce public resources. The economic crisis creates an opportunity to strengthen the evidence base of health care decision making in Hungary.

Key words: evidence based health policy, pricing and reimbursement, pharmaceutical expenditure, cost containment measures, middle income countries

Introduction

Scarcity of public resources, especially in challenging economic times, draws attention to the expenditure on health care. Pharmaceutical expenditures gained remarkable attention, as drugs are considered a major growth driver of health care spending [1, 2]. Middle income countries tend to spend higher proportion of their health care expenditure on pharmaceuticals compared to developed countries: they have to purchase innovative drugs at the same global price as high income countries due to manufacturers' response to international price referencing and parallel trade, whilst their manpower costs are lower [3]. Macroeconomists (e.g. at IMF or EU) pay attention to public pharmaceutical expenditures, however, their macro-level policy recommendations usually focus solely on cost-containment, and so do not consider implications on health outcomes.

Incorporation of health economics and health technology assessment (HTA) in healthcare decision making happened earlier in Hungary than in other Central Eastern European middle income countries. In the mid 90s the World Bank supported the establishment of two new academic centres in public health and health care management. The number of trained professionals was sufficient to set up HTA & health economic centres in Hungarian universities for academic research, graduate and postgraduate training. Methodological guidelines for economic evaluations were published in 2002 [4] . Cost-effectiveness evidence prior to the reim-

bursement of pharmaceuticals and medical devices has become mandatory in Hungary since 2003 and 2011, respectively. In 2004 the Ministry of Health established its public HTA Office for the critical appraisal of HTA chapters in the reimbursement applications submitted by pharmaceutical manufacturers. However, documents about the evidence base of new technologies and summary report of reimbursement decisions are not routinely available for public revision or scientific research as opposed to many other countries with fourth hurdle [5, 6]. Therefore is still room to improve the transparency [7].

Hungary has a single-payer health insurance system. The National Health Insurance Fund (NHIF) had continuous deficit between 1993-2006 [8]. The deficit varied from 3.4% to 12.6% between 1994 and 2002, and increased strikingly between 2003 and 2005, by reaching 31.2% in 2005 (375.3 billion HUF) [9] (1 EUR=248.05 HUF, average exchange rate in 2005). As a consequence, in the end of 2006 strict cost containment measures were implemented. The aim of this paper is to explore the implications of economic crisis on macro level health care decision making in Hungary.

Materials and methods

The process of pharmaceutical pricing and reimbursement decision was assessed with special focus on the timeliness of decisions, the transparency of decision-making process and the availability of objective and verifiable criteria for reimbursement. In addition we completed a longitudinal analysis of public health care and public pharmaceutical expenditure in Hungary between 1993 and 2011 based on NHIF data.

Results

29 official resolutions of pricing and reimbursement decisions by the NHIF were analyzed between January and June 2008. In 14 cases the NHIF granted reimbursement, in 15 cases the reimbursement claim was rejected. The average time period for pricing and reimbursement procedure between the submission of the reimbursement dossier and the official decision was 172 days (minimum 43 days; maximum 534 days). As the analysis excluded those pricing and reimbursement applications with no decision, these estimates are conservative. Applications waiting for the decision over longer periods could significantly increase the time scale of pricing and reimbursement decisions. Still, several pricing and reimbursement applications with over 180 days of evaluation period were observed. In addition no objective and verifiable criteria in the pricing and reimbursement resolutions of innovative pharmaceuticals could be justified. These factors indicate serious problems with the timeliness, transparency and consistency of pharmaceutical pricing and reimbursement decisions. Figure 1 indicates the revenues and expenditures of the Health Insurance Fund in Hungary. After the 31.2% deficit in 2005, the expenditure has been considerably reduced since 2007.

Figure 2 depicts the overspending of the Hungarian public pharmaceutical budget. Between 1994-2006 the actual public pharmaceutical spending was higher than the planned budget in each year. The highest overspending percentage ((actual – planned)/planned) was observed periodically, i.e. 21.5% in 1994, 32.1% in 1998, 36.6% in 2002 and 30.4% in 2006. Since 2007 serious cost containment measures have been implemented, in 2007 and 2008 even net savings were realised in the public pharmaceutical budget. Since 2011 the Hungarian government has introduced further cost-containment measures for the public pharmaceutical spending between 2012-2014. According to the Széll Kálmán plan, the public pharmaceutical spending has to be reduced by more than 35% in 3 years.

The annual growth rate of nominal pharmaceutical public expenditure was considerable until 2006 (see Figure 3). After the implementation of cost-containment measures, the public pharmaceutical expenditure decreased in 2007 and remained constant between 2008-2010. Different forms of payback mechanisms for pharmaceutical companies (including general clawback and risk-sharing agreements) have been introduced since 2003. In 2011 pharmaceutical companies already covered 15.8% of public pharmaceutical spending in Hungary, therefore the actual public spending is significantly less than what is presented in annual reports.

If we correct for inflation (see Figure 4), the real growth of pharmaceutical spending showed increase between 2000-2006, and significant decrease between 2006 and 2008. Figure 3 and 4 also depict the implications of the Széll Kálmán plan. The Hungarian public pharmaceutical budget will be reduced by 100.5 billion HUF in 2012 and by additional 37 billion HUF in 2013 and 2014 [10].

As part of this, reduction will be transferred to other channels of financing pharmaceuticals (i.e. approximately 30 billion HUF is allocated for central NHIF tender for special high cost drugs), the net impact of Széll Kálmán plan could be less dramatic than indicated on Figure 3 and 4.

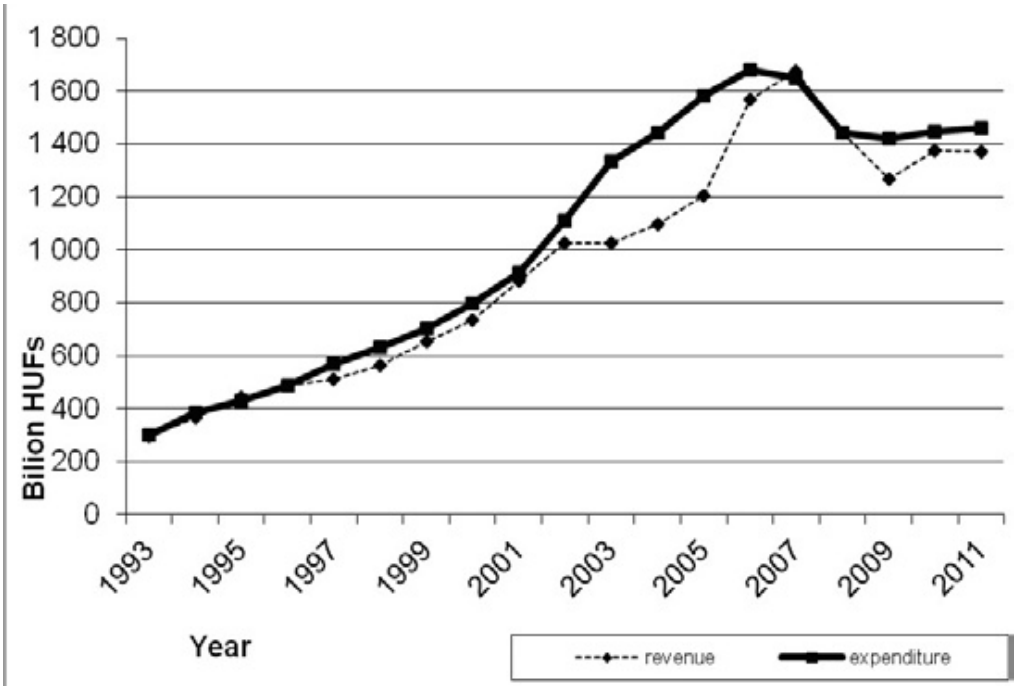

Figure 1. Actual revenues and expenditures of the National Health Insurance Fund (1993-2011, billion HUF)

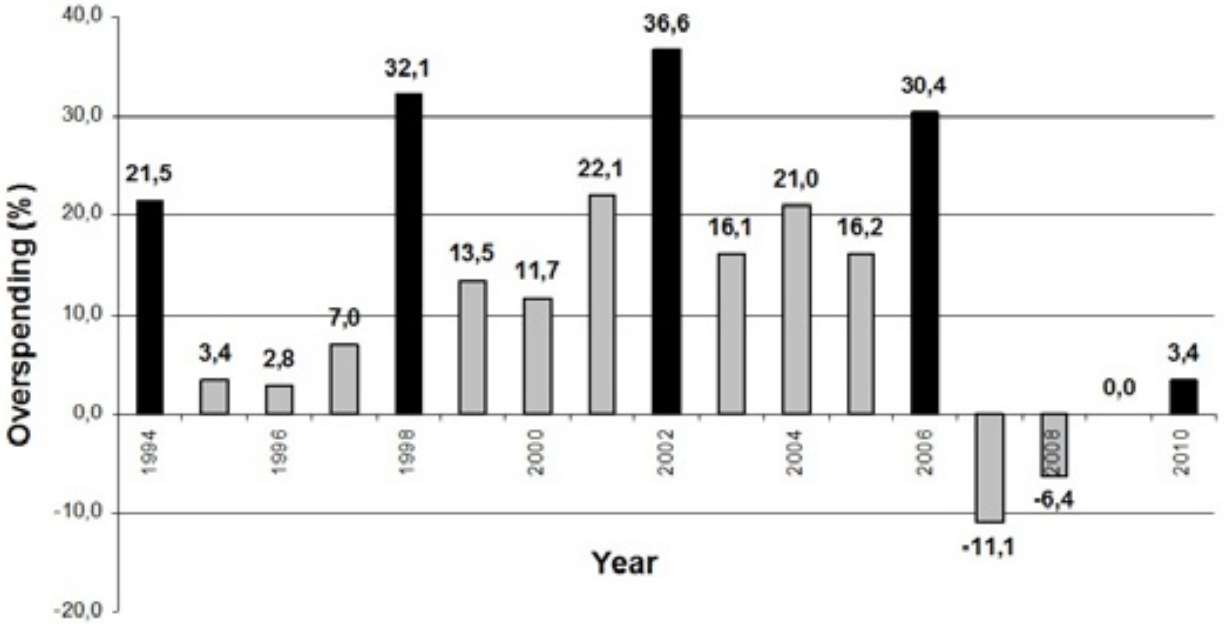

Figure 2. Overspending of the Hungarian public pharmaceutical budget compared to thebudget plan (1994-2010) ((actual – planned)/planned)

Figure 3. Real public pharmaceutical spending in Hungary with and without payback adjustedfor the annual consumer price index (1994-2014, billion HUF) *based on target expenditure for2011, **based on proposed budget for 2012 by assuming 3% inflation rate, ***based on Széll Kálmán Plan by assuming 3% inflation rate

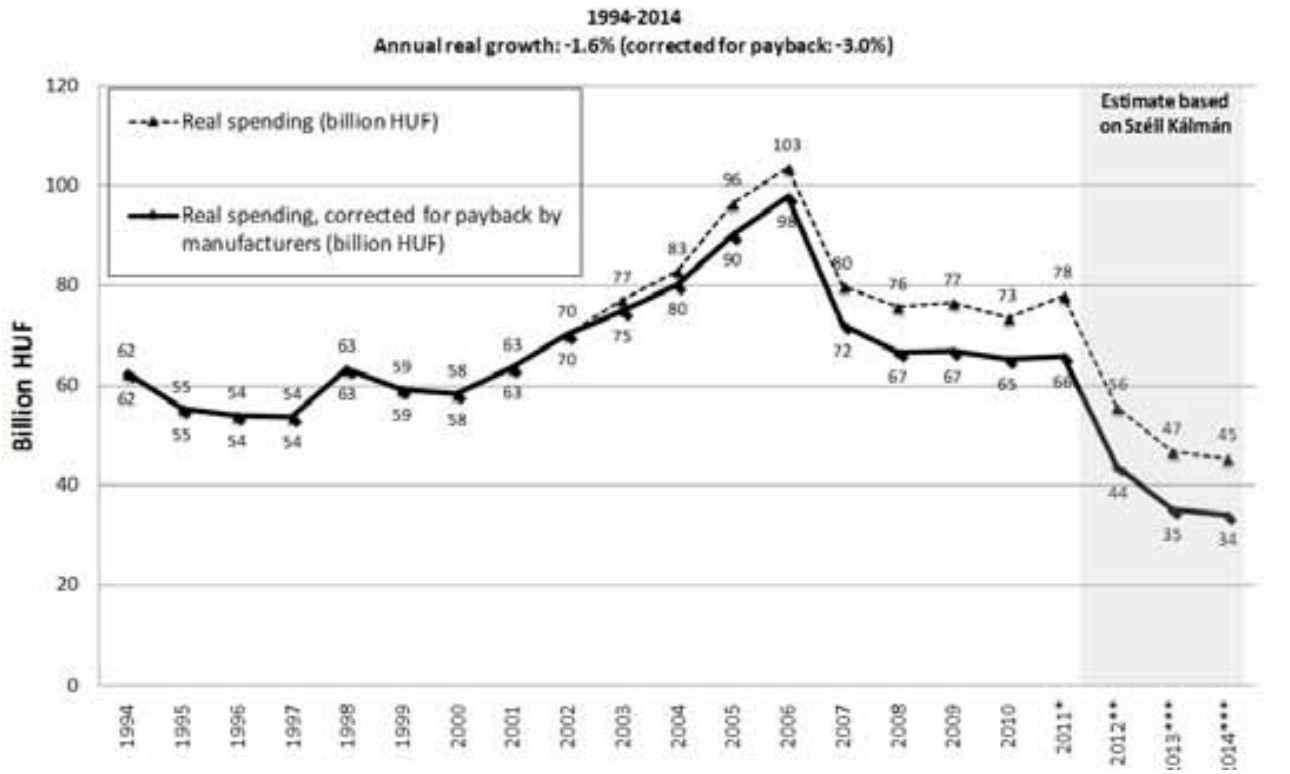

Figure 4. Nominal public pharmaceutical spending in Hungary, with and without payback(1994-2014, billion HUF) *based on target expenditure for 2011, **based on proposed budget for2012, ***based on previously released version of the Széll Kálmán Plan

Discussion:

Figure 1 and Figure 3 indicate similar trends, and therefore confirms that pharmaceutical expenditure played significant role in the growth rate of public health care spending in Hungary. Figure 2 indicates that peaks of overspending the public pharmaceutical spending correlate with the 4-year parliamentary elections (1994, 1998, 2002, and 2006).

Figure 1, 3 and 4 reflect the serious cost containment measures implemented in the financing of health care services and pharmaceuticals after 2006 [11]. The implementation of the Széll Kálmán plan would result in negative annual real growth (-1.6%) rate within a 20-year period from 1994 to 2014 according to Figure 4 (-3.0% if real spending is corrected by payback by pharmaceutical companies). If the Széll Kálmán plan is fully implemented, the actual public pharmaceutical spending corrected by the contribution by pharmaceutical manufacturers would be 45% lower in 2014 compared to 1994. This reduction may shift additional financial burden of pharmaceutical spending to private households. As a consequence of cost-containment measures after 2006 the Hungarian health care sector is currently seriously underresourced and close to collapse. By 2011 hospitals had cumulated a huge deficit. Despite significant reduction of acute care beds, only a few hospitals were closed. Consequently the economies of scale and scope of hospitals were decreased.

The low salary of Hungarian health care professionals has been escalated to a human resource crisis. Many young physicians and nurses left the country in recent years and moved to Western Europe for significantly higher salary and career opportunities. There is a constant shortage of primary care physicians and specialists (e.g. anaesthesiologists, pathologists, traumatologists). The average age of primary care physicians is over 62 years, and many GP practices are vacant, especially in the countryside. Hundreds of young resident physicians planed to hand in their resignations.

In such a difficult economic period it is easier to justify the implementation of evidence based health policy. Consideration of cost-effectiveness evidence prior to major policy and reimbursement decisions would be essential to improve the allocative efficiency of health care financing, especially when public resources are highly limited. The authors believe that economic crisis creates an opportunity to strengthen the evidence base of decision making in Hungary, especially since there is a strong organisational structure of health economics and health technology assessment.

However, since 2006 budget impact has been the main focus of policy and reimbursement decisions, and no objective and verifiable criteria in reimbursement resolutions of innovative pharmaceuticals could be justified. Limited transparency of processes and decisions is currently one of the most critical issues in the Hungarian health care decision making. Although we could analyze only those cases with resolution (as there are several open cases without resolution for years), the time period for pricing and reimbursement decision of pharmaceuticals was still longer in several cases than the 90 + 90 days recommended by transparency directive of the European Union [12].

Conclusion

Hungary has sufficient human resource capacity and initial experience to implement evidence based health care financing and health policy. However, reimbursement and policy decisions are still not fully transparent, and as a consequence of the economic crisis, the emphasis is currently on cost-containment, i.e. budget impact instead of cost-effectiveness analysis. The most critical question for policy-makers is whether they really want to improve the rationale of health care decision making or they should just concentrate on reducing the public health care spending, as experienced in recent years. Implementation of evidence based health policy is more complicated route in the short-term, but it may pay off in the long-term.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 21-23
DOI: 10.7365/JHPOR.2012.1.5

Health technology assessment in reimbursement policy of the Slovak Republic

assoc. prof. Tomas Tesar, PhD., MBA
UNION health insurance fund, Bratislava, the Slovak Republic.

Abstract

Evidence suggests that availability of medicines on the Slovak market is both comprehensive and prompt. The low co-payment rate of reimbursed products results in easy access to highly priced patented products. There is always at least one treatment available in determined therapeutic classes with no co-payment. Evidence suggests that Slovak pharmaceutical expenditures do not result in the most cost effective outcomes. The use of HTA in the decision-making process is vague.

Key words: HTA, decision-making process, reimbursement, Slovak Republic

According to OECD Health Data (2010), spending on pharmaceuticals in Slovakia (US$ 489 per capita in PPP) is at the same level as the OECD (US$ 490) and much higher than in Hungary (US$ 454), the Czech Republic (US$ 363) or Poland (US$ 274). Combined with the lower economic performance of Slovakia (US$ 22 193 per capita in PPP) compared to the OECD average (US$ 33 271) this means that pharmaceutical expenditure in Slovakia is 2.2% of GDP compared to 1.5% GDP in the OECD, or 28% of total health care spending versus 16% in the OECD. The Slovak Ministry of Health is responsible for determining which pharmaceuticals are reimbursed and at what share of the retail price reimbursement will be made. In the decision-making, the Ministry is assisted by an advisory body called the Categorisation Committee. The recommendation of the Categorisation Committee can be overruled by the Minister of Health. Decisions regarding the reimbursement level are made once the maximum retail price has been established. A single application is filed for both pricing and reimbursement. Applicants must submit the basic drug information (name, manufacturer, authorisation holder, pharmaceutical form, pack size and strength), evidence on effectiveness, the standard therapeutic dose (STD) and the number of the standard therapeutic doses (STDs)/pack. Applicants also present the desired reimbursement rate, the proposed indication and any prescribing restrictions.

The Categorisation Committee considers several factors when selecting the reimbursement category, which defines the rate of reimbursement: the efficacy, the morbidity and mortality reduction, the indications and contraindications, the incidence of side effects, treatment doses for the given indication, the frequency of administration, the interaction profile, the level of patient acceptance and the relative improvement of the drug compared with current standard treatment options. For those products designated as eligible for partial reimbursement, the decision on reimbursement level is based on three main considerations: the therapeutic benefit of the drug, its retail end price, and the reimbursed prices of other products within its reference category. The reasoning underlying particular reimbursement decisions is disclosed.

The positive list can include drugs, which are reimbursed with restrictions, e.g. they can be prescribed by certain specialists only, or in narrower indications than specified by the summary of product characteristics (the description of the product's properties and conditions of use, such as pharmaceutical form and strength, authorised applications, adverse reactions, etc.) or, in the case of certain oncology products, only in certain hospitals as well.

Price changes for a particular drug may influence the reimbursement of other pharmaceuticals in the same 5-digit or 4-digit ATC group. Internal reference pricing provides the basis for determining the actual reimbursement amount paid for drugs that have equivalents on the Slovak market. Reference pricing is generally applied to drugs with the same active ingredient (5-digit ATC). The actual reim-

bursement amount cannot be higher than that of the cheapest drug in the same 5-digit ATC category. For some therapeutic groups, internal reference pricing is extended to pharmaceuticals with the same molecular structure (4-digit ATC): the actual reimbursement of products with different active ingredients is linked to the cheapest alternative in that 4-digit ATC category. The price per STD of the cheapest available drug in the ATC group is the selected reference for reimbursement. The co-payment for other drugs in the reference group with a higher price per STD is the difference between the actual retail price and the price of the reference product after adjustment for the STD per pack size.

The prices of pharmaceuticals covered by health insurance companies are regulated, both in the ambulatory and inpatient sectors. After obtaining an authorization to enter the market, the ex-factory price of the pharmaceutical is determined by the Ministry of Health through external reference pricing. The ex-factory price may not exceed the second lowest prices of the same pharmaceutical sold across the EU. If the price of a drug for the Slovak market exceeds this level it can be rejected from the reimbursement list.

The prices of OTC pharmaceuticals and prescription pharmaceuticals not covered by health insurance have been deregulated. Since 2008, there is degressive system in place, which sets margins separately for distributors and pharmacies based on the ex-factory price (Szalay et al. 2011). The Categorisation Committee consists of 11 members. Ten of the eleven have permanent positions and one is a temporay expert, rotating according to the topic of disscusion. Five of the committee members are representatives of health insurance funds, 3 members are representatives of the Slovak Ministry of Health and the rest are representatives of the Slovakian Medical associations. The Categorisation Committee is assisted by 3 different boards: the medical, the economic and pharmacoeconomic board. The medical board is one of 22 medical expert groups organized by therapeutic areas. The economic board deals with drug pricing.

The submission for reimbursement from the side of pharmaceutical companies has to include pharmacoeconomic analysis for all new molucules, new indications or galenic forms of drugs. The board for pharmacoeconomics analyses dossiers related to economic studies submitted for categorisation process of drugs. There is no doubt that economic evaluations of drugs should aid the decision-making process in terms of enhancing the information on which decisions are based, allows decision-makers to make informed choices based on evidence, and contributes to an efficient resource allocation. The first Slovak guideline for pharmacoeconomic analysis was revealed on the website of the Ministry of Health of the Slovak Republic on the 26th of September in 2008. These methodological guidelines, provide guidance to manufacturers, sponsors and healthcare providers preparing health economic evaluation to support submissions to secure reimbursement for goods and services provided from public funds under the control of the health insurance funds and the Slovak Ministry of Health. They aim to stimulate the provision of standardised, reliable and good quality information for the Categorisation Committee. The ultimate objective of the guidelines is to facilitate the cost-effective use of scarce healthcare resources. In line with recommendations from the Ministry of Health, the pharmaceutical is assessed using cost-minimization, cost–effectiveness, and cost–utility analysis. The general principle is that the analysis should adopt the perspective of the audience targeted by the authors of studies. For the reimbursement process from public funds it has to be the perspective of health insurance companies. In the case of studies with a time horizon longer than 1 year the principles of time preference and the opportunity costs of investments should be taken into account through discounting. In the base case both future health gains and costs should be discounted at 5%. When the more effective therapy has higher costs than the alternative intervention, the incremental cost-effectiveness ratio must be calculated. In these cases the Categorisation Committee considers whether the unit of additional health improvement is 'worth' its additional cost. The recommended threshold of a cost-effective new technology was set in the Slovak republic € 18 000 - € 26 500/ per a quality-adjusted life year (QALY). Pharmaceuticals with lower costs per QALY than € 18 000 are considered cost-effective. In contrast, pharmaceuticals that exceed € 26 500 per QALY are considered non-cost-effective. Interventions with cost-effectiveness ratios between the lower and upper limit are subject to further consideration. Our decision-making approaches suggest that no single threshold value should apply to all interventions but cost per QALY results should be judged together with overall budgetary

impact of a treatment in question. However, there is significant room for improvement because the use of relevant HTA in the decision-making process is inaccurate within the Slovak Republic.

Evidence suggests that Slovak pharmaceutical expenditures do not result in the most cost-effective outcomes. According to study of Kaló at al. (2008), several potentially not cost-effective pharmaceuticals have been reimbursed in Slovakia. It is especially true if we consider that strategic pricing of the innovative products are not based on small markets with low purchasing power (like Slovakia). The price level of new drugs is adjusted to wealthier countries with greater willingness to pay for a quality adjusted life year gain. It can be concluded that economic evaluations of drugs and medical devices are mandatory in the Slovak Republic but the quality of evaluations and critical appraisals are rather poor. In addition to the available Slovak health economic evaluation guidelines a detailed checklist for appraisal processes have to be prepared. Approved changes in the legislation within the Slovak republic from 2011 emphasize the role of HTA for the reimbursement policy.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 24-28
DOI: 10.7365/JHPOR.2012.1.6

System of medicinal maintenance in Russia

Roza Ismailovna Yagudina
Head of Department of Organization of Medicinal Provision and Pharmacoeconomics of First Moscow state Medical University named I.M. Sechenov, Moscow

Abstract

The Russian pharmaceutical market has been a continuously developing and growing structure that includes a range of participants in different levels of organization. Annual market research illustrates the increase of volumes of all of the market spheres either in economical or in natural values. Therefore the perspective of prescription drug insurance might become the new force of the market development and it is likely to redefine the whole system of medicinal maintenance in Russia. Some aspects of pharmaceutical market in Russia were presented in this article.

Keywords: medicinal maintenance, reimbursement programs, prescription drugs insurance, pharmaceutical market

Medicinal maintenance of the population is one of the primary problems in any system of public health services all over the world. The Russian Federation isn't an exception and by the current moment it possesses an advanced system of medicinal maintenance that includes several market spheres which are commercial and hospital markets and the market of preferential medicinal maintenance.

Registration

The first stage of the circulation of pharmaceuticals that directly concerns medicinal maintenance is registration of the medical product as it separates biologically active substances from pharmaceuticals themselves. Since 2010 responsibility for the State Marketing Authorization have been allocated to Department of State Marketing Authorization of Medical Products that is a department of Ministry of Healthcare of Russia. At present there is the State Register of Medical Products that contains all the pharmaceuticals registered in the country.

According to the data obtained on the 3rd of February 2012 there are 17 161 registered in Russia medical products process by inland and foreign manufacturers; about 90% of them are pharmaceutical, while 10% are pharmaceutical substances used for production of pharmaceuticals. Whereas in 2011 Register of Medical Products was contained over 18 900 items, and in 2010 – over 19 300, that showed gradual decrease of quantity of registered pharmaceuticals and annual accurate reconsideration of the list of the registered drugs.

Russian pharmaceutical market is a complex and advanced structure that can satisfy the requirements of population and government in medical products by means of its organization and multitude of participants. The pharmaceutical market itself consists of the four main subdivisions that are wholesale market, retail market, hospital market and preferential provision market. Manufacturing and distributing are the two main states of circulation of medical products in the system of medicinal maintenance and they are carried out by variety of market insiders.

Manufacturing

According to the data of 2011 in Russia there are over 1 500 functional pharmaceutical manufacturers presented by 460 inland producers and about 1 100 foreign producers.

Distribution

The primary market participants that take place in the process of drugs dispensing are pharmaceutical distributers, pharmacies and medical and preventive treatment facilities. Total quantity of pharmaceutical distributors was about 2 400 in 2011. Pharmacies in Russia are presented with several types that are pharmacies that has license for selling all kinds of medicines (OTC, Rx and narcotic drugs), pharmacies that are prohibited

to sell narcotic drugs but can sell OTC and Rx medicines and pharmacies that are allowed to sell only OTC medicines. Total quantity of licensed pharmacies in Russia in 2011 was about 64 855; about 44% them were able sell all types of drugs, 52% - only OTC and Rx drugs and less than 1% - only OTC drugs. In countryside and under-populated areas drugs dispensing effects by means of over 200 000 preventive treatment facilities as well those also include about 19 824 feldsher-midwife stations that have license for drug dispending. The structure and the main participants of Russian pharmaceutical market are presented in the figure 1.

Market volumes

According to the data of Market Research Center "Pharmexpert" total market volume in natural units (in packs of pharmaceuticals) shows annual increase in the last years; it is presented in the figure 2.

Dynamics of drug consumption in natural units shows stable annual market size. Distribution among the primary market spheres that are commercial (retail) and hospital markets and the market of preferential medicinal maintenance shows annual domination of commercial market segment. The size of retail market segment in 2010 have been about 4 395 000 000 packs (92% of the total market size), the size of the hospital market - 265 000 000 packs (6%) and preferential medicinal maintenance market - 91 800 000 packs (2%). Market volumes in financial units (Euro) also present annual market growth; it is presented on figure 3.

Distribution of market volumes among the primary market spheres in financial units has been showing high annual priority and growth of commercial (retail) market since 2005. The size of retail market segment in 2010 has been about € 10 258 314 440 (77% of the total market size), the size of the hospital market - € 942 807 500 (7%) and preferential medicinal maintenance market - € 2 068 391 900 (16%).

As can be seen from the above there is shown stable growth of Russian pharmaceutical market in natural and financial units since 2005 till nowadays.

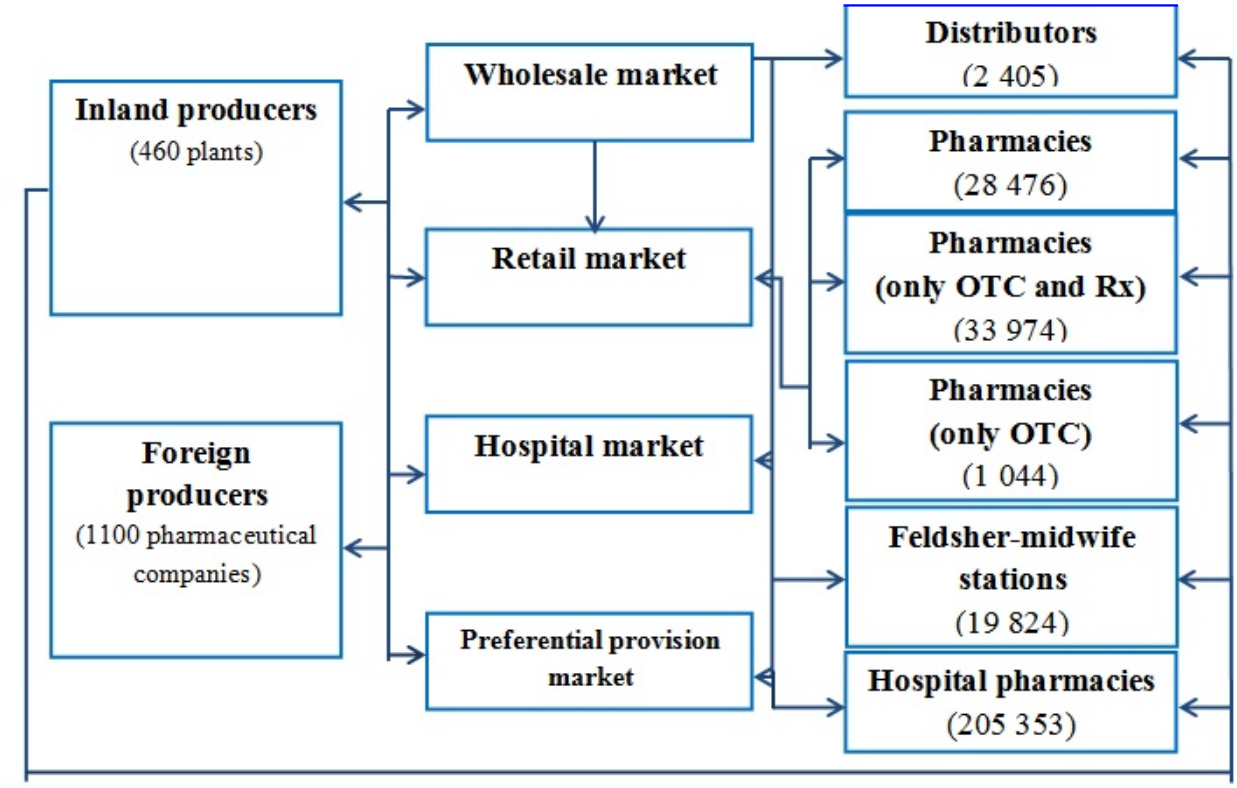

Figure 1. Structure of the Russian pharmaceutical market.

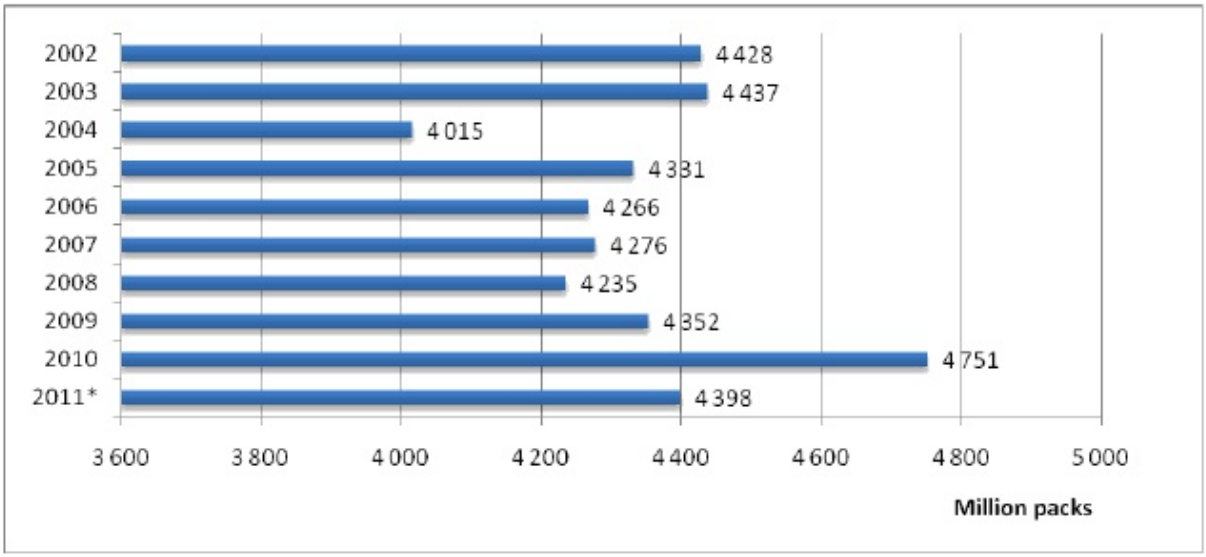

Figure 2. Market volume in natural units (in packs of pharmaceuticals).

**** Data does not include preferential medicinal maintenance market segment.***

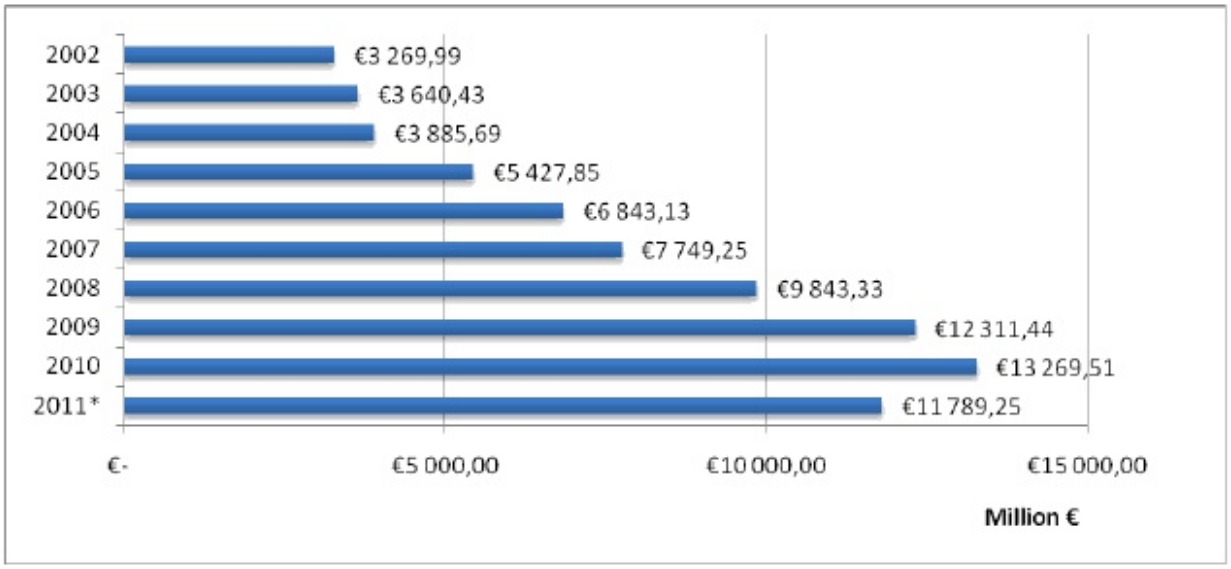

Figure 3. Market volume in financial units (in Euro).

*** Data does not include preferent ial medicinal maintenance market segment .**

Medical products consumption

Using the data of Market Research Center "Pharmexpert" there were composed tops of medical products that were the most frequently used in 2011 in Russia in natural and economical units. Medical products presented with international nonproprietary names (INN) were ranged according to the consumption volumes in different market segments. The most frequently used drug in natural units in retail market is Xylometazoline; in hospital market - sodium chloride; in preferential medicinal maintenance market – human genetically engineered insulin. Top-5 pharmaceuticals in natural units according to the market segment value are presented in table 1.

Medical products in financial units were either arranged according to the volume of the consumption. The most frequently used drug in financial units in retail market is combination of Polyvitamin and Multimineral: in hospital market - sodium chloride; in preferential medicinal maintenance market – human genetically engineered insulin. Top-5 pharmaceuticals in natural units according to the market segment value are presented in table 2.

Table 1. Top-5 pharmaceuticals in natural units in Russia (2011).

Commercial (retail) market	Hospital market	Preferential medicinal maintenance market
Xylometazoline	Sodium chloride	Human genetically engineered insulin
Pancreatine	Ceftriaxone	Blood-coagulation factor VIII
Polyvitamin+Multimineral	Heparin sodium	Insulin glargine
Nimesulide	Levofloxacin	Epoetin alfa
Methylphenylthiomethyl-dimethylaminomethyl-hydroxybromindol-ethyl carboxylat	Meropenem	Interferon beta-1b

Table 2. Top-5 pharmaceuticals in financial units in Russia (2011).

Commercial (retail) market	Hospital market	Preferential medicinal maintenance market
Polyvitamin+Multimineral	Sodium chloride	Imatinib
Methylphenylthiomethyl-dimethylaminomethyl-hydroxybromindol-ethyl carboxylat	Meropenem	Rituximab
Xylometazoline	Oxaliplatin	Blood-coagulation factor VIII
Phospholipids	Docetaxel	Bortezomib
Pancreatine	Ceftriaxone	Glatiramer acetate

System of preferential medicinal maintenance

Nowadays in Russia there exists a system of Government Reimbursement for the preferential patients that includes a number of federal and regional programs.

In the beginning of 2005 there have been started a program of Additional Pharmacological Support (APS) that had the reimbursement drug list in the base and gave an opportunity to improve quality and accessibility of preferential provision of medicines for vulnerable social group. There was developed List of Prescription Medicines in Additional Drug Supplement in the National Social Care during the time of the program realization; it was main characteristics were organization according to the INN, validation of maximum sale price.

Table 3. Market volumes of "7 diseases" sphere.

Disease	Natural units	Financial units
Myeloleukemia	2 195 334	€ 804 132 926,81
Hemophilia	262 462	€ 345 840 925,24
Multiple sclerosis	1 044 537	€ 185 187 052,03
Transplantations	375 166	€ 178 995 858,21
Gaucher disease	311 801	€ 37 797 795,76
Cystic fibrosis	14 952	€ 27 222 176,01
Pituitary dwarfism	115 656	€ 23 410 373,91

These characteristics help to decrease disproportion in preferential medicinal maintenance market. The main issues of APS are personalization of the given pharmacological support, normalization of financing of preferential patients and organization of data connection and data reporting in reimbursement pharmacological and medicinal support.

In 2008 program called "7 diseases" was separated from the APS program. It is a program of ambulatory medicine reimbursement of patients with the rare and high-cost diseases that are hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, multiple sclerosis, myeloleukemia and organs and (or) tissue transplantation. Therefore this new federal program become one of the priory reimbursement programs of drug supply that is responsible for government financing of preferential patients by the means of centralized purchases of medical products. Total market volume in preferential medicinal maintenance segment of "7 diseases" in 2011 on natural units was about 2 195 300 packs, and in financial units – about € 804 132 900. Distribution among the diseases is presented in table 3.

Perspectives of prescription drug insurance

The first idea of prescription drug insurance appeared in 2008 but there was no opportunity to develop it at that moment. According to the Minister of health and social development of the Russian Federation Tatyana Golikova now there is a perspective to develop the system of prescription drug insurance by 2015. This system is about vital and necessary medical products that are presented in the list of the Vital and Essential Medicines. Two approaches are considered: insurance - more difficult both more expensive; and compensation. At the first stage the main aim is to provide with medicines those for whom it's necessary and first of all to solve the regional problem. But in general it is a question of providing with medical care of all the patients in the out-patient sphere.

There is either a system called Population Drug Coverage that works by the means of regional purchases of medical products. The sources of financing nowadays are different level budgets (regional and municipal), budget of the Compulsory Health Insurance fund and personal means of population.

Conclusion

As can be seen from the above Russian pharmaceutical market is a continuously developing and growing structure that includes a multitude of participants in different levels of organization. Annual market researches illustrate increase of volumes of all of the market spheres either in economical or in natural values. Therewith the perspective of prescription drug insurance might become the new forcer of market development and is likely to redefine the whole system of medicinal maintenance in Russia.

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 29-38
DOI: 10.7365/JHPOR.2012.1.7

Decision-making processes related to drug pricing and reimbursement. Is Poland far away from global standards?

Robert Kranc
Polish Society of Pharmacoeconomics, ISPOR Polish Chapter, Section of Health Technology Assessment School of Medical Science in Białystok

Marcin Czech
Department of Pharmacoeconomics, Warsaw Medical University Polish Society of Pharmacoeconomics, ISPOR Polish Chapter, Board of Directors

Abstract

A substantial funding from healthcare budgets in the majority of countries is devoted to drugs. In order to make the best use of these scarce public resources, special agencies were established in order to assess efficacy, effectiveness, safety and cost-effectiveness of drugs. Based on their recommendations decisions regarding pricing and reimbursement are made coupled with guidelines for prescribers. Decisions of four agencies: Common Drug Review (CDR) from Canada, the National Institute for Health and Clinical Excellence (NICE) from the UK, Pharmaceutical Benefits Advisory Committee (PBAC) from Australia, Polish Agency of Health Technology Assessment (AOTM) were analysed and compared, main difficulties and controversies of decision making process were discussed. Two case studies were added for more detailed analysis.

Key words: medical decision making, health technology assessment, Polish Agency of Health Technology Assessment, HTA

Introduction

Drug expenditure consumes a substantial proportion of funds allocated to health care in numerous countries in Europe and elsewhere, and this pool seems to grow each year. This trend is observed, among others, in Canada [1, 2], the UK [3], Australia [4] and the US [5, 6], where federal expenditure on the Medicaid and Medicare Part D is expected to total $4,299 billion within the next four years. The situation is similar in Poland, where according to recent reports the pharmaceutical market will be worth almost PLN 31 billion in 2011 in retail prices [30].

In order to control drug spending and assess new medicines, special agencies assisting in reimbursement decisions have been established in a number of countries, particularly National Institute for Health and Clinical Excellence (NICE) in the UK [8-11], Pharmaceutical Benefits Advisory Committee (PBAC) in Australia [12-14] and Common Drug Review (CDR) in Canada [15, 16]. In Poland, this role is performed by the Agency for Health Technology Assessment (Agencja Oceny Technologii Medycznych – AOTM). It is an institution established by the Minister of Health to develop reports related to assessment of health care services. Its duties include formulating recommendations on the inclusion of health care services into the list of guaranteed benefits, delisting of benefits and change of the level or the manner of providing or financing of benefits.

In the first part of this paper the structure and rules of operation of these four agencies will be presented. Then, their recommendations for selected medicines will be analysed retrospectively to identify the values and decision points as well as additional factors accounted for by NICE, PBAC, CDR and AOTM in their decisions. The selection of agencies reflects the fact that the decisions of all of them are based on the evidence of clinical efficacy and cost effectiveness and that they all publish information about their decisions in English.

Commmon Drug Review

The health care system in Canada is a universal system based on financing from public funds, though access to some drugs varies across provinces and territories. Each province has its own drug

financing plan and its own specific guidelines on drug reimbursement. In 2002, the federal government, heads of provinces and the Ministry of Health, concerned with notable differences in reimbursement of drugs and, consequently, access to medicinal products, established the Common Drug Review (CDR) process [15]. Each manufacturer wishing to have a new drug added to reimbursement lists has to submit both clinical efficacy and cost effectiveness data for such a drug in the CDR process. CDR determines whether the given drug should or should not be reimbursed and defines the criteria for and the rate of reimbursement. Each CDR opinion, which contains a recommendation and presents the budget impact of funding, constitutes the basis for a decision whether the drug will be listed and reimbursed. In addition to the CDR process, manufacturers are required to submit their reimbursement dossiers to the Canadian Expert Drug Advisory Committee (CEDAC). It is an independent nationwide body which consists of eleven experts (physicians, pharmacists, health care research specialists and experts in health economics) and, since 2006, two public representatives unrelated to medical science. The Committee formulates its own recommendations on drug reimbursement and its rate. About 90% of reimbursement decisions in Canada are in agreement with these recommendations [2]. There is also the Patented Medicines Prices Review Board (PMPRB), a federal government agency which was established in 1987 by the Parliament to assure general access to medications through price- related regulations. PMPRB sets the maximum price which may be charged for a patented medicine, taking into account the price of the drug in the given market, the prices of other drugs from the same therapeutic class in the given market, the prices of the given drug and other drugs from the same therapeutic class in other countries as well as the Consumer Price Index (CPI) [17].

Once a drug is placed on the market, the manufacturer has to submit initial price data to PMPRB, which carries out a price review in line with the PMPRB Excessive Price Guidelines. The PMPRB's Human Drug Advisory Panel (HDAP) reviews the evidence of the clinical efficacy of the given medication and decides whether it is a breakthrough in medicine or a substantial improvement in treatment of a particular disease (a category 2 drug), a new active substance which brings a moderate or no advance (a category 3 drug) or a new molecule from a group of well-known medicines (a category 1 drug). PMPRB collects data and then determines the actual average sale price of each product. Prices of category 2 drugs are capped by the maximum price which is determined on the basis of the current prices within the same therapeutic class in Canada or on the basis of the mean price of the same drug in seven reference countries, namely UK, US, France, Germany, Switzerland, Sweden and Italy. The prices of category 3 drugs are generally capped at the maximum prices of comparable medicines in the same therapeutic class, if any; otherwise, they may be capped at international mean prices. Prices of any patented drugs cannot exceed the international maximum prices. If a price exceeds the one determined by PMPRB, the manufacturer has the right to submit additional evidence to support the higher price it charges. If the price remains unacceptable to PMPRB, the manufacturer may reduce it voluntarily or the case is referred to court. PMPRB monitors mean sale prices of drugs, updating the data every six months. Drug prices in Canada seem close to European mean prices and are much lower than those charged in the US [17].

The National Institute for Health and Clinical Excellence

In the UK, there is a public health care system as well as a free market in terms of drug prices. There is also a small private health care system parallel to the public one. Formally, the prices are determined by drug suppliers. The government administration, however, has some mechanisms to control its expenditure, e.g. through negotiations with manufacturers and distributors on their profit margin on drug sales. The ministry sets the profit ceiling and if it is exceeded the difference is paid back by pharmaceutical companies. Thus, the British system provides for upper (as well as lower) constraints for company's profits without differentiating prices depending on the therapeutic value of drugs. In theory each registered product is added to the reimbursement list, though in fact a lot of physicians refrain from prescribing it, while awaiting a recommendation by the National Institute for Health and Clinical Excellence (NICE).

NICE was set up in 2005 to formulate nationwide guidelines for health promotion and develop effective methods of prevention and treatment.

The Institute assesses the clinical efficacy and cost effectiveness of various therapies and formulates recommendations based on this appraisal. The recommendations are then used by the National Health Service and communicated to the medical community. NICE also aims to ensure that every citizen has equal access to high quality care and medical procedures. Currently, the organisation is the world's leader in setting norms and standards regarding high quality medical services as well as an important source of guidelines adopted worldwide [18]. NICE's recommendations provide the basis for negotiations under the Pharmaceutical Price Regulation Scheme (PPRS). NICE's decisions concern both the clinical efficacy / cost effectiveness and the budget impact of particular medicines or health technologies [19]. Medicines are available to virtually all people living in the UK who are covered by the National Health System (NHS), except for preparations which have not been appraised by NICE; for them, decisions are made on the local level and may differ from one region to another. NICE evaluates drugs according to specific clinical issues selected by the British government. Typically, the whole class of drugs is assessed during a single review in a multiple technology assessment procedure [10].

Pharmaceutical Benefits Advisory Committee

Australia also has a public health care system with a parallel small private care system. All Australian citizens have access to medicines under the Pharmaceutical Benefits Scheme (PBS). The manufacturer of a medicine submits an application for a recommendation to the Pharmaceutical Benefits Advisory Committee (PBAC). This is an independent body set up in 1953, which makes its recommendations and offers advice to the Ministry of Health on drug reimbursement. PBAC carries out assessment of the clinical efficacy and costs vs. alternative treatments and, since 1993, also the cost effectiveness analysis. PBAC submits its recommendations to the Ministry of Health and Ageing as to medicines, procedures or medical devices which should be subsidised by the Australian government. The Minister of Health refrains from listing particular drugs until positive recommendations are made by PBAC. PBAC receives advisory information from its sub-committees, namely on cost effectiveness from the Economic Sub-Committee and on utilisation and financial forecasts from the Drug Utilization Sub-Committee.

The Australian system is referred to in a number of studies as one of the best health care systems in the world, as it provides for universal and affordable access to high quality medical care, pharmaceuticals and hospital services. Its priority is to assist in maintaining people's healthy lifestyle through active lifestyle promotion and disease prevention. The responsibility for health care is split between the federal and state governments. 70% of health care costs are financed by the government (namely 47% by the federal government and 23% by state authorities), while 30% comes from sources such as insurance systems or private charges. As much as 8.5% of Australia's Gross Domestic Product is spent on health care. Health technology appraisal is carried out, inter alia, by the Adelaide Health Technology Assessment (AHTA), which is part of the University of Adelaide Discipline of Public Health. This team consists of sixteen members, including experts in clinical epidemiology, public health, psychology, pharmacy, medicine, health economics, biostatistics and bioethics. AHTA performs systematic reviews of medical technologies, interventions and procedures, then produces guidelines to provide a rational basis for health care decision-making. AHTA's tasks include medicinal product assessment, vaccine research, health care assessment and research and development of new guidelines related to these issues [20].

Agency for Health Technology Assessment

A medicine seeking reimbursement from public funds in Poland is subject to the appraisal by the Agency for Health Technology Assessment (AOTM). AOTM assesses the applications based on guidelines of January 2010, which are available at the Agency's website [www.aotm.gov.pl]. The Health Technology Assessment (HTA) Guidelines are a set of information guiding the work of AOTM's analysts, which has been developed for conducting transparent analyses summarising health, social, economic and ethical data for particular medical technologies. The Agency's activity is based on scientific evidence, which, for example, demonstrates whether a medicine is effective and safe for patients. This information is necessary in a process of making decisions which shape the health policy of the

state. Complete assessment includes clinical efficacy analysis, economic analysis and analysis of health care system impact. Medical technology assessments constitute the basis for recommendations made by the independent Consultation Council, which has been recently replaced by the Transparency Council, on financing of health services. Taking into account all recommendations by the Consultation Council, 64.5% of them were in agreement with inclusion or non-inclusion to lists of reimbursed drugs, the list of therapeutic health programs or the catalogue of active substances used in chemotherapy. This figure increases to 69.7% for the relation between Council's recommendations on financing of particular medications and the presence of their active substances on reimbursed drug lists [31].

Each opinion of the AOTM Consultation Council regarding financing or non-financing of pharmaceuticals or medical technologies is disclosed to the public. Recommendations are always supported by the rationale and the manner of their development is indicated. The relevant documents describe a health program, the current standard treatment and the analysis of the proposed treatment and its efficacy and safety. In addition, the costs of treatment and its budget impact are presented. Finally, the references used by AOTM's analysts are listed.

Data Sources and uncertain variables in reimbursement decisions

In our analysis we have used data for reimbursement decisions made by CDR, NICE and PBAC, which have been collected by Clement et al. [21]. The time frame was from July 2005 (for PBAC), February 2001 (for NICE) or January 2004 (for CDR) to December 2008. The information regarding ultimate decisions made by the agencies whether to issue a recommendation or not has been gathered. Three categories of outcomes have been considered, namely listing, listing with criteria and non-listing. In order to present the committees' decisions in the clinical context and in line with previous studies [12], it has been indicated whether recommendations concerned life saving/maintaining drugs (less than 50% mean five-year survival rate) or drugs aimed at life extension and/or quality-of-life improvement, or whether other options related to specific conditions were taken into account. In addition, we have collected data on primary end-points in the relevant studies, namely clinical end-points (e.g. death, MI), clinical scales used (e.g. American College of Rheumatology 20% improvement criteria (ACR20) in rheumatoid arthritis) [22] and surrogates (e.g. BP changes, changes in parathyroid hormone levels, etc.) [23, 24]. We have focused on the issues indicated as doubtful in the assessment by the committees; these has been defined as clinically and economically uncertain (no, little or considerable uncertainty). Considerable uncertainty occurred in cases when efficacy data had been based on non- randomised clinical trials, wrong comparators had been used in randomised trials or intermediate end-points (surrogates) had not been validated. Economic uncertainty occurred in cases when structural irregularities in the economic model applied had been found or the cost effectiveness assumptions had been completely different from the assessing body's point of view.

Furthermore, to illustrate similarities and differences between CDR, NICE, PBAC and AOTM in a qualitative manner, two medicines assessed by all four agencies have been chosen for case studies. We have analysed various key problems faced in evidence analysis as well as the influence on reimbursement decisions of the data evaluation process itself. The case studies concerned (i) ranibizumab, an injection solution used in age-related macular degeneration (AMD) to improve affected vision and/or prevent further vision loss, and (ii) teriparatide, a medicine used in osteoporosis treatment in post-menopausal women as well as men at a high risk for fracture. AOTM's decisions have been analysed separately. The analysis has covered recommendations made in 2009 and 2010.

Analysis of results

In the analysed period, CDR reviewed 121 applications (114 new submissions and 7 re-submissions), while PBAC reviewed 282 applications (207 new submissions and 75 re-submissions). NICE conducted assessments of 144 health technologies, out of which 47 have been excluded as not concerning drugs; hence, we have considered 97 applications, which covered 199 medicines (184 new drugs and 15 re-submissions). The characteristics of applications reviewed by the agencies are presented in the Table 1. Note a high number of applications re-submitted upon previous rejection which were received by PBAC: as much as 75 out of 282 applications, or 26.6%, were re-submissions (with narrower medical indications or reduced price).

Table 1. Basic characteristics of all submissions to CDR, NICE and PBAC (RCT – randomised clinical trial, CDR – Common Drug Review (Canada), NICE – National Institute for Heath and Clinical Excellence (UK), PBAC – Pharmaceutical Benefits Advisory Committee (Australia) after Clement FM et al. [21]

Characteristics	CDR n=121	NICEn=199	PBACn=282
Re-submission	7	15	75
Life-threatening disease (≤50% survival rate)	22	38	70
Purpose of Drug Treatment			
1. Quality-of-life improvement	56	90	116
2. Life extension	14	60	63
1. & 2.	51	49	103
Clinical Uncertainty			
No	14	39	38
Little	57	105	121
Considerable	50	54	123
Clinical Evidence Weight			
RCT with a right comparator	95	169	201
RCT with a wrong comparator	23	20	55
No randomised trials	3	10	26
Study End Points			
Clinically significant end points	56	90	116
Clinical scales	14	60	63
Surrogates	51	49	103
Invalid surrogates	51	49	103
Drugs for which it is necessary to determine QALY/Cost per QALY in order to make a decision	73	192	203
Cost-effectiveness Data			
Cost minimisation analysis	43	13	88
Cost-effectiveness analysis	17	15	55
Cost-utility analysis	55	171	138
Cost-consequence analysis	6	0	1
Economic Uncertainty			
No	4	16	20
Little	28	86	65
Considerable	41	90	118

Table 2. AOTM's decisions in 2009–2010. (Yes – financing; No – non-financing)

Year	Number of Decisions Communicated on AOTM's website	Yes	No	Listing with Criteria	Temporary Listing	Rationale for the Decision
2009	66	16	25	21	4	1. Part of health program 2. Provided that a price ceiling is set 3. Provided that it becomes a guaranteed benefit 4. Provided that cost-effective financing with a set price ceiling lower than the cheapest drug from the same group is introduced 5. Provided that a common therapeutic group is established with a price ceiling at the cheapest drug from the group 6. Upon a significant reduction in drug cost within a therapeutic health program 7. Temporarily, e.g. for a period of two years 8. In centres specialising in treatment of the disease and upon price reduction 9. Provided that the treatment cost close to the cost-effectiveness level recommended by WHO is achieved
2010	15	2	11	1	1	1. Temporarily, e.g. for a period of three years 2. Provided that a common price ceiling is set

As the table shows, a key element and a condition for AOTM's positive recommendation is the price, for which a ceiling should be set within the given group of drugs; the condition is a significant reduction in a price within the given therapeutic group (the price ceiling is set at the cheapest drug within the group). A medicine may obtain a temporary listing recommendation e.g. for a two-year period, after which a new opinion by AOTM is required. Medicines used to obtain positive recommendations if they were to be used in centres specialising in treatment of the disease and provided that the treatment cost close to the cost- effectiveness level recommended by the World Health Organization could be achieved.

Problems with clinical efficacy and cost data

Over 40% of all submissions reviewed by CDR and PBAC involved considerable clinical uncertainty, which was much frequent compared to NICE with uncertainty at 27.3% or 54/ 199 (p=0.009).

This is most likely attributed to the fact that NICE evaluates groups of drugs with a longer record in the market, which enables better assessment. Twenty six out of 121 submissions reviewed by CDR (or 21.7%) and 81 out of 282 submissions reviewed by PBAC (or 28.8%) were based on non-randomised clinical trials or randomised trials with a wrong comparator. Very frequently, surrogates were the primary end-points of clinical studies. The estimation of the cost-per-QALY (cost to quality adjusted life years) ratio is required in case of analyses conducted by NICE. The fact that this ratio needs to be determined to make a decision was reflected in economic uncertainty, which stood at 46.1% (90/192), 58.2% (118/ 203) and 55.7% (41/73) for submissions reviewed by NICE, PBAC and CDR, respectively. Note the fact that considerable economic uncertainty was often based on clinical uncertainty (57/245 or 23.4% of cases). This demonstrates the crucial importance of quality clinical evidence in drug-related decisions [21].

NICE made positive recommendations for 87.4% (174/199) of submissions as compared to 49.6% (60/121) listing recommendations issued by CDR and 54.3% (153/282) by PBAC. The listing rates were lower for CDR and PBAC in case of considerable clinical and economic uncertainty, but higher if proper clinical end points had been used. The list of decisions issued by NICE does not seem related to the existence or non-existence of economic uncertainty, which might indicate the identification of subgroups for which this uncertainty may be lower and the cost-utility ratio may be more acceptable. There is some evidence for the threshold range in decisions made by particular agencies, though some medicines obtained positive decisions despite exceeding it. Thirteen submissions (namely 4, 8 and 1 for CDR, NICE and PBAC, respectively) were rejected for the proposed patient populations as a result of economic assessment, yet recommended for more limited subpopulations in which the cost-per-QALY was higher (owing to higher efficacy of drugs and reduced costs in such subpopulations). For 66 submissions which involved considerable economic uncertainty (namely 7, 6 and 53 for CDR, NICE and PBAC, respectively), the listing rates were 28.6% (2/7), 66.6% (4/6) and 3.8% (2/ 53) for CDR, NICE and PBAC, respectively. In 91 cases, the same drug was assessed for the same indications by more than one of these agencies. Note a low consistency rate for recommendations formulated by CDR vs. PBAC (k=0.27) and NICE vs. PBAC (k=0.13) and a moderate consistency rate for recommendation decisions made by CDR vs. NICE (k=0.55), full consistency being at k=1. For 19 medicines assessed by all three agencies, the listing rates stood at 52.6% (10/19), 84.2% (16/19) and 73.6% (14/19) for CDR, NICE and PBAC, respectively. Furthermore, we have conducted qualitative analysis of the most frequent recommendation discrepancies between the agencies. NICE always looked for narrow niches of small patient populations in which drugs could be used and recommended them for such populations, while PBAC used price negotiations in order to ensure cost effectiveness and adopted a different approach to listing drugs in the given therapeutic class. CDR was reluctant to list subsequent, me-too drugs from the given group, whereas PBAC followed a cost minimisation policy by making use of price competitiveness of new drugs.

Ranibizumab

Each agency has recommended reimbursement of this medicine in age-related macular degeneration (AMD). Clinical data from randomised trials with a right comparator had demonstrated that ranibizumab reduced the risk of blindness incidents in AMD patients. Despite high cost, the drug clearly improved the quality of life (considering the effects of blindness). Each agency has set a reimbursement ceiling for the drug, shifting a portion of expenses onto the manufacturer. Initially, in February 2008, ranibizumab did not obtain a positive recommendation of AOTM on its financing in treatment of patients with exudative age-related macular degeneration. However, upon another application, the medicine obtained a listing recommendation in treatment of neovascular (oxidative) AMD, though the active substance was not included in the list of therapeutic health programs.

Teriparatide

Each agency has admitted that there was a significant reduction in the risk of vertebral and non-vertebral fractures vs. placebo. However, they all have agreed that biophosphates would have been a more proper comparator in randomised trials. CDR and PBAC have also pointed out to lack of clinical trials in patients with intolerance to biophosphates or patients continuing biophosphate treatment

despite recurrent fractures, who could get additional benefits from treatment with other medicines. Considering the clinical uncertainty, high costs and non-acceptable results of the cost-effectiveness analysis, CDR and PBAC have not included teriparatide into recommendation lists. NICE has been of opinion that the use of this medicine will be cost-effective in a small subpopulation of patients with severe osteoporosis in whom biophosphates have failed to bring improvement, and recommended teriparatide for this subpopulation.

In 2008, AOTM decided not to recommend financing of teriparatide; the active substance was not included into the list of therapeutic health programs or the catalogue of active substances used in chemotherapy.

Discussion

NICE, CDR and PBAC are institutions which consider both the efficacy/safety and cost-effectiveness of drugs in their listing decisions. While analysing their reimbursement decisions, we have noted some differences concerning various drugs and their subgroups. It is not surprising, considering the differences in the decision-making processes adopted by these agencies. Moreover, differences in decisions resulted less from interpretation of evidence for the clinical or economic effectiveness than from discrepancies in the evaluation process itself, which might reflect differences in the range of risk factors analysed, including search for drugs with quality evidence for clinical efficacy and cost-effectiveness or the importance of competitive drugs in the evaluation process.

The Australian system allows manufacturers to submit applications an unlimited number of times, while changing the price, indication and related evidence. If we consider only the latest attempts for drugs which have been previously rejected in the given indication, the listing rate for PBAC increases to 62%, which seems to suggest that re-submission actually influences the agency's decision-making process. This was also the case with teriparatide, as in the process of final acceptance both the more restrictive indications and lower price were considered. Modified re-submissions are also nothing unusual in Canada, even though more strict re-submission criteria have been adopted and no price negotiations are possible there. There is a growing role of risk-sharing in decision-making processes, especially in Australia, to minimise uncertainty related to both financing base and cost-effectiveness. According to some previous studies, the agencies accounted for varying quality of evidence provided by manufacturers wishing their drugs to be listed [14,25,26], particularly in terms of the quality of experimental studies provided to support the clinically significant effect. While all agencies noted problems with quality and validity of economic data, each of them attempted to solve them in a different manner. NICE used independent economic analyses, while CDR conducted its own sensitivity analysis. PBAC adopted an organised approach to presentation of clinical and economic evidence, focusing on the process of translating clinical data into cost-effectiveness evidence.

This analysis has certain limitations. The NICE and PBAC data are based exclusively on the information in the public domain. Despite the fact that extensive summaries are disclosed to the public, some issues may remain unnoticed, particularly those related to the manner of proceeding, while other aspects, e.g. related to risk-sharing instruments, are confidential. Another limitation is the fact that only a small number of drugs have been assessed by all three agencies, which makes comparisons between them less clear. This is partly reflected in the fact that, unlike other agencies, NICE can chooses which drugs or groups of drugs should be reviewed and in which situations, whereas, notably, CDR has not reviewed drugs used in chemotherapy since 2007. Finally, considering the variety of medicines and the ways of their financing, statistical analysis of the grounds for positive or negative decisions has not been possible. The results seem to indicate that there are some differences in using the information on clinical efficacy and cost-effectiveness in the decision-making process, but further research is required to identify their causes.

Although this study does not provide a direct answer to the question whether the existence of these three agencies improves the health care efficiency, some previous studies have demonstrated that the Australian system, which is based on a policy of price reductions (prices lower than in 38 comparable prices) without compromising on public health, provides for improved quality of activities in this area [27].

What conclusions can be drawn from the analysed material which could be useful for people making

reimbursement decisions in the health care sector, particularly in countries where health technology assessment has not become the golden standard in reimbursement procedures yet? Firstly, the existence of these four agencies confirms that it is possible to set up an institution responsible for comparing the efficacy and cost-effectiveness of pharmaceutical products seeking reimbursement. While cost-effectiveness analysis is not required for all drugs, cost data are critical in the cases where it is necessary to provide information on the quality to price ratio. Secondly, the existing differences between agencies in the decision-making processes demonstrate that these may be adapted to local health care conditions. In fact, the key element of sustained development of these agencies seems to be their ability to adapt to national decision-making processes [28,29]. As demonstrated by the case study of ranibizumab, cost-effectiveness analyses do not have to be a barrier for financing of even expensive drugs, if there is strong evidence for their efficacy at least in some patient subpopulations or there are other factors apart from simple cost-and-benefit statements [11]. Moreover, decision-makers do not necessarily have to make simple dichotomic reimbursement decisions, as a medicine may be reimbursed for a specific subpopulation in which it is considered cost-effective or may be included in a patient co-payment list. The most frequent reason for the Agency for Health Technology Assessment to recommend non-financing of medicines was excessive cost or lack of sufficient hard clinical evidence to support the drug efficacy. Other grounds for non-financing decisions included drug failure to bring new quality to treatment or excessive discrepancies in the reliability of scientific evidence. Another reason for negative decisions was high incidence of adverse reactions reported during clinical trials. The Council often recommended financing of such drugs exclusively within a new health program or in a newly established therapeutic group. According to its members, in case of subsequent me-too drugs, a cost-effective method of financing with a price ceiling lower or equal to the price of the cheapest drug from the same group should be proposed. Decisions were often issued for two or three years and upon expiration of this period another recommendation was made. The materials provided by applicants, including the Summary of Product Characteristics, for medicinal products seeking inclusion into the reimbursement scheme were analysed and experts in the relevant area were consulted. Very frequently, AOTM would modelled its activities on the Canadian or Australian system; in some specific cases, NICE's opinions on drugs were used. AOTM's commitment to follow in the footsteps of the most experienced HTA bodies seems the right option, which will provide for more efficient use of limited health care resources in Poland.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 39-48
DOI: 10.7365/JHPOR.2012.1.8

Współpraca kosmetologa z dietetykiem w zabiegach odchudzających jako innowacyjna strategia zapobiegania globalnej epidemii otyłości

Dorota Koligat
Katedra i Zakład Farmakoekonomiki i Farmacji Społecznej Uniwersytetu Medycznego im. K. Marcinkowskiego w Poznaniu

Monika Madajczyk
Katedra i Zakład Farmakoekonomiki i Farmacji Społecznej Uniwersytetu Medycznego im. K. Marcinkowskiego w Poznaniu

Elżbieta Nowakowska
Katedra i Zakład Farmakoekonomiki i Farmacji Społecznej Uniwersytetu Medycznego im. K. Marcinkowskiego w Poznaniu

Abstrakt

Wstęp: Powszechność występowania otyłości wzrosła do skali epidemii. Ze względu na fakt, że problem nadmiernej masy ciała ma wymiar nie tylko zdrowotny, ale i estetyczny, terapia otyłości powinna być prowadzona kompleksowo z uwzględnieniem kooperacji specjalistów odrębnych dziedzin typu kosmetologia i dietetyka. Celem badań było potwierdzenie zasadności stworzenia zintegrowanego systemu opieki nad ludźmi otyłymi, a także ocena współpracy kosmetologa z dietetykiem w zabiegach odchudzających.

Metoda: W badaniach wzięło udział 56 pacjentów oraz 62 specjalistów. 30 pacjentów poddawało się terapii nadmiernej masy ciała w gabinecie dietetycznym i/lub kosmetycznym, a 26 stanowiło grupę badaną. Głównym narzędziem badawczym były anonimowe kwestionariusze, odrębne dla grupy pacjentów i terapeutów.

Wnioski: Istnieje zasadność prowadzenia kompleksowej opieki nad populacją ludzi otyłych. Jednoczesne stosowanie dietoterapii i wyszczuplających zabiegów kosmetycznych zapewnia osiągnięcie lepszych rezultatów, niż terapie prowadzone osobno. Kosmetolodzy są bardziej świadomi potrzeby podejmowania współpracy z dietetykami w terapii nadmiernej masy ciała.

Słowa kluczowe: terapia otyłości, dietetyka, kosmetologia, otyłość, epidemiologia, terapia otyłości

Abstract

Introduction: The prevalence of obesity has increased to the epidemic scale. Due to the fact that the problem of excess body weight has a dimension not only health, but also aesthetic, obesity therapy should be carried out comprehensively taking into account the cooperation of specialists such distinct areas of cosmetology and dietetics. The aim of this study was to confirm the validity of an integrated system of care for obese people, and an assessment of cooperation between a specialists such as dietician and cosmetologist in therapy of obesity.

Method: The study involved 56 patients and 62 professionals. 30 patients included into therapy of obesity in the center of dietary and / or cosmetic, and 26 included into the study group. The main research tool was an anonymous questionnaire, a separate for the group of patients and therapists.

Conclusions: There are merits of comprehensive care for a population of obese people. Concomitant use of diet therapy provides better results than the treatments carried out separately. Cosmetologists are more aware of the need to cooperate with nutritionists in the treatment of obesity.

Key words: obesity therapy, dietetics, cosmetology, obesity, epidemiology, treatment of obesity

Wstęp

Powszechność występowania otyłości czyni z niej jeden z najpoważniejszych problemów krajów rozwiniętych. Mówi się nawet o globalnej epidemii. Według najnowszych danych ponad połowa dorosłej populacji w Polsce cechuje się nadmierną masą ciała, natomiast otyłość dotyczy, co piątej osoby [1]. Problem ten coraz częściej dotyczy również dzieci. Przewiduje się, iż w przyszłości epidemia otyłości będzie nadal się rozszerzać, dlatego też istotne jest podjęcie działań zmierzających prewencyjnych zapobiegających rozprzestrzenieniu się globalnej epidemii [1, 2].

Otyłość to przewlekła choroba, która charakteryzuje się nieprawidłową masą ciała, przekraczającą przyjętą normę. Wiąże się z nadmiernym gromadzeniem się tkanki tłuszczowej w wyniku powiększania objętości adipocytów, tak zwana hipertrofia, i/lub tworzenia nowych komórek tego typu, co określa się terminem hiperplazji. O otyłości mówi się, gdy wartość BMI wynosi 30 kg/m2 lub więcej. Terminem pokrewnym jest nadwaga, którą rozpoznaje się przy BMI od 25 – 29,9 kg/m2 [3, 4, 5, 6].

Otyłość jest chorobą zaliczaną do chorób o złożonej patogenezie. Wśród czynników mających wpływ na jej powstanie wymienia się czynniki genetyczne, środowiskowe, zażywanie określonych leków, a także niektóre choroby. Dotychczas nie ustalono dokładnie, jak silne znaczenie w etiologii otyłości mają poszczególne czynniki. Szacuje się, iż genotyp w 25 - 40%, a według niektórych źródeł nawet w 70%, odpowiada za problemy z nadmierną masą ciała i gromadzeniem się tkanki tłuszczowej, gdyż to właśnie on wpływa na regulację apetytu, proces termogenezy, wrażliwość tkanek na insulinę oraz na podstawową przemianę materii [4,8].

Wraz ze wzrostem uprzemysłowienia wzrasta również liczba osób otyłych, co wiąże się przede wszystkim ze zmianą trybu życia na siedzący oraz spożywaniem taniej i powszechnie dostępnej żywności typu fast food, a także wysoko przetworzonych produktów spożywczych określanych terminem junk food [9].

Nadmierna masa ciała jest dobrze udokumentowanym czynnikiem ryzyka wielu chorób. Uważa się, iż w najbliższym czasie choroby będące konsekwencją otyłości staną się dominującymi przyczynami zgonów w krajach wysokorozwiniętych. Do chorób i zaburzeń zdrowotnych związanych z nadmierną masą ciała należą między innymi: nadciśnienie tętnicze, niedokrwienna choroba serca, cukrzyca typu 2, dyslipidemie, zaburzenia hormonalne, choroby narządu ruchu, nowotwory, zespół bezdechu sennego [1]. Zapobieganie otyłości, przez wzgląd na jej konsekwencje, jest niezwykle istotne. Prewencja obejmuje przede wszystkim przestrzeganie zasad racjonalnego żywienia oraz utrzymywanie aktywności fizycznej na odpowiednim poziomie. Ogromne znaczenie dla przeciwdziałania otyłości ma edukacja żywieniowa oraz zmiana nawyków żywieniowych na prawidłowe [3].

Leczenie nadwagi i otyłości powinno być zindywidualizowane i dostosowane do każdego pacjenta. Wybierając terapię, głównie bierze się pod uwagę wiek, płeć, stopień otyłości oraz współistniejące choroby osoby leczonej. Udowodniono, iż najwłaściwszym schematem leczenia jest utrata zbędnych kilogramów w tempie 2 – 4 kg/miesiąc, aż do osiągnięcia spadku masy ciała o ok. 10%. Wówczas konieczna staje się kilkumiesięczna stabilizacja osiągniętego efektu. Dopiero wtedy możliwa jest dalsza bezpieczna dla zdrowia i trwała redukcja masy ciała. Terapia otyłości może obejmować nie tylko leczenie dietetyczne i związane z aktywnością fizyczną, ale również farmakologiczne oraz chirurgiczne, zwanym bariatrycznym [3, 9].

Nadwaga i otyłość, a także nieprawidłowo prowadzone leczenie nadmiernej masy ciała mogą być przyczyną powstawania różnego rodzaju defektów skóry, takich jak cellulit, czy rozstępy. Znaczne wahania masy ciała mogą również doprowadzić do utraty elastyczności skóry, która staje się wiotka i nieestetyczna. Aby zapobiec tym defektom i prawidłowo ukształtować sylwetkę, oprócz dietoterapii i zwiększenia aktywności fizycznej, stosuje się kosmetyczne zabiegi wyszczuplające, które nie tylko wpływają na kondycję skóry, ale również poprawiają krążenie krwi i chłonki, redukują obrzęki i zastoje, przyspieszają spalanie podskórnej tkanki tłuszczowej, a także wyrównują jej rozmieszczenie.

Materiał i metoda

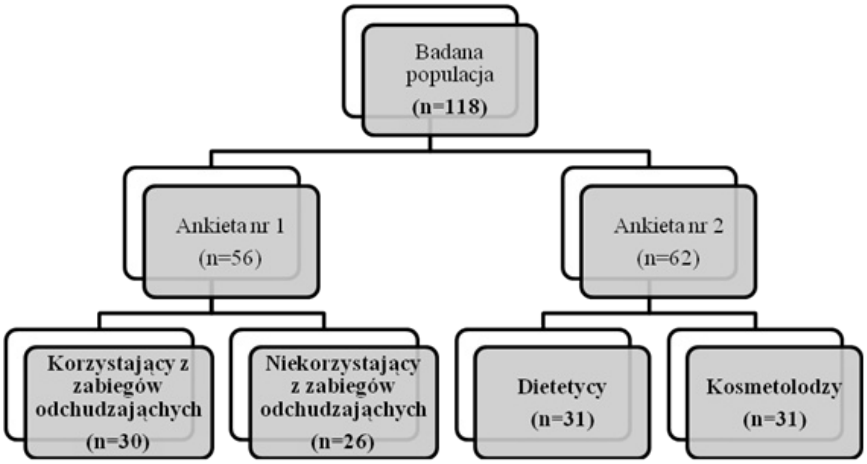
W badaniach wzięło udział 118 osób obu płci, w tym 56 pacjentów (39 kobiet i 17 mężczyzn) w wieku od 18 do 65 lat.

Uwzględniono szczegółowy podział grupy na 30 osób, poddanych terapii nadmiernej masy ciała w gabinecie dietetycznym i/lub kosmetycznym oraz 26 osób niekorzystających z usług specjalisty w terapii nadmiernej masy ciała.

Ponadto do badania włączono grupę specjalistów prowadzących terapię otyłości, w tym 31 dietetyków i 31 kosmetologów (60 kobiet i 2 mężczyzn) w wieku od 24 do 53 lat. Badaną populację podzielono na 4 podgrupy (Rycina 1.).

Głównym narzędziem badawczym wykorzystanym podczas badań były anonimowe kwestionariusze, które sporządzono w dwóch wersjach: dla świadczeniodawców oraz pacjentów.

Kwestionariusz skierowany do pacjentów składał



Rycina 1. Struktura badanej populacji

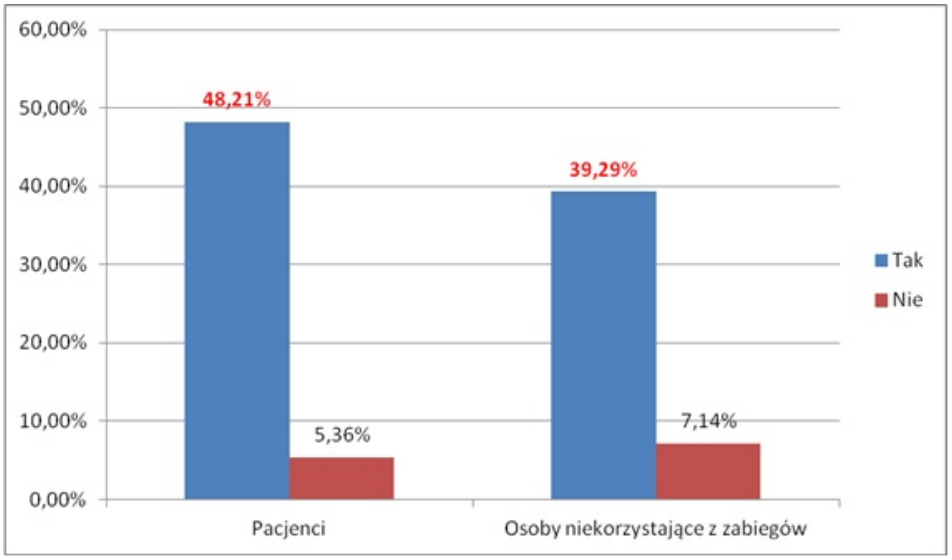
się z 20 pytań poruszających aspekty zdrowotne, aktywność fizyczną, stosowanie diety odchudzającej i wyszczuplających zabiegów kosmetycznych, a także kwestie związane z opinią pacjenta na temat współpracy dietetyków z kosmetologami w terapii nadmiernej masy ciała. Ponadto ankieta zawierała pytania dotyczące danych socjodemograficznych takich, jak wiek, płeć, masa ciała, wzrost, miejsce zamieszkania oraz wykształcenie.

Kwestionariusz skierowany do świadczeniodawców zawierał 14 pytań. Poza metryczką odnoszącą się do wieku i płci, kwestionariusz ten poruszał kwestie dotyczące czasu, miejsca i rodzaju wykonywanego zawodu oraz opinii na temat współpracy z drugim ze specjalistów w leczeniu nadmiernej masy ciała.

Wyniki

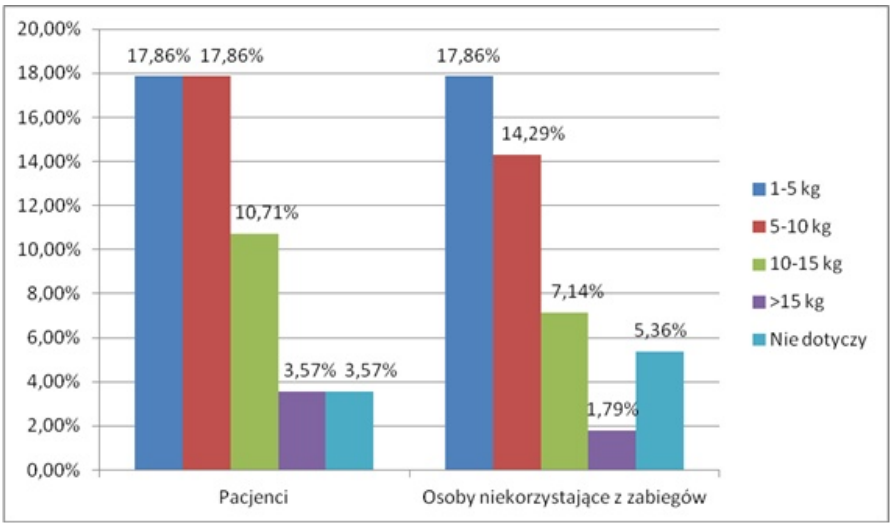
Większość pacjentów oraz osób, które nie korzystały z zabiegów odchudzających deklarowała chęć zredukowania masy ciała, co odpowiadało 48,21% i 39,29% badanej populacji. Uzyskane wyniki są istotne statystycznie (Rycina 2.).

Respondenci mieli za zadanie określenie ilości masy ciała, jaką chcieliby zredukować (Rycina 3.). Najczęstszą odpowiedzią udzielaną przez ankietowanych były 1 do 5 kg oraz od 5 do 10 kg masy ciała (odpowiednio po 17,86% populacji dla pacjentów oraz 17,86% i 14,29% populacji dla pozostałych badanych). Różnice w częstotliwości udzielanych odpo-



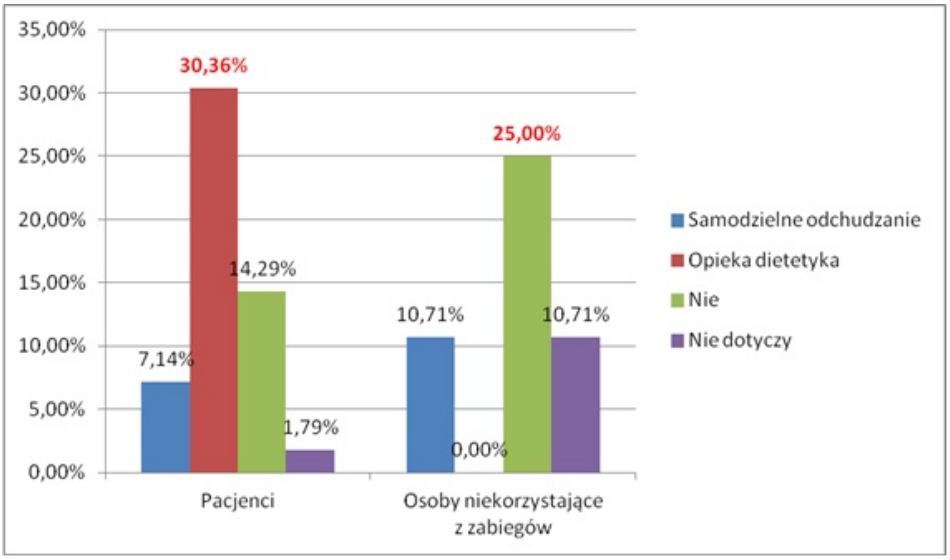
Źródło: Opracowanie własne

Rycina 2. Ocena częstości deklarowania chęci zredukowania masy ciała przez badaną populację



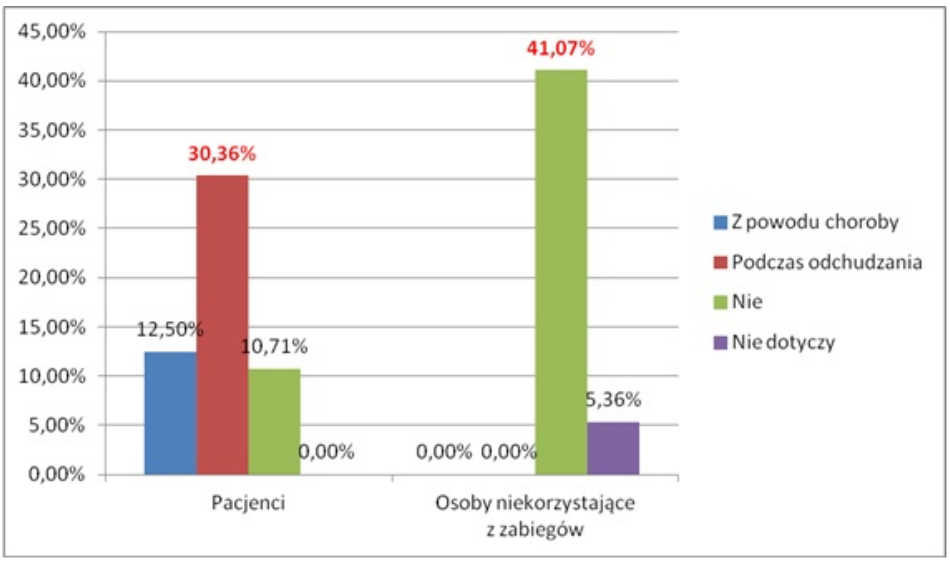
Źródło: opracowanie własne

Rycina 3. Rozkład zbędnej ilości kilogramów



Źródło: Opracowanie własne

Rycina 4. Ocena częstotliwości stosowania diet odchudzających przez badaną populację



Źródło: Opracowanie własne

Rycina 5. Analiza częstotliwości i przyczyn korzystania z usług dietetyka przez badaną populację

wiedzi nie były istotne statystycznie.

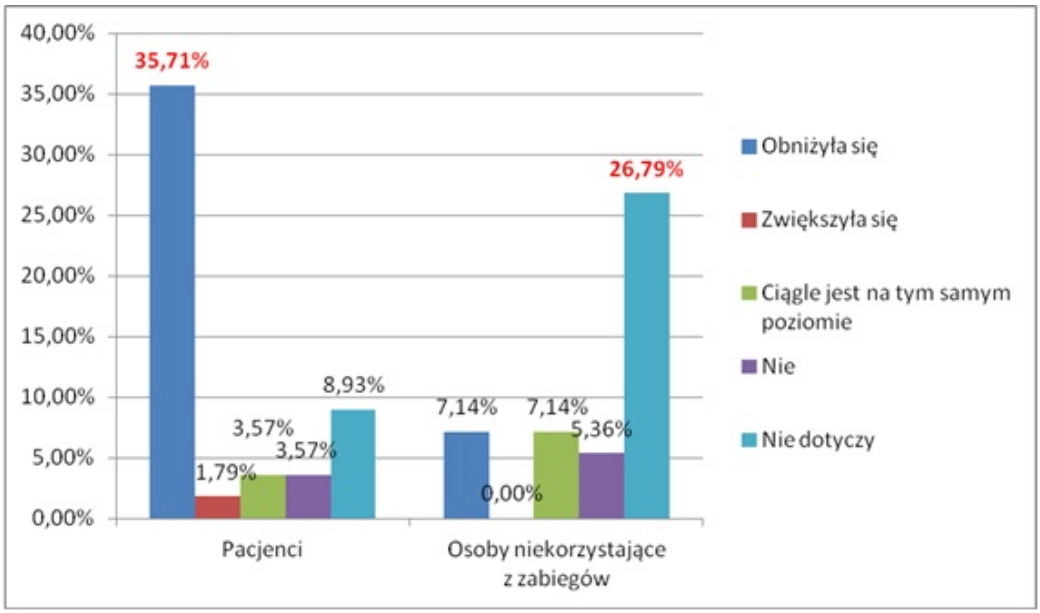
30,36% pacjentów spośród populacji badanej deklarowało, iż w celu redukcji nadmiernej masy ciała korzystało z usług dietetyka. Osoby, które nie miały kontaktu z usługami świadczonymi przez terapeutów w celu redukcji tkanki tłuszczowej, istotnie najczęściej udzielali odpowiedzi, iż obecnie nie stosują żadnej dietoterapii odchudzającej (25,00% populacji) (Rycina 4.).

Na pytanie dotyczące celowości korzystania z usług dietetyka, większość pacjentów (30,36% badanej populacji) odpowiedziała, iż usługi te służyły redukcji nadmiernej masy ciała powyższych. Uzyskane wyniki były istotne statystycznie (Rycina 5.).

Przy pomocy ankiety uzyskano informacje dotyczące zmiany masy ciała badanej populacji, w trakcie stosowania diety odchudzającej. Grupa pacjentów statystycznie istotnie często (35,71% populacji) odpowiadała, iż w wyniku stosowania diety ich masa ciała uległa znaczącej redukcji. W drugiej podgrupie (grupa kontrolna) utratę kilogramów deklarowało 5 - cio krotnie mniej osób, niż w przypadku pacjentów (7,14% populacji). Wynik ten, który nie był istotny statystycznie, może wskazywać na wysoką skuteczność i zasadność prowadzenia profesjonalnych terapii odchudzających (Rycina 6.).

Pacjenci zapytani o ilość kilogramów, jaką utracili postępując zgodnie z zasadami dietoterapii, najczęściej zaznaczali wartości znajdujące się w przedziale 1-5 kg (17,86% populacji), następnie 5 - 10 kg (16,07% populacji) lub, że to pytanie ich nie dotyczy (16,07% populacji). Z istotną częstotliwością pozostała część populacji (35,71%populacji) odpowiadała, iż pytanie o redukcję masy ciała ich nie dotyczy, natomiast inne osoby, które nie korzystały z usług dietetyka i kosmetologa w celach odchudzających, najczęściej deklarowały niską utratę masy ciała.

Ze statystycznie istotną częstotliwością (23,21% populacji) pacjenci deklarowali, iż stosowali wyszczuplające zabiegi kosmetyczne, natomiast osoby, które nie korzystały z usług terapeutów w celu zredukowania masy ciała, z jednakową statystycznie istotną częstotliwością wybierali dwie pozostałe odpowiedzi - 21,43% populacji chciałoby rozpocząć korzystanie z usług kosmetologa, a 25,00% badanych nie odczuwa takiej



Źródło: Opracowanie własne

Rycina 6. Analiza zmiany masy ciała wśród badanej populacji w związku ze stosowaniem diety odchudzającej

Tabela 1. Częstotliwość poddawania się zabiegom kosmetycznym - badana populacja

	Tak	Chciał(a)bym zacząć	Nie
Pacjenci	13	11	6
% ogółu	23,21%	19,64%	10,71%
Osoby niekorzystające z zabiegów	0	12	14
% ogółu	0,00%	21,43%	25,00%
Ogół	13	23	20
% ogółu	23,21%	41,07%	35,71%

potrzeby - (Tabela 1.).

Pacjenci deklarowali, że najczęściej korzystali z masażu fizykalnego (23,21% populacji), bądź wcale nie mieli wykonywanych wyszczuplających zabiegów kosmetycznych (21,43% populacji). Osoby, które nie korzystały z usług terapeutów, oprócz wybierania odpowiedzi, że pytanie ich nie dotyczy (37,50% populacji), zaznaczali zabiegi, z których chcieliby skorzystać (Tabela 2.).

Ponadto deklarowano, że korzystali z zabiegów wyszczuplających w celu szybszej redukcji masy ciała (19,64% populacji). Osoby, które do tej pory nie korzystały z usług terapeutów, tak jak w przypadku poprzedniego pytania, odpowiadali w jakim celu chcieliby skorzystać z zabiegów kosmetologicznych. Najczęściej wybieranym przez tych badanych argumentem przemawiającym na korzyść usług świadczonych przez kosmetologów była szybsza redukcja masy ciała (16,07% populacji) oraz wyszczuplenie konkretnych partii ciała (14,55% populacji), ale częstotliwość wybierania tych odpowiedzi nie była istotna. Analizując kolejne pytanie dotyczące przyczyn korzystania z zabie-

Tabela 2. Ocena preferencji i deklaracja wobec zabiegów kosmetycznych

	Ender-mologia	Mezo-terapia igłowa	Mezote-rapia bezigłowa	Masaż	Elektro-stymu-lacja	Body Wrap	Rolletic	Nie dotyczy
Pacjenci	4	0	0	13	4	4	4	12
% ogółu	7,14%	0,00%	0,00%	23,21%	7,14%	7,14%	7,14%	21,43%
Osoby niekorzystające z zabiegów	0	0	0	5	0	1	0	21
% ogółu	0,00%	0,00%	0,00%	8,93%	0,00%	1,79%	0,00%	37,50%
Ogół	4	0	0	18	4	5	4	33
% ogółu	7,14%	0,00%	0,00%	32,14%	7,14%	8,93%	7,14%	58,93%

gów wyszczuplających, obserwuje się tendencję do kierowania się troską o własne zdrowie (25,00% populacji) oraz estetykę zewnętrzną (21,43% populacji). Osoby, które z tych usług nie korzystały, zadeklarowały, iż chciałyby rozpocząć terapię nadmiernej masy ciała również w celu poprawy swojego wyglądu (19,64% populacji).

Na pytanie dotyczące skuteczności dietoterapii oraz zabiegów kosmetycznych stosowanych w celu redukcji nadmiernej masy ciała obie badane grupy najczęściej odpowiadały, iż najkorzystniejsze efekty przynosi jednoczesne korzystanie z usług obu rodzajów terapeutów (39,29% populacji w przypadku pacjentów oraz 19,64% populacji dla osób niekorzystającychających z zabiegów odchudzających). Żaden z respondentów nie uznał zabiegów kosmetycznych jako najskuteczniejszych w terapii otyłości, a jedna osoba (1,79% populacji) z drugiej podgrupy (grupa kontrolna) uznała, iż żadna z usług nie przynosi satysfakcjonujących rezultatów. Większość pacjentów deklarowała, iż nie uprawia żadnego sportu i nie wykonuje ćwiczeń fizycznych, ale mimo tego jest aktywna w ciągu dnia (23,21% populacji). Codzienne ćwiczenie wykonywało 3 przedstawicieli badanej populacji, w tym 1 pacjent oraz 2 osoby niekorzystające z zabiegów odchudzających (Tabela 3.).

Podczas realizacji badań grupa dietetyków i kosmetologów odpowiadała na pytania ankietowe, które dotyczyły głównie ich poglądów na temat współpracy oraz roli usług przez nich świadczonych w terapii nadmiernej masy ciała. W trakcie analizowania zebranego materiału badawczego obserwuje się trend świadczący o tym, iż na ogół dietetycy nie rozmawiają ze swoim pacjentami na temat uzupełnienia dietoterapii zabiegami kosmetycznymi (25,81% populacji). W przypadku kosmetologów, największa liczba deklarowała, iż osoby korzystające z ich usług są zainteresowane równoczesnym zaangażowaniem dietetyka i kosmetologa w prowadzeniu terapii odchudzającej (24,19% populacji) a także prezentują preferencje skierowane w stronę podlegania monoterapii (19,35% populacji). Pozostałe z udzielonych odpowiedzi nie były udzielone w ilościach istotnych statystycznie.

Badania przeprowadzone na potrzeby niniejszej pracy miały za zadanie ocenić powszechność oraz częstotliwość równoczesnego korzystania przez pacjentów z usług kosmetologa i dietetyka. Wyniki przeprowadzonych badań wskazują, iż równoległe poddawanie się zabiegom kosmetycznym i dietetycznym nie jest rzadkim zdarzeniem, bowiem znaczna część dietetyków (22,58% populacji) deklarowała, że pacjenci informują o tym, iż znajdują się również pod opieką kosmetologa. Jednocześnie istotnie duża grupa dietetyków (19,35% populacji) udzieliło odpowiedzi przeczącej. Statystycznie istotna większość biorących udział w badaniach kosmetologów (22,58% populacji) twierdziła, że ich klienci informują ich stosowaniu dietoterapii (Tabela 4.).

Tabela 3. Ocena aktywności fizycznej badanej populacji

	Codziennie	3 razy w tygodniu	Duża aktywność w ciągu dnia	Niska aktywność
Pacjenci	1	6	13	10
% ogółu	1,79%	10,71%	23,21%	17,86%
Osoby niekorzystające z zabiegów	2	7	8	9
% ogółu	3,57%	12,50%	14,29%	16,07%
Ogół	3	13	21	19
% ogółu	5,36%	23,21%	37,50%	33,93%

Tabela 4. Powszechności równoległego korzystania z usług kosmetologa i dietetyka - opinia świadczeniodawców

	Tak	Nie	Nie mam zdania
Dietetycy	14	12	5
% ogółu	22,58%	19,35%	8,06%
Kosmetolodzy	22	3	6
% ogółu	35,48%	4,84%	9,68%
Ogół	36	15	11
% ogółu	58,06%	24,19%	17,74%

Statystycznie istotna ilość dietetyków i kosmetologów (odpowiednio 33,87% i 50,00% populacji) biorących udział w analizie uważało, iż współpraca obu specjalistów wywiera korzystny wpływ na proces odchudzania. Na podstawie przeprowadzonych badań wnioskuje się, iż korzyści wynikające ze współpracy kosmetologa z dietetykiem znane są głównie kosmetologom, bowiem w większości to oni deklarowali chęć podjęcia współpracy w zakresie prowadzenia terapii wyszczuplających (Tabela 5.).

Dokonano także ewaluacji opinii świadczeniodawców na temat wyszczuplających zabiegów kosmetycznych. Obie grupy specjalistów w statystycznie istotnym stopniu uznały, iż zabiegi te powinny być nieodłącznym elementem terapii odchudzających (20,97% populacji dla dietetyków i 43,55% dla kosmetologów), mają wpływ na kondycję skóry (odpowiednio 40,32% i 29,03% populacji) oraz przyspieszają redukcję tkanki tłuszczowej i masy ciała (odpowiednio 30,65% i 37,01% populacji).

Prowadzone badanie poruszało także kwestię dotyczącą wizji prowadzonej działalności. Badani kosmetolodzy i dietetycy mieli za zadanie wyrazić opinię na temat możliwości podjęcia współpracy w prowadzeniu terapii wyszczuplających. Znaczna część terapeutów deklarowała chęć rozpoczęcia współpracy z drugim ze specjalistów (22,58% dla dietetyków i 32,26% dla kosmetologów). Większe zainteresowanie wspólnym prowadzeniem terapii nadmiernej masy ciała wykazywała grupa kosmeto-

Tabela 4. Powszechności równoległego korzystania z usług kosmetologa i dietetyka - opinia świadczeniodawców

	Tak	Nie	Nie mam zdania
Dietetycy	14	12	5
% ogółu	22,58%	19,35%	8,06%
Kosmetolodzy	22	3	6
% ogółu	35,48%	4,84%	9,68%
Ogół	36	15	11
% ogółu	58,06%	24,19%	17,74%

Tabela 6. Ocena wiedzy na temat usług świadczonych przez drugiego ze specjalistów

	Duża	Średnia	Mała	Nie mam zdania
Dietetycy	5	15	9	2
% ogółu	8,06%	24,19%	14,52%	3,23%
Kosmetolodzy	6	21	1	3
% ogółu	9,68%	33,87%	1,61%	4,84%
Ogół	11	36	10	5
% ogółu	17,74%	58,06%	16,13%	8.06%

logów (Tabela 6.).

Statystycznie istotna większość dietetyków i kosmetologów krytycznie odniosła się do własnego stanu wiedzy na temat usług świadczonych przez drugiego ze specjalisty określając jej poziom, jako średni (odpowiednio 24,29% i 33,87% populacji). Pozostałe wyniki nie były istotne statystycznie (Tabela 6.).

Dyskusja

Nadmierna masa ciała stała się poważnym problemem współczesnego świata. Według najnowszych danych przytoczonych w publikacji Jarosz i in. (2010) ponad połowa dorosłej populacji w Polsce ma nadmierną masę ciała, a otyłość dotyczy, co piątej osoby [1]. Badania przeprowadzone na potrzeby niniejszej pracy potwierdziły powyższe stwierdzenie, bowiem 56,70% cechowało się nadmierną masą ciała, w tym u 30,00% nadwagą, a u 26,7% otyłością. Podobnie sytuacja kształtowała się w grupie kontrolnej, którą stanowiły osoby niekorzystające z usług kosmetologa i dietetyka: 57,69% posiadało nadwagę, w tym 34,62% nadwagę, a 23,08% otyłość. W zestawieniu z danymi uzyskanymi podczas badań przeprowadzonych w USA, wartości te prezentują się bardziej korzystnie. Według U. S. Department of Health and Human Services, National Institutes of Health i National Institute of Diabetes and Digestive and Kidney Diseases (2010) około 68,0% dorosłych obywateli USA ma nadmierną masę ciała, w tym 34,2% nadwagę, a 33,8% jest otyła [10]. Dodatkowo jedno z badań dowiodło, że im jest większa różnica pomiędzy rzeczywistym stanem fizycznym, a subiektywną percepcją pacjenta, tym większe jest niezadowolenie z własnego ciała [11].

Według Pietrzykowskiej i wsp. (2008) około 1 do 2% osób o prawidłowej masie ciała i 6 do 12% osób z nadwagą ma negatywne wyobrażenie własnego ciała [11]. Wśród badanej populacji wyniki te nie zostały potwierdzone. Niezadowolenie z własnego ciała (chęć zredukowania własnej masy ciała) deklarowało 48,21% pacjentów oraz 39,29% osób niekorzystających z zabiegów odchudzających. Wysoki odsetek populacji niezadowolonej z własnego ciała i w związku z tym z obniżoną jakością życia podkreśla znaczenie problemu jakim jest otyłość.

Liczne wyniki badań dowodzą, iż osoby podlegające terapii otyłości lub krótko po jej zakończeniu odznaczają się wyższym wydatkiem energetycznym ze względu na uprawianie ćwiczeń fizycznych. Tymczasem pomiędzy grupą pacjentów i osób, które nie korzystały z usług terapeutów nie zauważono znaczących różnic, za wyjątkiem grupy nie uprawiającej sportu, ale wykazujących dużą aktywność w ciągu dnia.

30,36% respondentów biorących udział w badaniu realizowanym na potrzeby niniejszej pracy deklarowało, iż stosowało dietoterapię otyłości. 23,21% badanych korzystało z wyszczuplających zabiegów kosmetycznych, a 41,07% wykazało chęć skorzystania z nich. Wśród ankietowanych największą popularnością cieszyły się masaże odchudzające (23,21%), a pozostałe zabiegi kosmetyczne były

świadczone 28,56% badanych. Osoby biorące udział w badaniu (30,36%) stosowały również domowe kosmetyki wyszczuplające. Wyniki dotyczące stosowania dietoterapii, korzystania z zabiegów kosmetycznych oraz uprawiania sportu, uzyskane w badaniu ankietowym przewyższyła wartości uzyskane w analizie Załęskiej - Żyłki i wsp. (2008).

Uzyskane wyniki potwierdzają szerokie występowanie problemu otyłości wśród populacji. Ponadto udowodniono, że estetyka i zdrowie są istotną kwestią dla społeczeństwa, ponieważ znaczna część osób podejmuje działania w celu walki z otyłością. Dodatkowo potwierdzono także, że istnieje konieczność stworzenia zintegrowanego systemu walki z otyłością, który skupiałby specjalistów klinicznych z wielu dziedzin.

Wnioski

1. Otyłość stanowi istotny problem społeczny o tendencji rozwojowej.

2. Mimo swojej istoty, otyłość nadal stanowi marginalny problem, którego proces niwelowania i prewencji jest stosunkowo rzadko podejmowany.

3. Brak jest stosownych narzędzi oraz kompleksowej terapii otyłości.

4. Stosowanie terapii nadmiernej masy ciała pod opieką specjalisty zapewnia lepsze efekty niż w przypadku samodzielnego odchudzania się.

5. Jednoczesne zastosowanie dietoterapii i wyszczuplających zabiegów kosmetycznych zapewnia lepsze efekty niż każda z usług świadczona osobno.

6. Domowe, wyszczuplające zabiegi kosmetyczne oraz ćwiczenia fizyczne nie są powszechnie stosowane, co świadczy o niskim poziomie świadomości populacji w kwestii konieczności uzupełniania profesjonalnych zabiegów codziennymi terapiami domowymi oraz o metodach leczenia i zapobiegania otyłości.

7. Dietetycy charakteryzowali się niższą wiedzą na temat wyszczuplających zabiegów odchudzających niż deklarowali podczas badań, oraz niższą wiedzą na temat potrzeb swoich pacjentów. Powyższe świadczy o niskim zainteresowaniu współpracą z kosmetologiem w terapii nadmiernej masy ciała.

8. Kosmetolodzy wykazywali większe zainteresowanie podjęciem współpracy zastosowanie dietoterapii i z dietetykiem ze względu na świadomość dużego znaczenia dietoterapii oraz zabiegów wyszczuplających w leczeniu nadmiernej masy ciała. Ponadto byli bardziej świadomi potrzeb pacjentów.

9. Istnieje zasadność stworzenia zintegrowanej opieki specjalistów nad populacją otyłą.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 49-55
DOI: 10.7365/JHPOR.2012.1.9

Safety aspects and access to biological treatment in Poland

Karina Jahnz-Różyk
Military Institiute of Medicine, Department of Immunology and Clinical Allergology. Warsaw, Poland.

Joanna Mazurek
Military Institiute of Medicine, Department of Immunology and Clinical Allergology. Warsaw, Poland.

Abstract

The term "biological drugs" (or biological agents, or biologics) is usually applied to denote a class of medicinal products (either already approved to trading or in clinical trial stages), manufactured by means of biological processes, involving recombinant DNA technology. These medications are divided into three types – key signalling proteins (e.g. erythropoietin), monoclonal antibodies and receptor constructors. It has been shown in many clinical studies that biologics offer additional therapeutic options, which are effective for treatment of many diseases in the fields of rheumatology, oncology, dermatology, pneumonology and others. However, the access to these medicines is different in various European countries and depends on many aspects, including adverse episodes, complex regulatory standards and pharmacoeconomic aspects. Selected problems of access to biologics for therapeutic purposes are discussed in this article, both in Polish and European perspective. Seemed to be safe biological agents (named biologicals too) can produce unwanted, adverse side-effects.

The side-effects in the course of treatment with biologicals may result from excessively secreted cytokines during treatment, hypersensitivity reactions, cytokine balance disturbances, cross reactions or nonimmunological reactions. Clinically, the first type is usually manifested by influenza-like symptoms. Hypersensitivity reactions depend on the degree of antibody humanisation, the applied adjuvant and, what is important, these are often delayed immunological reactions, mediated by T lymphocytes. Autoimmune reactions are a serious threat for affected patients. The syndrome of disturbed cytokine balance may, however, manifest itself by the occurrence of tuberculosis, listeriosis or granulomatosis, while such complications have also been observed in patients treated with anti-TNF alpha. Non immunologically determined symptoms, such as circulatory failure or hearing loss, may be dangerous as well.

Key words: biologics, adverse side-effects, access

Biotechnology

The present era of biotechnology began in 1953 with the discovery of the double-helix model of DNA structure by James Watson and Francis Crick, followed by the discovery of restrictive enzymes by Werner Arber [1, 2]. The studies of those researchers have made it possible to demonstrate that a transfer of animal or human gene to a bacterial cell leads to formation and production of such proteins as insulin or the growth hormone, extremely useful in the therapy of many dangerous diseases. The observed occurrence of DNA recombination was a prompt and a starting point to launch genetic engineering, while the discovery of monoclonal antibodies by Milstein and Koehler was another step on the way of progress in medicine, crowned with the Nobel prize in medicine 1984. At present, biotechnology finds applications in various fields of medicine but also in food production, crime investigation techniques or waste management technologies [2].

Biological drugs

Biological drugs belong to biopharmaceutical products, formed in biotechnological processes, most often in colonies of live cells and not by chemical synthesis [2]. The significant differences between a chemically obtained drug and a biological drug result from the fact that a biological drug has got a bigger molecular weight and is digested in the gastric tract, the latter feature enabling its parenteral administration. The complexity of technological processes, associated with the production of biological drugs, is observable

during the process of obtaining the, so-called, follow-on or biosimilar biologics, which, however, are always the products which merely imitate innovative biological drugs, unlike generic drugs, which are the exact copies of original medicinal products.

Biological drugs include, among others, vaccines, blood and blood-derived preparations, antitoxins, growth hormones, human insulins, cytokines, monoclonal antibodies, recombined therapeutic proteins and allergens. The application of a biological artificial valve or genic therapy are also examples of biological therapy.

In this article authors are focusing on the new class of drugs, commonly called biological agents or biological response modifiers, or simply "biologicals", that have became available for the therapy of various conditions, for example: neoplastic, autoimmune, inflammatory, cardiovascular, haematologic dermatologic, infectious, allergic and others. After their introduction the marked clinical improvement has been observed in many cases. Biologicals have proven to be useful tools in numerous inflammatory and neoplastic diseases. Their direct and focused effect makes them superior to other anti-inflammatory, immunosuppressive or cytotoxic drugs, which can produce severe generalized and unwanted side-effects. This success has driven the development of an increasing number of biological agents. Biological agents comprise proteins can be subdivided into three following groups, such monoclonal antibodies, cytokines (natural antagonists) or fusion proteins (soluble cytokine receptors or ligands). The biological drugs, which are most frequently used in clinical practice, interfere in the immunological system of man – exerting their effects on inflammatory and/or neoplastic cells, most often via the mechanism of suppressing cytokines, chemikines and their receptors [3]. In the therapy of chronic and neoplastic diseases, monoclonal antibodies, some cytokines – including mainly interferons (IFN-alpha, IFN-beta), soluble receptors for cytokines or soluble, cellular ligands have been finding successful applications.

Monoclonal antibodies

Antibodies are very numerous class of biologicals. The original monoclonal antibodies are used for therapeutic purposes nowadays. They are of the mouse origins. But the novel molecular techniques help to modify they structure that is similar to human. The majority of antibodies which are in use, are chimeric (ex. abciximab – cardiology), characterized by "– ximab" and consist of 50-90% human protein; humanized (e.g. omalizumab – allergology) "–zumab" are in 95% humanized; and fully human antibodies (e.g. adalimumab – rheumatology; dermatology and angiology) – ending "– mumab". Antibodies directed to cytokines block action of them (e.g. anti-IL5 or anti-TNF). Antibodies can block cell-bound molecules (e.g. efalizumab – anti-LFA-1 antibody or basilximab or daclizumab – anti-IL-2Receptor antibody). There is an another group of antibodies with ability to inactivate or in contrary to that to activate the select type of cells (for example antibodies against cluster of differentiation molecules – they can deplete or kill tumour cells or temporarily activate the target cell in order to increase efficiency of immune system)

The first monoclonal antibodies, which could have been formed by fusion of spleen B lymphocytes and myeloma cells, were exclusively murine, thus, any attempts of their clinical application were associated with complications, resulting from hypersensitivity reactions to a foreign protein. A progress in genetic engineering brought about an increased participation of the human gene in the process. This is how the mixed forms of monoclonal antibodies have been formed, including chimeric antibodies (75% of human sequences), humanised antibodies (95% of human sequences) or fully human antibodies. The last type of the above-mentioned antibodies are formed by the "phage display" technique or the technique to generate transgenic animals.

Monoclonal antibodies exert various effects on the immunological system – they can, for example, act against soluble proteins (e.g., anti-TNF, anti-IL-2), against the superficial receptors of cells (anti-CD20), against IgE (omalizumab), against neoplastic antigens (e.g., EGFR (epidermal growth factor receptor) – cetuximab, anti-HER2 – transtuzumab) [4, 5].

Cytokines

Cytokines like for example interferon α and β, interleukin 2 are widely used in infection and neoplastic diseases. Their structure have been modified by polyethylene glycol, which reduces degradation of a particle. The amino acid sequence

is identical to human proteins but part after glycosylation might be different [6, 7].

Fusion proteins

Third group consists of fusion proteins. These particles behave like receptors to natural cytokines or ligands blocking natural receptors. In order to solubilize and prolong the half-life of these normally cell-bound molecules, they are bound to the Fc part of human immunoglobulin IgG1. Soluble cytokine receptors are named using the ending -cept, for example etanercept, the soluble tumour necrosis factor α receptor. Soluble cell ligands disturb the cell-to-cell communication. For instance co-stimulation of cells or their migration can be blocked. An example: the interaction of CD28 or CTLA4 (on T cells) with CD80/CD86 on antigen-presenting cells can be blocked by abatacept - soluble chimeric human protein consisting of the extracellular domain of CTLA-4(CD152) and the Fc part of human IgG. Both of the biologicals, mentioned above are used in treatment of rheumatoid arthritis [5, 6, 7].

Biological drugs in the world

Therefore biological response modifiers became numerous and preferable group of drugs. The progress in this field is based on a better understanding of immunopathology of many diseases. At the other side the application of novel biotechnological methods allows to produce recombinant proteins like cytokines as well as humanized antibodies at a large scale. The wide use of biological agents is a challenge for modern medicine. The in vitro and in vivo studies, concerning the mutual reactions of cells, cellular mediators, cytokines, chemokines and receptors, have brought about a considerable progress, regarding the actual knowledge and on-going cognition of immunological mechanisms in man [3]. The results of the studies have unveiled many interesting facts, regarding the pathomechanism of inflammation, disease from autoimmunity or neoplasm occurrence, while also becoming the base of searching for possibilities of therapeutic influences on various diseases. The following biological drugs have been approved for use in clinical practice:

-Adalimumab (Humira, Abott), an antibody directed against against TNF-alpha, recommended in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylytis;

-Alefacept (Amevive, Astellas), recombinant LFA-3/IgG Fc construct, indicated in psoriasis

-Anakinra (Kineret, Amgen), IL-1 neutralising cytokine, recommended in the treatment of rheumatoid arthritis;

-Bevacizumab (Avastin, Genentech), an antibody, directed against the vascular endothelial growth factor (VEGF-A), recommended in the therapy of colorectal carcinoma;

-Cetux imab (Erbitux, Bristol-Myers Squibb) – an antibody, directed against the epidermal growth factor receptor (EGFR), recommended in the therapy of metastatic colorectal carcinoma;

-Etanerecept (Enbrel, Wyeth), an antibody for the TNF-alpha receptor, bound to Fc fragment of the human IgG antibody, recommended in the treatment of rheumatoid arthritis and juvenile arthritis and psoriasis

-Denileukin diftitox (Ontak, Eisai), recombinant diphtheria toxin/IL-2 construct - indicated in treatment of cutaneous T-cell lymphoma

-Filgrastim (Neupogen, Amgen), recombinant G-CSF used in haematology and oncology to treatment of neutropenia

-Inflix imab (Remicade, Centocor), an antibody, directed against TNF-alpha, recommended in the therapy of rheumatoid arthritis, Crohn's disease and psoriatic arthritis;

-Omalizumab (Xolair, Novartis Pharma), an antibody, directed against Immunoglobulin E, used to improve asthma control in patients with severe, chronic, allergic asthma;

-Palivizumab (Synagis, Abott), an antibody, directed against F protein of respiratory syncytial virus (RSV) (type A and B), recommended in the prophylactics against RSV infections in children with chronic pulmonary disease (bronchopulmonary dysplasia);

-Ranibizumab (Lucentis, Novartis Pharma), an antibody, directed against the vascular endothelial growth factor (VEGF-A), recommended in the therapy of age-related exudative maculopathy;

-Ritiximab (Rituxan, Genentech; Mabthera, Roche), an antibody, binding with CD20 – the transmembrane antigen – on B lymphocyte surface and neoplastic cells. Recommended for treatment of lymphomas, mainly those of B lymphocytes.

-Trastuzumab (Herceptin, Roche) – an antibody,

directed against HER 2 protein (a product of ber2/neu antigen), recommended in the therapy of metastatic mammary carcinoma with enhanced HER2 protein expression.

During the recent years, the market of biological drugs has been dominated by vaccines and monoclonal antibodies (www.imshealth.com). Following the data of IMS Health for the year 2009, the total sale of monoclonal antibodies, mainly TNF-alpha, exceeded the sales value of generic drugs, amounting to USD 40 billion. As much as 80% of sold monoclonal antibodies were applied in oncological indications and chronic inflammatory/autoimmunological diseases. In oncology, the highest sales values were recorded for avastin, herceptin and rituxan, while humira, remicade and rituxan were most often administered in chronic inflammations.

It is worth emphasising that the costs of biological therapies considerably exceed the costs of drugs produced on chemical basis. Therefore, biological therapies are not available for patients where therapies are not reimbursed. Together with the increased costs of such therapy and the hope of patients for longer life of good quality various doubts appear, regarding the assumed higher efficacy of biological therapies over reference therapies. An eleven-year, post-marketing observation of 4,911 patients with rheumatoid arthritis, treated with biological therapy, demonstrated a much smaller clinical effect and, thereby, lower cost effectiveness than it was observed in phase III clinical trials [7, 8 , 9, 10, 11, 12] .

Biological drugs in Poland

The current use of state-of-the-art therapies is an economic problem at any country. Poland ranks the 50th position in the world, regarding the gross domestic product (GPD). The annual cost of omalizumab therapy for one patient with severe asthma approximates the level of the gross domestic product per one inhabitant (in 2008, GPD / per capita = PLN 58,273.00). The average cost of therapy with TNF-alpha of patient with rheumatoid arthritis varies – depending on applied drug – between PLN 45,000.00 and 60,000.00. The availability of biological drugs in Poland is possible thanks to therapeutic programmes, conducted by the National Health Care Fund, although the application processing to include a given therapy on the list of therapeutic programmes is a rather complex procedure [1]. The application, submitted to the Minister of Health, requesting to include patients with a definite medical indication in a specific therapeutic programme, lies within the competence of National Consultant in a given field of medicine. The application has to be supported by recommendation of the Agency for Evaluation of Medical Technologies (AOTM) [14]. AOTM's recommendation depends on documented clinical efficacy and should include a description of medical problem and of current clinical practice with a safety evaluation of a given therapy. A pharmacoeconomic analysis is also required, including an economic evaluation (e.g., cost-effectiveness or cost-utility) plus a health care budget impact analysis. At present, the following biological therapies have been approved into the therapeutic programmes of the National Health Care Fund:

-cancer therapy with trastuzumab,

-chronic myeloid leukaemia with imatinib

-intestinal stroma tumour with imatinib or sunitinib,

-multiple sclerosis with interferon beta,

-viral hepatitis B or A with interferon alpha,

-renal carcinoma with sunitinib,

And treatment of rheumatoid arthritis – with infliximab, adalizumab or etanerecept. The highest costs, arising from reimbursement of therapeutic programmes, were – in 2009 – generated by trastuzumab and imatinib [13].

The safety aspects of biological therapy

In biological therapy, the safety aspect in administration of biological drugs is of key importance for the treated patient [6]. Adverse effects, which may occur in the course of biological therapy, are classified and clinically manifested quite differently vs. the adverse effects of chemically produced drugs.

Biological agents differ strongly from classical drugs. They are not small chemical compounds as other drugs and they are not metabolized like classical drugs. As proteins, biological agents cannot be given orally. Their structure will be destroyed by gastrointestinal enzymes. They are administrated by intravenous, intramuscular or subcutaneous injections. Adverse side effects to these drugs are very heterogeneous and might differ from those produced by normal drugs.

Most of them might be unknown and appear after many years from drug withdrawal. The monitoring of them seems essential. Adverse side effects to chemical compounds, classical drugs can be generally divided into two types A and B. Type A reactions (named augmented) are predictable and due to pharmacology of the drug. There are dose-dependent reaction: for example bleeding with anticoagulants. Type B reactions (comes from bizarre - odd and very strange). These kind of the effects are not predicted from pharmacology of the drug. They are not dose dependent. They may occur during treatment with very small doses, sometimes after the first dose of the drug. These are hypersensitivity reactions. They include immune-mediated reactions like maculopapular exanthema or urticaria and also non-immunological effects like aspirin induced asthma. These classification is implemented by some authors [6, 7, 15] about three additional types of side adverse reactions to drugs: Type C (chemical) reactions - due to the chemical structure of the drug or its metabolite (examples: hepatotoxity of some drugs - isoniazid or paracetamol). Type D (delayed) reactions - some of them can occur many years after stopping the treatment - example bladder carcinoma after treatment with cyclophosphamide. Type E (end of treatment) reactions - related to the withdrawal of the drug, like seizure after stopping of anti-epileptic drugs. However biological agents differ from classical drugs. They are not chemical compounds, so called xenobiotics. They are proteins as similar to the human proteins as possible and they are not metabolised like xenobiotics but they are cytokines act like natural or antibodies neutralize natural proteins. It makes clear, that the distinct features of the biological drugs will differ from those caused by chemical compounds (classical drugs). Usually two groups of reactions are mentioned: rapid and delay side effects. The rapid adverse reactions are usually due to hypersensivity to drug. The delay reactions may appear after months or years of treatment or even after stopping of therapy and could result from the disturbances of the cellular response [15].

Based on the peculiar features of biological agents a new classification of these adverse side-effects of biological agents has been proposed – related but clearly distinct from the classification of side-effects observed with chemicals and drugs. This classification differentiates five distinct subclasses of side effects (named with Greek letters α - ε in contrast to standard classificatin of side effects elicited by classical, chemical drugs), based on mechanism of action and structure of biologicals [6, 7].

Type α (alpha) reactions due to high cytokine levels and high cytokine release syndrome. Most of the cytokines have a predominant local activity. It is so called paracrine action, directed to neighboring cells, or autocrine when the action is directed to cells producing the cytokine. Thus, for many cytokines only the local concentration is high. Some of cytokines have also systemic activity. If these kind of cytokine is applied therapeutically, or monoclonal antibody (ab) (ex. muromunab - anti - CD3ab) gives a signal to release cell mediators, high systemic concentration of various cytokines can produce severe, serious side effect, called "cytokine storm". It can determine the limitation of the use of the cytokine. A fever, myalgia, headache or even multi-organ failure may occur (ex. anti - CD28 ab).

Type β (beta) includes hypersensivity reactions - because of an immunological response to the biological agent (they might be immediate - IgE-mediated reactions or non-immediate (delayed) determined by IgG or T cells. The immunogenicity of the biological agents is determined by various factors, example - degree of humanization or various additional cofactors. Biological agents as proteins may evoke an allergic response. It depends on the degree of humanization of the applied protein. In the past, mouse antibodies (abs) as well as chimeric abs could elicit quite rapidly an immune response. The humanized or fully human abs have lower immunogenicity. However, the antigen-binding site of the monoclonal ab can generate an immunological response. Another problem is content of adjuvants in vials of the biological drugs. They may cause immunological reactions too [4, 6, 7].

Type γ (gamma) named as immune or cytokine imbalance syndrome - some side effects cannot be explained by high concentrations of the cytokines or by any immunological response directed to biological agent and they are not due to hypersensitivity. The immunodeficiency or the autoimmunity may occur. Data from clinical trials and pharmacovigilance has noted a higher incidence of infections among patients treated with anti-TNFα or efalizumab (anti-LFA1 ab). TNFα is essential for the control of the intracellular infections

like tuberculosis or listeriosis by stimulating of macrophage function. Common infections as well as various opportunistic infections, such tuberculosis, atypical mycobacteriosis, listeriosis, histoplasmosis, aspergillosis, pneumocyctosis or legionellosis can occur during anti-TNFα treatment. Efalizumab can inhibit migration of inflammatory cells like neutrophils and T-cells to the affected tissue. While this may be beneficial in some diseases, it may disturb optimal and correct control of infection. It is obvious that persevering observation for any signs or symptoms suggestive of infection is required during the therapy with some of biological agents [5, 6]. The normal immune system is well balanced. The correct Th1/Th2 balance, central and peripheral tolerance mechanisms, correct function of T-cells, optimal concentration of certain cytokines like TGFβ and IL10 are essential. A disturbance of this balance can result in autoimmunity or autoinflammatory disorders. There are growing number of reports of the paradoxical induction of autoimmune processes, overwhelmingly associated with anti-TNF agents. In the review, published in 2010, authors analyzed the clinical characteristics and outcomes of autoimmune diseases developing after biological therapies through a baseline Medline search [16]. They found more than 800 cases of autoimmune diseases secondary to biological therapies, including a wide variety of both systemic like: lupus, vasculitis, sarcoidosis and antiphospholipid syndrome. There were also organ-specific autoimmune processes (interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis and autoimmune hepatitis). The majority of cases appeared between one month and one year after initiation of the therapy with the biological agent and complete resolution was observed in nearly 75% of cases after cessation of the therapy. Some of the induced autoimmune diseases had the poorest outcomes like: interstitial lung disease, inflammatory ocular disease and central nervous system demyelinating diseases [4, 5, 6, 7, 16].

Type δ (delta) specifies crossreactivity reactions - these reactions may be due to expression of the same antigen on different tissue cells or to the reaction of antibody with a similar structure. Some receptors can be over expressed on tumour cells, but they are also present on normal cells too. Antibodies, which are directed to such structures (ex. cetuximab - anti-EGFR ab) can cause unexpected side effects [6, 7].

Type ε (etta) contains non - immunological side effects - very heterogeneous, might be quite frequent. Future observations are needed to classify them correctly. Some of them can be due to combined therapy with the biological drug and the classical drug (example: IFNγ and ribavirine for therapy of hepatitis C - anemia might be related to ribavirin). This classification, presented above, helps to better understand the clinical features of the various side-effects of biologicals, and to identify possible individual and general risk factors and to direct research in this novel area of medicine [6, 7].

Biological drugs are an added value in the therapy of many chronic diseases with inflammatory / autoimmune aetiology and of neoplastic diseases. Safety aspects of treated patients are a special concern, regarding these therapies. Taking into account the high costs of biological therapies, they are not born by patients in any country. In Poland, the available options include therapeutic programmes of the National Health Care Fund or patient treatment within highly specialist therapeutic procedures. Any hopes for cost reduction may be associated with the introduction of bio-derived drugs on one hand and with therapy risk distribution between a pharmaceutical company and the payer on the other, the latter is proposed in the new reimbursement act in Poland.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 56-60
DOI: 10.7365/JHPOR.2012.1.10

Asthma - is there an association between the quality of life and the levels of alexithymia?

Patrycja Grabowska-Krawiec
Military Institute of Medicine, Department of ClinicalImmunology and Allergology. Warsaw, Poland.

Karina Jahnz-Różyk
Military Institute of Medicine, Department of Clinical Immunology and Allergology. Warsaw, Poland.

Tomasz Targowski
Military Institute of Medicine, Department of Internal Diseases, Pneumonology and Allergology. Warsaw, Poland

Abstract

In psychological theories, difficulties of affect regulation, defined as alexithymia, are correlated with asthma but the association between alexithymia, asthma and quality of life has not been explained yet. The aim of the study was to: 1) determine the prevalence of alexithymia in patients with asthma, 2) evaluate the associations between the quality of life and the levels of alexithymia.

Methods: Alexithymia was assessed with the TAS- 20 (Toronto Alexithymia Scale). The prevalence of this disorder in patients with asthma was compared to that in healthy subjects. Quality of life was evaluated with: AQLQ by Juniper for asthmatics. The associations among alexithymia, and the quality of life were estimated by data analysis. The data were analyzed using Pearson correlations, t-Student test. A p value ≤ 0.05 was required for statistical significance.

Results: Fifty healthy people and fifty one asthmatic outpatients of Military Institute of Medicine in Warsaw, Poland participated in the study. Twenty percent of asthmatics and only four percent of healthy people reported high alexithymia scores. A higher alexithymia score was associated with worse quality of life.
Conclusions: The prevalence of alexithymia is higher in patients with asthma. The coexistence of asthma and alexithymia is associated with deterioration of patient's quality of life.

Key words: alexithymia, asthma, quality of life.

In the world, about 300 million people are affected by asthma. There are four million patients with asthma in Poland [1]. Experts of GINA (Global Initiative for Asthma) indicate that only half of asthmatic can achieve good control of illness symptoms. Psychological factors like alexithymia (disorder of affect regulation) can be one of the reason [2-8]. Only a few authors tried to define the relationship between alexithymia and asthma.

Shortness of breath – typical asthma symptom is very subjective feeling. That's why for evaluation of the course of the disease, not only pulmonary function tests but also patients' quality of life questionnaires should be used. Following the WHO definition of health, health related quality of life (HRQL) can be defined as the physical, psychological, and social domains of health, as perceived by the patient, which are influenced by the patient's experiences, beliefs, and expectations of their disease and treatment.

There have been many studies on the quality of life for patients with bronchial asthma [9-13] but the association between alexithymia and patient's quality of life has not been explained yet.

The aim of the study was to:

1. Determine the prevalence of alexithymia in patients with asthma,

2. Evaluate the associations between the quality of life and the levels of alexithymia.

Methods

The study protocol was approved on 03/02/2007 by the Bioethics Commission of the Military Medical Institute in Warsaw - Resolution No. N404 111 32/3491

The study comprised 101 people from Warsaw and its environs (fifty one asthmatic outpatients of Military Institute of Medicine in Warsaw and fifty healthy subjects) without pulmonary (other than asthma), cardiovascular or neoplastic diseases, with at least medium education.

Alexithymia was assessed in both groups by the TAS-20 (Toronto Alexithymia Scale) which consists of three subscales: 1) difficulties in identifying feelings (IDE), 2) difficulties in communicating, discrebing feelings (COM) 3) externally oriented thinking (EOT)[14-16]. Those who scored below 52 points were classified as non-alexithymic, between 52-60 - borderline alexithymic and those who scored more than 60 were classified as alexithymic [14]. The prevalence of this disorder in patients with asthma was compared to healthy subjects .

The quality of life was evaluated only in the asthmatic group by Juniper AQLQ (Asthma Quality of Life Questionnaire) [17,18] which consists of four subscales (domains): D1- symptoms; D2-activity limitation; D3-emotional function; D4-environmental stimuli. The greatest value of the overall indicator of quality of life that can be achieved using the AQLQ is 7 and it should be interpreted as the best quality of life (lack of symptoms and limitations caused by illness).

The data was analyzed using Pearson correlations, linear regression and analysis of variance (ANOVA) in SPSS. A p value ≤ 0.05 was required for statistical significance.

Results

Fifty healthy persons (20 male, 30 female, mean age 40 years ± 11) and fifty one outpatients of Military Institute of Medicine in Warsaw, Poland (20 male and 31 female with asthma; mean age 46 years ± 12) participated in the study. Twenty percent of asthmatics (20%) turned out to be alexithymic (TAS-20≥61), 23% reported borderline alexithymia scores (TAS-20 between 52-60), and 57% reported low alexithymia scores (figure 1). Four percent of healthy people reported high alexithymia scores, 6% - borderline alexithymia, 90% - low alexithymia (figure 1). Alexithymia mean scores were not statistically different across sociodemographic variables. Patients with asthma had significantly higher TAS-20 global scores as compared to healthy people [(mean scores: 48.56 ± 12.67 vs. 40.06 ± 9.58 (p = 0.0001)]. The analysis of the data revealed that alexithymia and its elements (IDE, COM and EOT) are significantly negatively related to quality of life (AQLQ) and its various domains. The strongest dependency occurred between total TAS-20 and AQLQ (r=-0.30, p=0.0001)(table 1.).

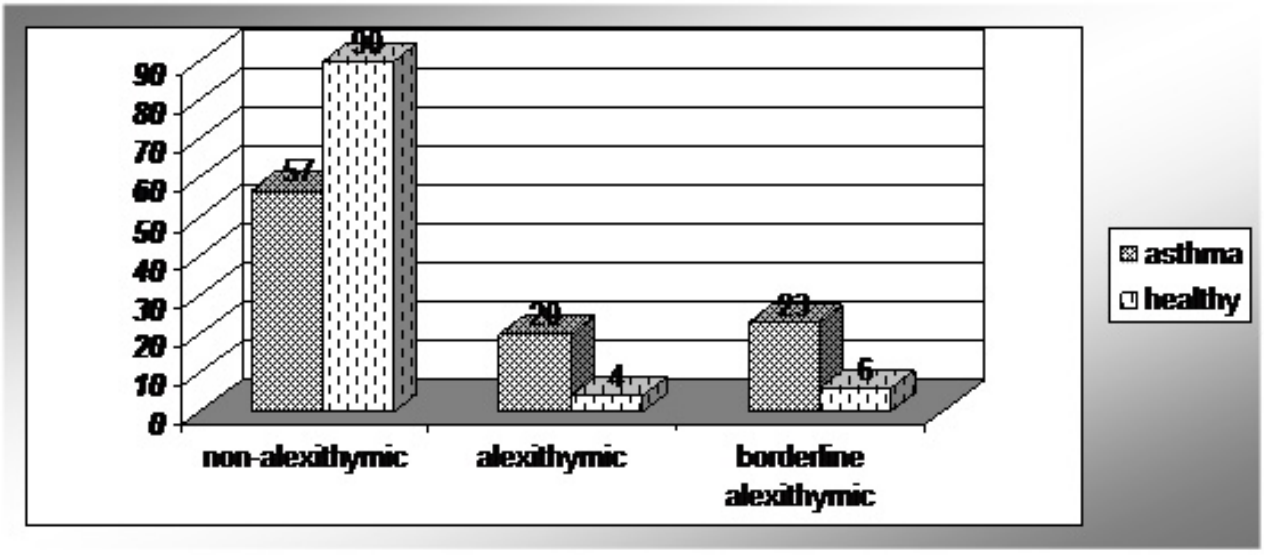

Figure 1. Prevalence of alexithymia in asthmatics and healthy people (%)

Table 1. Correlations between TAS-20 and AQLQ in the study group

		IDE	COM	EOT	Total TAS-20
AQLQ	Pearson's linear correlation (r)	-0,40	-0,46	-0,47	-0,30
	Level of significance (p)	0,003	0,001	0,02	0,0001
D1	Pearson's linear correlation (r)	-0,35	-0,44	-0,44	-0.30
	Level of significance (p)	0,01	0,001	0,03	0,0001
D2	Pearson's linear correlation (r)	-0,39	-0,44	-0,46	-0,30
	Pearson's linear correlation (r)	0,004	0,001	0,02	0,0001
D3	Pearson's linear correlation (r)	-0,35	-0,45	-0,44	-0,31
	Level of significance (p)	0,01	0,001	0,02	0,0001
D4	Pearson's linear correlation (r)	-0,42	-0,40	-0,23	-0,40
	Level of significance (p)	0,002	0,003	0,1	0,0002

Discussion

When inflammatory etiology of bronchial asthma was discovered, it was believed that treatment with corticosteroids allows for good control of asthma symptoms. Unfortunately, it was shown that anti-inflammatory treatment is not efficacious enough and sometimes the intensity of asthma symptoms is affected by psychological problems, like anxiety, depression and alexithymia [2, 5, 19].

Alexithymia is a personality trait characterized by a limited ability to identify and describe emotions [20]. Alexithymic is someone who defines emotions in terms of somatic sensations or behavioral reactions [20].

Some authors presented data demonstrating the frequent occurrence of alexithymia among patients with asthma, especially severe and difficult (near-fatal asthma) [3, 4, 21, 22].

Another analysis showed that patients with asthma and alexithymia, are more vulnerable to more frequent and longer hospitalizations because of asthma exacerbations [3, 23]. Patients can often underestimate the severity of asthma exacerbation because of the difficulty in distinguishing illness symptoms from somatic signs of emotional arousal [4, 24].

GINA experts reveled that patient's non compliance is very frequent element disturbing good control of disease [19]. Compliance to treatment depends on many factors, mainly on patients' believes, knowledge about the disease, trust in the doctor [19]. That's why recently increasing attention is paid on subjective patient's evaluation of his psychosocial and health status. Evaluation of the quality of life is one of the best non-medical methods to measure it. Quality of life is also important element of pharmacoeconomic evaluation of asthma as a social and economic problem in many countries.

There have been many studies on the quality of life for patients with bronchial asthma. These studies focus on the relationship between health related quality of life and many other factors like: the type, severity of symptoms, drugs, education, gender, age, mental disorders, etc. [9-13].

The association between alexithymia and asthma control or patient's quality of life has not been explained yet. Kelly Chugg [25] in 2009 presented the pilot study in the group of 25 asthmatic patients. She found that high levels of alexithymia was associated with worse asthma control score, poor adherence and worse quality of life.

That study revealed that the prevalence of alexithymia was higher for patients with asthma. The coexistence of asthma and alexithymia was associated with deterioration of patient's quality of life.

Conclusions

It seems reasonable to claim that alexithymia can modulate illness perception and quality of life [26, 27]. It is therefore reasonable to test if the emotional education of patients with asthma can improve their compliance, quality of life or symptoms control.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 61-80
DOI: 10.7365/JHPOR.2012.1.11

Mabthera (rituximab): a cost-effective therapy in hematology

Monika Russel-Szymczyk
Roche Polska Sp. z o.o.

Monika Szkultecka-Dębek
Roche Polska Sp. z o.o. Millitary Institute of Medicine, Department of Internal Diseases, Pneumonology and Allergology. Warsaw, Poland

Abstract

Current economic situation makes payers in most countries face dilemmas regarding decisions on financing of health care services, including medicines. The choice of what is essential, necessary and whether it is worth financing from public resources are the questions asked by decision makers. One of the tools that were designed and implemented to assist their choices was health technology assessment. However, designed as a supportive tool often becomes a trap impeding or delaying introduction of innovative technologies into daily clinical practice. The example of rituximab (Mabthera) shows that some innovative technologies can stand up to stringent requirements of technology assessment and threshold and in variety of indications proves to be cost-effective therapeutic option. Hereby presented results of cost-effectiveness analysis for rituximab in the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia confirm that Mabthera brings clinical benefits to patients and is as well cost-effective option for the public payer in Poland.

Keywords: rituximab, lymphoma, DLBCL, CLL, FL, cost-effectiveness

Introduction

Nowadays, due to the worldwide economic crisis, the payer attaches special importance to money allocation in the health care sector. In many countries health technology assessment (HTA) plays an important role in the decision making process of drug reimbursement. In Poland the HTA agency, AHTAPol (Agency for Health Technology Assessment in Poland), was created to support the Minister of Health in the reimbursement decisions. The requirements for the HTA documentation to be fulfilled are described in the AHTAPol HTA guidelines, the latest version dated April 2009. Each new technology has to be proven to be an effective, safe and cost-effective treatment. Additionally the budget impact should be calculated. This applies to all newly introduced drugs and new indications for already used technologies. In 2011 Polish Parliament enacted a new legal act regarding reimbursement procedures, which has been in force since January 2012.

Among other regulations the new Reimbursement Act clearly defines the threshold for cost-effectiveness and cost-utility analysis, which has been set at 3xGDP (Gross Domestic Product) per capita level, taking the mean value for GDP per capita from the last 3 years. For 2012 it has been calculated at 99 543 PLN.

The important implication of such regulation is that there are no exceptions. The threshold remains the same for all technologies, including oncology, rare diseases and orphan drugs. Reviewing the AHTAPol President's Recommendations it seems very rare and unlikely for an innovative oncology/hematology treatment to meet those criteria.

Mabthera (rituximab) a genetically engineered monoclonal antibody has been registered and approved for use in different indications in hematology (non-Hodgkin's lymphoma, NHL; chronic lymphocytic lymphoma, CLL) and in rheumatoid arthritis. It has been used successfully in clinical practice for over a decade and is now a renowned and widely studied drug. The economic aspects and cost-effectiveness of Mabthera use have also been subjects of investigations in many countries. Likewise in other countries, in Poland the use of Mabthera in all registered indications and across wide population of patients was consistently proven to be safe and cost-effective.

Methods

We have reviewed the analyses prepared for Mabthera in the following indications and submitted for the assessment by AHTAPol:

Non-Hodgkin's lymphoma:

-previously untreated patients with stage III-IV follicular lymphoma (FL),

-maintenance treatment of follicular lymphoma patients responding to induction treatment (1st and subsequent lines),

-CD20 positive diffuse large B-cell non-Hodgkin's lymphoma,

Chronic lymphocytic leukemia:

-previously untreated and relapsed/refractory chronic lymphocytic leukemia (1st and 2nd line treatment).

The analyses were performed in line with the AHTAPol guidelines. The cost-effectiveness analyses were preceded by systematic reviews of the literature. Analyses considered Polish clinical treatment practice, standards of care, as well as the adverse events treatment patterns and costs. Data was identified and gathered using a questionnaire filled in by Polish clinical experts from different oncology centers. Corresponding incurred costs were calculated from the Polish public payer (National Health Fund, NHF) perspective. Markov models were used and cost-effectiveness and cost-utility techniques applied to calculate incremental cost-effectiveness and cost-utility ratios. Sensitivity analysis was performed to assess the impact of change in crucial assumptions on the overall results and conclusions.

Results

Follicular lymphoma

Previously untreated patients with stage III-IV follicular lymphoma

The treatment of patients with stage III-IV follicular lymphoma with rituximab in combination with chemotherapy is financed by the public payer in Poland through a therapeutic program. Immumochemotherapy is recommended by Polish and international organizations as an effective and safe treatment of FL patients. The analysis aimed at assessing the clinical efficacy, safety and cost-effectiveness of rituximab administered with chemotherapy CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma.

Systematic review of Medline, Cochrane and Embase databases allowed for identification of randomized clinical trials (RCT) directly comparing R-CVP vs. CVP (Marcus 2005, Markus 2008, Markus 2010) and R-CHOP vs. CHOP (Hidemann 2005, Buske 2006) regimens used in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma. Patients received rituximab at 375 mg/m2 day 1 of each 21 day chemotherapy cycle for maximum 6 cycles with CVP and 6-8 cycles with CHOP.

The analysis demonstrated that addition of rituximab to CVP treatment statistically significantly improves: overall survival (OS), time to treatment failure (TTF), median duration of response (RD), median disease free survival (DFS), median time to next lymphoma treatment (TNLT), overall and complete response rate (Tab 1.). The estimated 4-year survival was significantly higher in R-CVP group than in patients receiving CVP alone (83% vs. 77%, p=0.029).The safety profile of R-CVP treatment was favorable. No deaths related to R-CVP were reported. Two patients were withdrawn from the study due to rituximab infusion related reactions. There were no differences between analyzed groups in relation to frequency of infections and neutropenia related sepsis.

Patients receiving rituximab with CHOP regimen had significantly lower risk of experiencing treatment failure, disease progression and disease relapse in comparison to those treated with CHOP alone (Table 2). The overall survival and overall response rates and were also higher in R-CHOP group. The non-hematological adverse events were more frequent with CHOP treatment, however grade 3 and 4 granulocytopenia was observed more often in patients treated with R-CHOP regimen. The probability of disease progression related death was higher in CHOP treated patients.

Clinical analysis demonstrated that rituximab in combination with CVP or CHOP chemotherapy is an effective and safe treatment for previously untreated patients diagnosed with stage III-IV follicular lymphoma. Moreover, long term follow-up data indicate that treatment with rituximab renders positive and durable effects, with favorable safety profile maintained.

Table 1. Results of R-CVP vs. CVP treatment comparison in previously untreated patients diagnosed with stage III-IV follicular lymphoma

End point	R-CVP (N=162)	CVP (N=159)	RR*** (or HR) (95% CI)	NNT*** (or NNH) (95% CI)	P value^
Time to treatment failure (TTF; median, months)	27 (95% CI: 25-37)	7 (95% CI: 6-9)	-	-	<0.0001*
Time to progression (TTP; median, months)	34 (95% CI: 25-37)	15 (95% CI: 12-18)	-	-	<0.0001*
Duration of response (RD; median, months)	38 (95% CI: 28 – not reached)	14 (95% CI: 9-18)	HR: 0.48 (0.36-0.62)	-	<0.0001**
Disease free survival (DFS; median, months)	not reached (95% CI:35 – not reached)	21 (95% CI: 14-38)	-	-	<0.0001*
Time to next lymphoma treatment (TNLT) or death (median, months)	49 (95% CI: 32 – not reached)	12 (95% CI: 10-18)	-	-	<0.0001*
No overall survival- 4-years follow-up (% patients) #	17%***	23%***	0.74 (0.48-1.15)	-	0,029
No overall treatment response ((ORR): CR+CRu+PR; n (%) patients) #	31 (19%)***	69 (43%)***	0.44 (0.31-0.63)	5 (3-7)	<0.0001**
Stable disease- 30 month follow-up (SD; n (%) patients) #	150 (93%)***	126 (79%)***	1.17 (1.07-1.28)	NNH: 7 (5-17)	0.0008
Disease progression- 30 month follow-up (PD; n (%) patients)	17 (11%)	31 (20%)	0.54 (0.31-0.93)	11 (6-86)	0.03
Death (n (%) patients)	31 (19%)	46 (29%)	0.66 (0.44-0.99)	-	0.054***
Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST; months)	50.31	41.97	-	-	<0.001

*** Log-rank test stratified by centre, ** Test X2, *** calculated based on available data, ^ p value from clinical trials (exc. death rate), # positive endpoints (OS, ORR, SD) were converted into negative endpoints in order to standardize conclusions regarding RR for all analysed endpoints.**

Table 2. Results of R-CHOP vs. CHOP treatment comparison in previously untreated patients diagnosed with stage III-IV follicular lymphoma

End point	R-CHOP N=223	CHOP N=205	RR* (95% CI)	NNT* (95% CI)	P value^
Treatment failure (TTF; % patients)	32%	65%	0.52 (0.42-0.63)	3 (2-4)	<0.0001
No disease response to the treatment (RD; % patients)#	34%	65%	0.54 (0.44-0.67)	3 (3-5)	<0.0001
No overall survival (OS; % patients)#	10%	16%	0.61 (0.37-1.02)	-	0.0493
No overall treatment response (ORR; % patients)#	3%	9%	0.36 (0.15-0.84)	18 (9-87)	0.005
No stable disease (SD; % patients)#	98%	95%	1.04 (1.00-1.08)	-	0.081*
Disease progression during therapy (% patients)	1%	3%	0.26 (0.06-1.25)	-	0.14*

*** calculated based on available data, # positive endpoints (OS, ORR, SD, RD) were converted into negative endpoints in order to standardize conclusions regarding RR for all analysed endpoints, ^ p value from clinical trials (exc. stable disease and disease progression during therapy).**

Following confirmation of positive results of treatment with rituximab, cost-effectiveness and cost-utility analysis were performed. Data on clinical practice regarding the therapy of previously untreated patients diagnosed with stage III-IV follicular lymphoma, the therapy of treatment related adverse events and costs were gathered in 5 oncology centers in Poland using a detailed questionnaire. The three state Markov model (disease progression free, disease progression and death) was used to extrapolate clinical efficacy data from clinical trials and to translate experimental efficacy into life years gained (LYG) and quality-adjusted life years (QALY). The public payer's perspective was assumed as most treatment and treatment related costs are covered from public resources. The analysis time horizon was set at 26 years for both efficacy and cost assessment. The utility data were extracted from the Cost-effectiveness Analysis Registry (CEAR). Following costs were calculated and included:

-1st line chemotherapy costs (treatment administration costs and drug costs),

-patients' monitoring and care in disease progression free state,

-patients' monitoring and care in disease progression state,

-treatment related adverse events therapy.

Costs of active substances were retrieved from NHF and Minister of Health (MoH) published price lists. In line with AHTAPol guidelines cost were discounted at 5% and effects at 3.5%. Deterministic and probabilistic sensitivity analyses were performed to test the results from base case analysis.

The analyses results for both R-CVP vs. CVP and R-CHOP vs. CHOP comparisons show that the incremental cost-effectiveness (ICER, 36 189.31 PLN, 35 392.05 PLN respectively) and incremental cost-utility (ICUR, 41 191.65 PLN, 39 949.48 PLN respectively) ratios are far below assumed in the

Poland's cost-effectiveness threshold. Therefore the use of rituximab in combination with CVP or CHOP regimens in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma is a highly cost effective therapeutic option. The sensitivity analysis indicated that results were sensitive to change in the assumed time horizon, however still the calculated ratios remained far below the threshold.

Rituximab as a treatment option for previously untreated patients diagnosed with stage III-IV follicular lymphoma should be considered as highly effective and highly cost-effective from the the public payer's perspective in Poland.

Table 3. Cost-effectiveness and cost-utility analysis results: R-CVP vs. CVP

Parameter		Value
R-CVP	Life year (LY)	9.20520
	Quality-adjusted life year (QALY)	6.536
	Total costs (PLN)	152 419.54
CVP	Life year (LY)	7.68763
	Quality-adjusted life year (QALY)	5.203
	Total costs (PLN)	97 499.66
ICER: cost per LYG		**36 189.31**
ICUR: cost per QALY		**41 191.65**

Table 4. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP

Parameter		Value
R-CVP	Life year (LY)	10.27610
	Quality-adjusted life year (QALY)	7.502
	Total costs (PLN)	139 445.74
CVP	Life year (LY)	9.09245
	Quality-adjusted life year (QALY)	6.454
	Total costs (PLN)	97 554.12
ICER: cost per LYG		**35 392.05**
ICUR: cost per QALY		**39 949.48**

Maintenance treatment of follicular lymphoma

Maintenance treatment aims at maintaining as long as possible the response achieved with the induction therapy, allowing at the same time postponement of subsequent treatment lines. The ESMO (European Society for Medical Oncology) and NCCN (National Comprehensive Cancer Network) guidelines indicate rituximab maintenance as the most optimal and effective strategy to be implemented after induction in patients with follicular lymphoma. This therapeutic approach can be applied instead of watch and wait strategy and, as clinical trials results show, is regarded as highly effective and safe at the same time. The analysis prepared for rituximab assessed efficacy, safety and cost-effectiveness of maintenance monotherapy, both after 1st and subsequent lines of induction treatment, when administered in follicular lymphoma patients.

Maintenance treatment of follicular lymphoma patients responding to 1st line induction treatment

A systematic review was performed in Medline, Embase and Cochrane databases to identify available data on efficacy and safety of maintenance treatment in patients responding to 1st line induction treatment in comparison to watch and wait strategy. One relevant randomized clinical trial was identified. In PRIMA study (Salles 2010) patients received R-CHOP, R-CVP or R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantron) as an induction therapy and those who achieved response were randomized to either maintenance with rituximab monotherapy or watch and wait strategy. Rituximab in maintenance phase was administered at 375 mg/m2 every 8 weeks for maximum 12 cycles or until disease progression.

The results showed that administration of rituximab as the maintenance therapy reduces the disease progression risk by 45% in comparison to observation during 36 months of the follow-up. A 3-year progression free survival in the rituximab maintenance group was higher than in observation (74.9% vs. 57.6% respectively). Rituximab administered as maintenance treatment after 1st line induction also reduced risk of next anti-lymphoma treatment by 40% and risk of next chemotherapy by 38% in 36 months of the follow-up. It also statistically significantly improved the complete response and complete unconfirmed response rates at 2 years in patients who achieved partial response after induction treatment and at 36 months follow-up. The risk of death was reduced by 13% in rituximab maintenance group; however the results were not statistically significant.

The results of the PRIMA study indicated that maintenance treatment with rituximab has an acceptable profile with infections and neutropenia grade 3 and 4 more frequent in the rituximab group. The increased frequency of adverse events (infections and neutropenia) in the rituximab group did not translate into the increased risk of death due to adverse events. The overall results of the clinical efficacy and safety analysis indicate that rituximab should be considered as an option for patients who responded to 1st line induction therapy.

The economic evaluation of rituximab maintenance therapy after 1st line induction treatment was prepared from the public payer's perspective assuming 25 year (life-time) time horizon to capture all effects and costs that could appear throughout the whole patient's life. Direct medical costs were assessed based on the data regarding clinical practice of FL treatment and data related to medical resources use gathered in 5 oncology centers in Poland. The following cost categories were identified as important and included in the analysis: cost of drugs and drug administration, treatment-related adverse events costs, lymphoma relapse treatment costs and patient health monitoring costs. Costs were discounted at 5% and effects at 3.5% rate. The four health state Markov model (progression-free 1st line, progression-free subsequent line, progression and death) was used. Sensitivity analysis was performed testing the influence of critical parameters such as utilities values, different costs categories, length of time horizon and patient's body surface.

Mean number of cycles administered was 10.6 (the PRIMA study). Based on those data and assuming 1.81 m2 body surface area total dose of rituximab and drug administration costs were calculated.

Introduction of 1st line rituximab maintenance therapy resulted in gain of 1.4 life years and 1.3 quality adjusted life years compared to observation. The total incremental costs were 60 707 PLN which corresponded to an incremental cost-effectiveness ratio (ICER) of 43 348 PLN and an incremental cost-utility ratio (ICUR) of 47 357 PLN. Both values are below cost-effectiveness threshold assumed by the Polish public payer for cost-effective technologies.

Table 5. Results of clinical analysis: maintenance with rituximab vs. observation in follicular lymphoma patients responding to 1st line induction treatment; ns- not statistically significant

End point		Statistically significant advantage of rituximab maintenance	Statistically significant advantage of observation
		OR/HR (95% CI)	
Progression free survival (PFS)		HR=0.55 (0.44; 0.68)	-
3-year PFS		OR=2.20 (1.68; 2.87) RD=0.17 (0.12; 0.23) NNT=6 (5; 9)	-
Event free survival (EFS)		HR=0.59 (0.48; 0.72)	-
Overall survival (OS)		ns	
Next lymphoma treatment during 36 months follow-up		OR=0.52 (0.39; 0.70); RD=-0.12 (-0.18; -0.07) NNT=9 (6; 15) HR=0.60 (0.47; 0.76)	-
Next chemotherapy during 36 months follow-up		OR=0.56 (0.41; 0.76) RD=-0.09 (-0.14; -0.04) NNT=12 (8; 25) HR=0.62 (0.47; 0.81)	-
Complete response (CR/CRu) in patients who completed maintenance treatment or observation		OR=2.29 (1.77; 2.97) RD=0.19 (0.13; 0.25) NNT=6 (4; 8)	-
Complete response (CR/CRu) during 2 years in patients with partial response after induction		OR=2.56 (1.58; 4.14) RD=0.22 (0.11; 0.33) NNT=5 (4; 10)	-
Disease progression during 36 months follow-up in patients qualified to maintenance treatment or observation		OR=0.47 (0.36; 0.61) RD=-0.17 (-0.22; -0.11) NNT=6 (5; 10)	-
Disease progression risk during 36 months follow-up	**After R-CHOP induction**	HR=0.51 (0.39; 0.65)	-
	After R-CHOP induction	ns	
	After R-FCM induction	ns	
	Patients with CR/CRu after induction	HR=0.57 (0.44; 0.74)	-
	Patients with PR after induction	HR=0.48 (0.32; 0.72)	-
Quality of life	**FACT-G**	ns	
	EORTC QLQ-C30	ns	

Table 6. Cost-effectiveness and cost-utility analyses results: rituximab maintenance vs. observation

	Life years gained [LYG]	Incremental cost [PLN]	ICER [PLN/LYG]
Rituximab vs. observation	1.400	60 707	43 348
	Quality adjusted years gained [QALY]	Incremental cost [PLN]	ICUR [PLN/QALY]
	1.282	60 707	47 357

The results were sensitive to changes in discount rates, utilities values applied to the specific health states, length of time horizon. None of the tested scenarios resulted in values of ICUR and ICER exceeding the 99 543 PLN threshold, providing evidence that the rituximab treatment is cost-effective from the public payer's perspective. The probability of 1st line maintenance therapy with RTX being cost-effective was 100%.

Rituximab 1st line maintenance treatment of follicular lymphoma patients who responded to induction treatment is an effective, safe and highly cost-effective therapeutic option.

The maintenance therapy prolongs patient's life and at the same time improves their quality of life. Therefore, need for a structured financing from public resources of maintenance therapy with rituximab should be recognized, so that the option would be available for Polish lymphoma patients.

Maintenance treatment of follicular lymphoma patients responding to 2nd and subsequent lines induction treatment

Maintenance therapy with rituximab of follicular lymphoma patients responding to 2nd and subsequent lines of induction treatment has already been implemented into the daily clinical practice in Poland and is accepted as effective and safe option for patients who would otherwise be subjected to observation only. The therapy is financed from public resources through the therapeutic program. The analyses were prepared to confirm that the decision to finance this option for follicular lymphoma patients was justified and well-funded.

Systematic review of Medline, Embase and Cochrane databases revealed 2 publications of randomized clinical trials results: EORTC 20981-van Oers 2010 (induction with either R-CHOP or CHOP regimens) and Forstpointner 2006 (induction with R-FCM or FCM). Rituximab in maintenance phase was administered every 3 months for 2 years or until disease relapse at 375 mg/m2 dose in van Oers 2010 and in 2 courses, each consisting of 4 doses of 375 mg/m2/day given for 4 consecutive weeks, given 3 and 9 months after completion of salvage therapy in Forstpointner 2006 trial.

Rituximab administered as maintenance therapy reduced risk of disease progression by 45% in comparison to observation. The disease progression risk reduction was also noted in subgroup analysis in patients treated in induction phases with CHOP or R-CHOP regimen and those who achieved complete or partial response after induction treatment. In patients who received rituximab in maintenance therapy the response duration was significantly longer. There were no differences between compared options regarding 5-year survival, however the results were on the border line of statistical significance, therefore trend in improvement of this parameter could be observed as well.

The results of the clinical efficacy and safety analysis indicate that rituximab administration as the maintenance strategy in patients with follicular lymphoma, who responded to 2nd or subsequent lines of induction treatment is an effective and safe therapeutic option.

Economic analysis assessed the cost-effectiveness of rituximab maintenance therapy based on the results of clinical analysis. Life-time horizon was assumed as effects and costs of the maintenance strategy can be observed throughout whole patient's life. The four health state Markov model was used (progression free- induction, progression free- maintenance, progression, death). Discoun-

ting was performed at 3.5% for effects and 5% for costs (in the sensitivity analysis those were tested according to AHTAPol guidelines at 5% or 0% for both effects and costs and 0% for effects and 5% for costs). The data regarding utilities were derived from the CEAR. Data on clinical practice and resource utilization were gathered in the 5 oncology centers in Poland. Costs were calculated from the perspective of the public payer's and included costs of drugs, drug administration costs (induction and maintenance phase), costs of adverse events treatment, costs disease relapse therapy and patient's health monitoring costs. Sensitivity analysis (one- and multiway) tested changes in various parameters including: utility values, body surface area, administration costs changes, number of treatment cycles induction or maintenance, costs of adverse events therapy, time horizon.

The results showed that administering rituximab in maintenance therapy to patients with follicular lymphoma who responded to 2nd or subsequent line of treatment instead of subjecting them only to observation is not only clinically justified but cost-effective from the public payer's perspective as well. The ICER was 77 113 PLN/LYG and ICUR 92 612 PLN/QALY. Both results fall below the threshold of 99 543 PLN/QALY or LYG. The sensitivity analysis indicated that the base case results are robust and in all tested scenario cost-effectiveness ratios remained below the threshold.

Table 7. Clinical efficacy results: rituximab maintenance vs. observation in follicular lymphoma patients responding to 2nd or subsequent lines of induction treatment

End point		Statistically significant advantage of rituximab maintenance	Statistically significant advantage of observation
		OR/HR (95% CI or p value)	
PFS	Overall	HR=0.55 (p<0.0001)	ns
	After CHOP	HR=0.37 (p<0.001)	ns
	After R-CHOP	HR=0.69 (p=0.043)	ns
	Patients with PR after induction	HR=0.58 (p<0.001)	ns
	Patients with CR after induction	HR=0.48 (p=0.003)	ns
Duration of response (median)		p=0.035	ns

Table 8. Cost-effectiveness and cost-utility analysis results: rituximab maintenance vs. observation in follicular lymphoma patients responding to 2nd or subsequent lines of induction treatment

	Life years gained [LYG]	Incremental cost [PLN]	ICER [PLN/LYG]
Rituximab vs. observation	0.691	53 280	77 113
	Quality adjusted years gained [QALY]	Incremental cost [PLN]	ICUR [PLN/QALY]
	0.575	53 280	92 621

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia 1st line treatment

In patients with low grade chronic lymphocytic leukemia and slow course of the disease administration of chemotherapy can be postponed for years and watch and wait strategy applied instead. However, in some patients (about 1/3 of all cases) CLL has a more aggressive form and patient's condition deteriorates very quickly. In such cases chemotherapy should be indicated as soon as possible. The choice of chemotherapy depends on patient's general health status, age, the disease stage according to Binet or Rai classification and presence of prognostic factors. The treatment aims at achieving complete remission to prolong disease free survival, overall survival and improve quality of life (this is especially important in the older patients). There are several treatment options available; however most clinical recommendations issued by ESMO, NCCN, PUO (Polska Unia Onkologii, Polish Oncology Union) indicate immunochemotherapy with rituximab in combination with fludarabine and cyclophosphamide (R-FC) or chlorambucil monotherapy as the most optimal 1st line treatment in CLL patients. In Poland the use of rituximab in the 1st line treatment of CLL patients is financed from public resources through the catalogue of chemotherapy. The analyses were performed to assess whether the decision to finance this treatment is beneficial for patients and cost-effective from the public payer's perspective.

The systematic review performed within clinical efficacy and safety analysis helped to identify one randomized clinical trial GCLLSG CLL8 (German Chronic Lymphocytic Lymphoma Study Group) comparing the 1st line R-FC treatment with FC alone. The attempts to identify trials directly comparing R-FC vs. chlorambucil failed. Therefore indirect comparison with Bucher method was performed based on the results of GCLLSG and LFR CLL4 trials results; however due to differences in the characteristics of FC regimens used as a common comparator in both trials the results are prone to be burdened with errors.

In the GCLLSG study rituximab was administered on day 1 of each cycle at 375 mg/m2 (cycle 1) and 500 mg/m2 cycles 2-6 with standard dosages of FC regimen. In the 3-year follow up R-FC therapy prolonged progression free survival (in the general population and in subgroups analyzed: Binet stage B, patients with unfavorable prognostic factors, all age groups). Probability of achieving treatment response and complete remission was statistically significantly higher in R-FC group than in patients treated with chemotherapy alone. The overall survival was also significantly longer in patients receiving R-FC than FC (62.5 months vs. 46.8 months). The positive results for R-FC treatment were also confirmed in the subgroup analysis.

Further analysis showed that the addition of rituximab to FC regimen significantly reduces minimal residual disease levels, which can have impact on the prolongation of progression free survival.

The safety analysis indicated that R-FC increases probability of hematologic grade 3 and 4 adverse events occurrence, including neutropenia and leukopenia, although those incidents do not result in the increased probability of death. Moreover, administration of rituximab as an addition to FC regimen does not negatively influence the patient's quality of life. The overall safety profile was assessed as favorable.

Table 9. Clinical efficacy results: R-FC vs. FC in the 1st line treatment of CLL patients

Parameter	Hazard ratio (95%CI)	P value
Progression free survival	HR=0.56 (95%CI: 0.46; 0.69)	p<0.0001
Treatment response	RB=1.13 (95%CI: 1.07; 1.20)	p<0.0001
Complete remission	RB=2.05 (95%CI: 1.66; 2.56)	p<0.0001
Overall survival	HR=0.67 (95%CI: 0.48; 0.92)	p=0.012
Death	RR=0.75 (95%CI: 0.57; 1.01)	p>0.05

Table 10. Cost-effectiveness and cost-utility analysis results: R-FC vs. FC and R-FC vs. chlorambucil monotherapy in previously untreated CLL patients

Parameter	RFC vs. FC	RFC vs. chlorambucyl
Incremental LYG	0.921	1.826
Incremental QALY	0.893	1.779
Incremental costs	51 894.24 PLN	67 782.92 PLN
ICER: cost per LYG (PLN)	56 321.18 PLN	37 121.16 PLN
ICUR: cost per QALY (PLN)	58 080.35 PLN	38 107.03 PLN

The economic analysis was performed from the public payer's perspective for the comparisons of R-FC vs. FC and of R-FC vs. chlorambucil. Data on clinical practice and resources utilization were gathered in 4 oncology and hematology centers in Poland. The Markov model (progression free, progression, death) was used and cost-effectiveness and cost-utility analysis performed. Utility data came from CEAR data base. Only direct medical costs were considered as no other cost categories were identified as important for the payer. The following cost categories were included:

-1st and 2nd line therapy costs (drugs, drug administration, treatment efficacy assessment costs),

-Monitoring patient's health in progression free and progression states,

-Grade 3 and 4 adverse events treatment,

-Allogeneic stem cell transplantation costs,

-Cost of transfusion of 1 unit of blood.

Costs of drugs and procedures valuation were derived from NHF and MoH price lists. The time horizon for the analysis of costs and effects was set at 15 years (median survival of CLL patients is 3 to 10 years depending on disease stage). Discounting was applied according to AHTAPol guideline- 5% for costs and 3.5% for effects. The deterministic analysis testing influence of changes in FC and R-FC treatment costs, adverse events treatment costs, utility values, body surface area, time horizon (5 and 10 years) and discounting rates (0% for effects and costs, 5% for effects and costs, 0% for effects and 5% for costs). A probabilistic analysis was also performed.

The results of the economic analysis once again confirmed the value of rituximab treatment. ICER and ICUR values were for both comparisons (vs. FC and vs. chlorambucil) far below the threshold (56 321.18 PLN/LYG, 58 080.35 PLN/QALY and 37 121.16 PLN/LYG and 38 107.03 PLN/QALY respectively).

Sensitivity analysis results confirmed the cost-effectiveness and cost-utility of R-FC regimen. ICER and ICUR values remained far below the threshold in almost all variants of the analysis (except for the scenario when the time horizon was shortened to 5 years). The cost-effectiveness of R-FC vs. FC and of R-FC vs. chlorambucil were close to 100%.

Both clinical efficacy and economic analysis results confirm that rituximab is a beneficial and cost-effective treatment option for previously untreated CLL patients.

Chronic lymphocytic leukemia 2nd line treatment

Similarly as in previously untreated CLL patients, the 2nd line therapy (for patients with relapsed or refractory CLL) is selected by a physician according to patient's age, health state, lymphoma course and prognostic factors. The treatment aims at this stage at achieving best possible response, progression free survival and prolongation of treatment response duration, without compromising the safety aspects. As the comparators for R-FC scheme FC and bendamustine in monotherapy were selected after reviewing clinical guidelines (ESMO, NCCN). The 2nd line treatment of CLL patients in financed in Poland from public resources through the catalog of chemotherapy. In the systematic

review of Medline, Embase, Cochrane data bases, as well as ASCO (American Society of Clinical Oncology), ESMO and ASH (American Society of Hematology) conference abstract databases, one randomized clinical trial (REACH) directly comparing R-FC to FC treatment in patients with relapse or refractory CLL was identified, supplemented with abstract on quality of life of patients from REACH study presented at ASH conference. No trials directly comparing efficacy or safety of R-FC vs. bendamustine treatment were found, therefor an attempt to find data allowing for indirect comparison was made. However also this search was unsuccessful and the analysis authors concluded that there was no possibility to compare R-FC vs. bendamustine.

In REACH trial patients received rituximab on day 1 of each cycle at 375 mg/m2 in cycle 1 and 500 mg/m2 cycles 2-6. Rituximab was combined with the standard doses of FC chemotherapy. Immunotherapy was more efficacious than the FC scheme regarding progression of free survival, treatment response rate, complete and partial treatment response duration of treatment response and time to next lymphoma treatment.

Table 11. Clinical efficacy: R-FC vs. FC in patients with relapsed or refractory CLL

Parameter	R-FC vs. FC
Progression free survival (months); investigator's assessment	30.6 vs. 20.6; HR=0.65; 95%CI: 0.51; 0.82; p<0.001
Progression free survival (months); Independent Reviewing Committee	27.0 vs. 21.9; HR=0.76; 95%CI: 0.60; 0.96; p=0.0218
Treatment response; complete or partial; investigator's assessment	69.9% vs. 58.0%; RB=1.21; 95%CI: 1.06; 1.37; p=0.0034; NNT=9 (6; 26)
Complete response rate	24.3% vs. 13.0%; RB=1.86; 95%CI: 1.29; 2.69; p<0.001; NNT=9 (6; 21)
Partial treatment response	45,7% vs 44,9%; RB=1,02; 95%CI: 0,84; 1,22; p>0,05
Treatment response; complete or partial; Independent Reviewing Committee	61% vs. 49%; RB=1.24; 95%CI: 1.07; 1.45; p=0.0048; NNT=9 (5; 28)
Complete response rate; Independent Reviewing Committee	9% vs. 3%; RB=3.125; 95%CI: 1.47; 6.70; p=0.0046; NNT=17 (10; 44)
Stable disease	17.0% vs. 22.1%; RR=0.77; 95%CI: 0.55; 1.08; p>0.05
Disease progression	2.5% vs 5.4%; RR=0.47; 95%CI: 0.20; 1.09; p>0.05
Duration of response; months	39.6 vs. 27.7; HR=0.69; 95%CI: 0.50; 0.96; p=0.0252
Median time to next lymphoma treatment; months	Not reached vs. 34.3; HR=0.65; 95%CI: 0.49; 0.86; p=0.0024
Overall survival; months	Not reached vs. 52; HR=0.83; 95%CI: 0.59; 1.17; p=0.2874
Absence of minimal residual disease	43% vs. 31%; RB=1.38; 95%CI: 0.75; 2.64; p>0.05

Regarding a safety profile, there are no statistically significant differences between R-FC and FC groups in relation to probability of adverse events occurrence, including grade 3 and 4 adverse events, hematologic adverse events (neutropenia, thrombocytopenia, granulocytopenia or anemia). Quality of life analysis indicated that R-FC therapy prolongs time without disease manifestation, without increasing the risk of treatment related adverse events.

The economic analysis was prepared to assess the cost-effectiveness of R-FC treatment of patients with relapsed or refractory CLL. The calculations were done from the public payer's perspective with the 15 year time horizon for effects and costs assessment. Only following direct medial costs were considered:

-2nd and 3rd line therapy costs (drugs, drug administration, treatment efficacy assessment costs),

-Monitoring a patient's health in progression free and progression states,

-Grade 3 and 4 adverse events treatment,

-Allogeneic stem cell transplantation costs,

-Cost of transfusion of 1 unit of blood.

The three state Markov model was used and cost-effectiveness and cost-utility techniques applied. Utilities were found in the CEAR data base. Deterministic and probabilistic sensitivity analyses were performed. Discounting was performed (5% for costs and 3.5% for effects).

The R-FC treatment of patients with relapsed or refractory CLL was proven to be cost-effective from the public payer's perspective and moreover highly beneficial for patients. The results of sensitivity analysis provided evidence that conclusions on cost-effectiveness of rituximab treatment were sound and well-based.

Diffuse large B-cell lymphoma treatment

Rituximab in combination with CHOP chemotherapy is regarded as the golden standard of treatment of patients with diffuse large B-cell lymphoma. The R-CHOP regimen is financed from public resources in Poland through therapeutic programme. Immunochemotherapy is deeply set in clinical practice and the analyses were performed to justify the wide use and public financing of rituximab in the treatment of DLBCL patients.

Clinical analysis aimed at assessing the efficacy and safety of immunochemotherapy with rituximab in combination with CHOP regimen vs. CHOP alone in patients with diffuse large B-cell lymphoma. The systematic review covered among other Medline, Embase, Cochrane and CDR data bases and rendered publications on 2 randomized clinical trials for general DLBCL population and DLBCL patients with HIV co-infection. Rituximab was administered at 375 mg/m2 7 and 3 days before cycle 1 and 2 days before cycles 3, 5 and 7 every 21 days with standard dosing of CHOP regimen. Patients who achieved complete remission after four cycles received six cycles in total and those with continued response completed 8 cycles. In the HIV patients rituximab was administered at 375 mg/m2 2 days prior to each CHOP chemotherapy cycle.

Table 12. Cost-effectiveness and cost-utility analysis results: R-FC vs. FC in patients with relapsed or refractory CLL

Parameter	RFC vs. FC
Incremental costs (PLN)	48 772.15
Incremental LYG	0.62
Incremental QALY	0.61
ICER: cost per LYG (PLN)	78 709.13
ICUR: cost per QALY (PLN)	79 920.61

Patients who achieved partial or complete response received 3 monthly maintenance doses of rituximab also at 375 mg/m2.

The results of the analysis demonstrated that treatment with R-CHOP is effective and safe in all patients, regardless of age or potential HIV co-infection. Immunochemotherapy with rituximab prolonged overall survival, progression free survival, time to event and failure free survival, increased probability of complete and complete unconfirmed response. At the same time R-CHOP in comparison to CHOP alone associated with decreased probability of disease relapse, disease progression and disease progression during treatment, death due to lymphoma or an adverse event. The safety profile in general population and in patients with HIV co-infection was favourable. Although R-CHOP therapy was associated with higher risk of cardio toxicity, infusion related complications and shingles, the overall efficacy outweighed potential negative effects of R-CHOP treatment.

The economic analysis was based on the results of clinical efficacy and safety analysis. The cost-effectiveness and cost-utility analyses were performed from the public payer's perspective. All costs and effects were estimated in 30 year horizon (lifetime). The Markov model was applied with progression, progression free and death health states. The utility data were derived from the CEAR base. Patients were split into two subgroups according to age: ≥60 years and ‹60 years. The following costs were identified as crucial from the public payer's perspective and included in the analysis:

-Cost of drugs (1st and 2nd line chemotherapy),

-Drug administration costs,

-Costs of treatment efficacy assessment,

-Patient's health monitoring costs,

-Grade 3 and 4 adverse events treatment costs,

-Cost of autologous stem cell transplantation.

Only direct medical costs were included. Prices of drugs and costs of procedures were drawn from NHF and MoH price lists. Data on resource utilization and clinical practice were determined based on a questionnaire study conducted in the 5 Polish oncology and haematology centres. In line with AHTAPol guidelines costs were discounted by 5% and effects by 3.5% in the base case analysis. Deterministic and probabilistic analyses were performed. Various assumptions were checked for their impact on overall analysis results and conclusions.

Both in the under and over 60-year-old population the administration of R-CHOP instead of CHOP regimen alone allowed for gain in LYGs and QALYs. The incremental costs related to R-CHOP vs. CHOP were counterbalanced with efficacy gain rendering ICERs and ICURs values far below the threshold assumed in Poland.

All tested in sensitivity analysis options resulted in ICERs and ICURs (in both under- and over-60-years groups) far below the threshold, thus confirming efficacy and cost-effectiveness of R-CHOP treatment of patients with DLBCL.

Analyses performed for rituximab in combination with CHOP chemotherapy used in the treatment of DLBCL patients indicate that the position of rituximab as the golden standard is justified and sound. Both clinical and economic data show that administration of immunochemotherapy is beneficial for patients and cost-effective for the Polish public payer.

Table 13. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP in DLBCL over 60 patients

Parameter	R-CHOP vs. CHOP
Incremental costs (PLN)	50 905.10 PLN
LYG gain	1.696 LYG
QALY gain	1.462 QALY
ICER: cost per LYG (PLN)	30 009.60 PLN/LYG
ICUR: cost per QALY (PLN)	34 818.82 PLN/QALY

Table 14. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP in DLBCL under 60 patients

Parameter	Porównanie R-CHOP vs CHOP
Incremental costs (PLN)	47 825.94 PLN
LYG gain	2.721 LYG
QALY gain	2.321 QALY
ICER: cost per LYG (PLN)	17 577.27 PLN/LYG
ICUR: cost per QALY (PLN)	20 602.97 PLN/QALY

Discussion

Rituximab has been introduced into the clinical practice several years ago and since then became a standard addition to chemotherapy of patients with FL, DLBCL and CLL. In clinical trials Mabthera has proven its value with significant overall survival, progression free survival, event free survival and overall response time and rates improvement. The treatment with rituximab also allowed for prolongation of time to next lymphoma therapy and had a positive effect on the patient's quality of life. In terms of economic impact, the analyses that were prepared from the public payer's perspective in Poland showed that the clinical benefits are linked with very favorable economic results. In all analyzed indications Mabthera was highly cost-effective and conclusions drawn from these analyses justify financing of this treatment option from public resources. The economic results from Polish analyses were consistent with those published worldwide, where treatment with Mabthera was also proven to be cost-effective from the public payers' perspectives. Independent of health care system in which Mabthera was administered the treatment remained an effective and cost-effective option for the payers and societies (where societal perspective was assumed).

In Portugal analysis conducted for R-CVP vs. CVP treatment in previously untreated FL patients demonstrated that addition of rituximab to CVP regimen is cost-effective from Portuguese National Health System perspective (Braga 2010). Similar findings were published for the UK, where rituximab was added to MCP (mitoxantrone, chlorambucil, prednisolone), CVP, CHOP, and CHVP (cyclophosphamide, etoposide, doxorubicin, prednisolone, interferon alpha) regimens. In all of the analyzed options ICERs far below the threshold assumed for cost-effectiveness in the UK (Ray 2010). In the US were societal perspective was assumed economic analysis results also confirmed that addition of rituximab to chemotherapy is cost-effective in treatment of FL patients (Hornberger 2008). The same conclusions were drawn for maintenance treatment with rituximab after 1st line induction therapy in the Finnish health care system (Soini 2011) and for the maintenance treatment in the management of relapsed or refractory FL patients in French health care setting, where calculated ICERs fell below those observed for other therapies in the oncology (Deconinck 2010). Findings were similar in Sweden (Kasteng 2009).

Published data on cost-effectiveness of 1st line R-FC therapy of CLL patients showed that administration of Mabthera in this indication is cost-effective from a third-party payer and societal perspective in the US (Hornberger 2012). The same conclusions were drawn earlier from analyses conducted in the UK and Spain both for 1st and subsequent lines of CLL patients treatment with R-FC (Main 2010, Dretzke 2010, Casado 2011).

The DLBCL patients' treatment with rituximab also showed very good economic results in many countries. The analysis prepared by Canadian Centre for Applied Research in Cancer Control (ARCC) and British Columbia Cancer Agency confirmed that R-CHOP treatment in DLBCL patients in a cost-effective option for the payer. Similar results were observed in France (Best 2005) and the US where analyses confirmed that R-CHOP regimen is cost-

effective in older patients' population (Hornberger 2005).

The coherent clinical efficacy and safety data with positive economic analyses results place rituximab in a unique position amongst innovative oncology treatments. Regardless of health care or financing systems rituximab proves its value, even when confronted with rigid HTA requirements. Clinicians and payers have at their disposal highly valuable therapeutic option for patients.

Conclusion

Based on available randomized clinical trials results, numerous conference reports and health technology assessment dossiers prepared for Mabthera in treatment of patients with FL (I line and maintenance, II line maintenance), DLBCL and CLL (I and II line) in Poland it has been proven that it is an clinically effective and beneficial for patients and cost-effective for the public payer treatment option.

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 81-88
DOI: 10.7365/JHPOR.2012.1.12

A cost-effectiveness analysis of programmable baclofen pump therapy in children with spastic cerebral palsy

Jacek Walczak
Arcana Institute, Kraków, Poland

Marek Jóźwiak
The Children's Orthopaedic Surgery and Traumatology Clinic, University of Medical Sciences in Poznań,Poznań, Poland

Anna Jasińska
Arcana Institute, Kraków, Poland

Magdalena Garbacka
Arcana Institute, Kraków, Poland

Grzegorz Obrzut
Arcana Institute, Kraków, Poland

Wiktor Dardziński
Arcana Institute, Kraków, Poland

Abstract

Background: The purpose of this survey is to estimate profitability of using baclofen solution administered by an implanted programmable pump in treatment of spastic cerebral palsy in comparison to standard therapy of spasticity in Poland.

Methods: The cost-utility analysis of intrathecal baclofen treatment was performed from the perspective of public payer in 6 years' time horizon, using Markov model, constructed in the frame of computer program TreeAge® Pro Suite 2008. The target population are children with severe spasticity in cerebral palsy which is refractory to current treatment options. Annual discount rate was set equal to 5% both for costs and the health effects. Assumptions of the analysis were tested in one- and multiway sensitivity analysis.

Results: A gain of one quality adjusted life year (QALY) in child with spasticity costs 60 224 PLN (17 126 €) when standard treatment is replaced with baclofen pump therapy. Conclusion. Intrathecal baclofen pump therapy in children with spastic cerebral palsy is a cost-effective strategy in Poland.

Keywords: spasticity, intrathecal baclofen, baclofen pump, cost-utility, cerebral palsy

Introduction

Cerebral palsy is a non-progressive but non-constant disorder of posture and motion in children caused by central nervous system damage during an early stage of development, coexisting with some other symptoms: cognitive functions and speech development disorders, epilepsy, mental impairment, sight and hearing disorders. In Poland there are 2-3 children diagnosed with cerebral palsy per 1000 live births, giving 20-25 thousand children with this disease.

The purpose of spasticity management is to improve motor activity, preventing complications, decreasing pain and facilitation of nursing. Currently, there are several ways of increased muscular tone treatment: rehabilitation, farmacotherapy with oral spasmolytic medicines, focal treatment with botulinum toxin and orthopaedic surgeries aiming to reduce results of muscle contractures. The therapy with botulinum toxin in cerebral palsy in Poland is financed by NHF (National Health Fund) as the therapeutic program of spasticity treatment. Small invasiveness and lack of side-effects are advantages of rehabilitation, but on the other hand the

effect of reducing spasticity is short-lasting and temporary . One of the recent methods is a therapy based on subarachnoidal infusion of baclofen by the means of a programmable baclofen pump. This treatment is recommended especially for patients who suffer from severe, chronic spasticity, when conventional pharmacological therapy is ineffective in their case and when the outer pump with a transcutaneous catheter or the injections of a medicine directly into the spinal cord or into an internal organ are either not effective enough or uncomfortable for a patient .

In the analysis the costs and the health benefits of treatment with a programmable baclofen pump and the currently financed therapy of spasticity in children were compared.

Materials and methods

Population

The target population are children with significant, chronic spasticity of cerebral origin, who are refractory to available treatment methods and showing positive response to baclofen test dose.

Intervention

Intrathecal baclofen (ITB) continuously administered by an implantable, programmable infusion pump was assessed. Concomitant therapy includes rehabilitation, other medicines and orthopaedic surgery. Baclofen administered intrathecally in a continuous way by an infusion pump is recommended for treatment of patients with severe spasticity that cannot be effectively managed with oral baclofen.

Comparator

The compared strategy is current standard therapy, which includes rehabilitation, oral pharmacotherapy, focal treatment with botulinum toxin and orthopaedic surgery.

Clinical outcomes

The health effects in the cost-utility analysis are measured by the quality adjusted life-years (QALY) gained.

Perspective

The cost-utility analysis was performed from the perspective of public payer for health services in Poland (National Health Fund).

Time horizon

For battery working time is limited, the process of pump implantation must be repeated every 5-7 years [3, 4]. When the battery runs down the whole pump has to be replaced with a new one. Pump lifespan is also partially determined by durability of the membrane, through which the insertions supplementing medicine are made. The time horizon of the cost-utility analysis was 6 years, assuming that during such a period one infusion pump is used.

Analytical technique

In order to compare the two treatment options a cost-utility analysis (CUA) was carried out, the results of which are the additional costs for the quality adjusted life-year (QALY) gained when replacing standard treatment with ITB therapy. The cost-utility analysis was performed using Markov model, constructed in the frame of computer program TreeAge® Pro Suite 2008. Annual discount rate was set equal to 5% both for costs and the health effects. Assumptions of the analysis were tested in one- and multiway sensitivity analysis.

Data resources

The resources of data concerning efficacy and safety of the two treatments compared. Resource use were clinical trials found through systematic review method of retrieval, other economic analyses and opinions of medical experts.

Clinical effectiveness based on systematic review

The aim of the systematic review [5] was to evaluate the clinical effectiveness of the intrathecal baclofen in the treatment of spasticity due to various etiology on the basis of systematic literature review.

Only randomized trials including a control group were included into the analysis. One study met the inclusion criteria (randomized controlled trial, comparing intrathecal baclofen therapy plus conventional therapy versus conventional therapy alone), conducted in patients with intractable spastic cerebral palsy (CP). No randomized studies regarding clinical efficacy of baclofen pumps in spasticity treatment in other disease entities (multiple sclerosis, stroke, brain injury, spinal cord

injury) were found. Thus, analysis for these indications was based on non-randomized trials without control groups.

The comparative analysis in patients with CP revealed a positive impact of continuous intrathecal baclofen infusion (CITB) measured in Visual Analogue Score (VAS) after 6 and 12 months and in Child Health Questionnaire – Parent Form 50 (CHQ-PF50) after 12 months of therapy. The safety analysis in an open label phase revealed 51 cases of adverse events (AEs) and 29 device adverse events (DAEs). The results suggests high clinical efficacy and safety of the infusion of intrathecal baclofen in the therapy of spasticity of CP.

Model description

The decision model was performed using Markov model to compared ITB and standard therapy in 6 years' time horizon, whereas the length of a single cycle (frequency of patient's state changes) was set to be 1 year. In the constructed model the states representing crucial events in the course of cure of spasticity from clinical and economical points of view were singled out. In any fixed cycle a patient is only in one state and a transition to another state and staying within the same state happen with prescribed probabilities. There are costs, utilities and transition probabilities attributed to each state and this allows to evaluate long-term costs and health effects of the therapies analyzed. A graphical depiction of the model structure (health states and possibilities of transitions between them) is displayed on Figure 1.

In the compared strategies of spasticity treatment the following health states were singled out:

baclofen pump:

-success,

-failure,

-death.

standard treatment:

-survival,

-death.

The state of "success" in case of baclofen pump therapy was defined as an improvement of health condition, meaning the increased mobility, self-care and functional status, improvement of comfort and sense of well-being and decrease in pain. This state has ascribed costs connected with ITB and concomitant therapies and corresponding utility value. The model takes into consideration a possibility of the therapy failure, too, because of adverse events or lack of effectiveness (the state of "failure"), which can lead to the necessity of baclofen pump removal. In case of therapy withdrawal (because of severe side-effects making intrathecal infusion of baclofen impossible or the lack of getting the expected health effect) a patient switches to the standard treatment, but in some instances the baclofen pump can be implanted again allowing the intrathecal baclofen therapy to be continued. If the therapy fails then there are additional costs of removal of the baclofen pump and possibly the costs of repeated implantation; furthermore one takes into account a reduction in health state utility value.

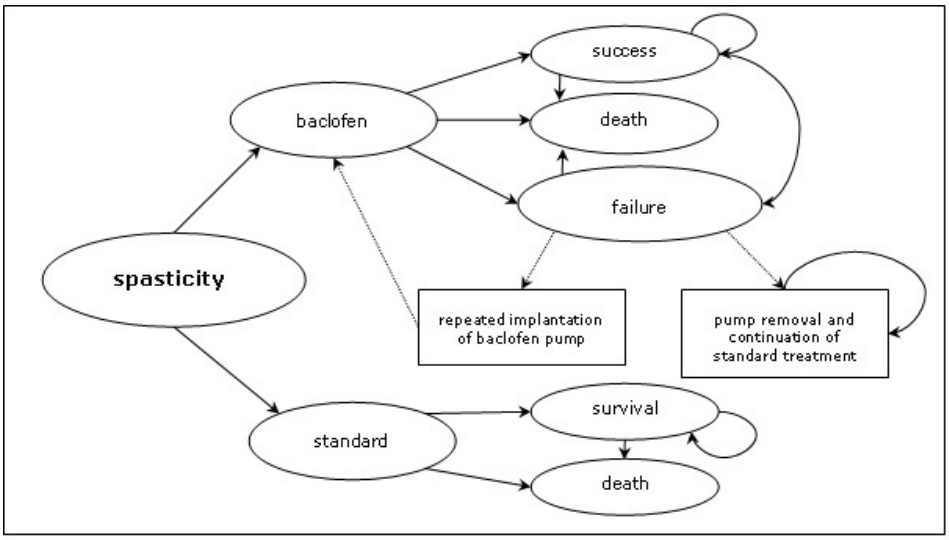

Figure 1. Structure of the model

The target population are children, who are refractory to available treatment methods, so in the standard therapy there are the state of "survival" involves average annual costs per patient with spasticity and an appropriate value of the utility index. All the states in the model take into consideration treatment costs of possible adverse effects/medical incidents connected with the therapies applied. With the same probability one can pass from each state to the state "death" (based on the evaluated death risk in cerebral palsy).

Cost analysis

In order to calculate the costs of both therapies compared the perspective of public payer (National Health Fund) was assumed. The following sources of direct costs linked to the medical treatment of spasticity were taken into consideration:

- ITB treatment: cost of baclofen test, cost of pump implantation/removal, costs of pump refill visits, costs of complications connected with ITB therapy and costs of concomitant therapy (rehabilitation, other medicines and surgical treatment),

- standard treatment: costs of rehabilitation (including orthopaedic equipment and outpatient visits), oral pharmacotherapy, focal treatment and surgical operations, costs of standard therapy (oral medicines and botulinum toxin) complications and costs of curing pressure sores.

An exact evaluation of expenditures resulting from spasticity treatment in Poland was made according to experts' estimations (questionnaires sent to specialist centers of spasticity treatment and rehabilitation in Poland) and available literature concerning the topic. The pricing of the discussed resources was carried out on the base of the National Health Fund charges (concerning medical services and medicines by the new clearing system based on Diagnosis Related Groups classification, valid since July 1, 2008) in agreement with perspective of the analysis. Evaluated average annual costs connected with spasticity management per one patient with baclofen pump and cured with standard treatment is displayed on the Table 1.

Considering the 1-year cycles in the cost-utility model, the costs of ITB complications treatment were counted in the year of therapy. The costs of complications arising from the ITB treatment were calculated as equal initially to 276 PLN and 48 PLN in the successive years of the time horizon of analysis (years 1-6).

Parameters of the model

Population

It was supposed in the model that patient beginning therapy is 12 years old on average (mean age was evaluated on the basis of patients' age data from clinical trials concerning effectiveness of the baclofen pump treatment).

Utilities

Utility weights for various health states occurring in the model com from the analysis of de Lissovoy et al. [6]. The lowest average utility value was obtained when there was no ITB therapy (in the population whose spasticity was not controlled by standard therapy) and it equals 0,125 (SD=0,058). The utility increased slightly in the initial phase of ITB therapy (with a pump) to the value of 0,162 (SD=0,048). As a result of the long-term treatment the average utility value attained 0,401 (SD=0,106) [6].

Withdrawal from therapy

Depending on a trial and period of time, the percentage of patients who withdraw from ITB therapy fluctuates from 4% [7,8] up to about 48% [9,10]. Probability of quitting the therapy because of adverse effects or lack of effectiveness in a 1 year cycle of treatment in the model was determined on the basis of the trial of Vender 2006 [11] since there were long period of time and a numerous group of patients considered and additional information about the number of patients with a repeated pump implantation procedures. The obtained percentage of patients withdrawing from the therapy (Pwithdraw=22,41%) was transformed into a risk of withdrawal per one cycle of the model (pc=4,95), assuming equal probability of therapy withdrawal in each cycle and using the formula (pc=1-(1-Pwithdraw)1/c), where denotes the number of years in the trial. The probability of a repeated pump implantation after its removal was evaluated according to the percentage of total abandoning of therapy also from Vender et al. [11] (it is equal to 0,885).

In case that severe unwished effects have shown up, which result in compulsory removal of the baclofen pump, the health state utility index was assumed to lower by 50% for a half of year.

Table 1. Costs of spasticity treatment – ITB therapy and standard treatment

Component of costs		Child with baclofen pump [PLN]	Child cured with standard treatment [PLN]
Baclofen test		624	-
Implantation/reimplantation of baclofen pump *		33 700	-
Pump removal procedure		7 700	-
Control visits in order to refill pump	The 1st year	11 060	-
	Consecutive years	12 640	-
Complications resulting from ITB treatment	At most 60 days after pump implantation	276,20	-
	At least 60 days after pump implantation	511,63	-
Standard treatment	Rehabilitation	5 293	7 439
	Orthopaedic equipment	6 009	6 009
	Oral medicines	8,2	58,1
	Focal treatment with botulinum toxin	287,1	2 647,6
	Orthopaedic surgery	1 285	3 597,9
	Outpatient visits in an orthopaedic clinic	109,5	109,5
Complications resulting from standard therapy	Oral medicines	-	7,96
	Botulinum toxin	-	414
Pressure sores treatment		-	154

***including cost of procedure, cost of medical device and Lioresal Intrathecal, cost of in-patient stay**

Mortality

Information on mortality rate of children with cerebral palsy was calculated on the basis of general mortality of children population with cerebral palsy in United Kingdom excerpted from Hemming 2005 [12]. No analogical Polish data were identified in the search. The probability of 5-years' survival for a 10-years old child was evaluated as 0,973 and as 0,963 for a 15-years old child.

Annual probability of death for patients in separate age groups was calculated using the formula, where "h" denotes the relative hazard, it equals 0,00553 for children between 10 and 15 years old and 0,00756 for those between 15 and 20 years old.

RESULTS

Cost-utility analysis

A compilation of health effects and costs per one patient, which were obtained as a result of the cost-utility model calculation is displayed in Table 2.

The incremental cost-utility ratio (ICUR) for the comparison of continuously administered ITB therapy to standard therapy (ST) of spasticity in a 6 years' time horizon was determined from the following formula:

ICUR = (costITB - CostST) / (EffectITB - EffectST)

The cost-utility analysis proved that ITB treatment together with concomitant therapy is more expensive but more effective than standard therapy.

Total costs of baclofen pump therapy amount to 142 369 PLN (40 485 €)[1], whereas the costs of standard therapy come to 64 252 PLN (18 271 €) in 6 years' time horizon. The incremental cost-utility ratio (ICUR) equals 60 224 PLN/QALY (17 126 €/QALY).

In conformity with the recommendation of the AOTM[2] Consultative Council [13] and a principle accepted by WHO (World Health Organization) and on the basis of CSO[3] [14] data the profitability threshold in Polish circumstances is 91 914 PLN (26 137 €) for a unit of effect. Thus, the ITB therapy is a cost-effective strategy in Poland.

Sensitivity analysis

In order to investigate an influence of a change of the key parameters and the settings of model on results of the cost-utility analysis, one-way and multi-way sensitivity analyses were performed.

The results of one-way sensitivity analysis confirmed that ITB therapy of spasticity in children remains more expensive, but still more effective than standard treatment (Table 3). The value of ICUR fluctuated within -40,7% (assuming that the frequency of visits in order to refill the baclofen pump is once per 3 months) up to +26,5% (assuming higher probability of abandoning the therapy because of adverse effects or lack of effectiveness of the therapy), only when 1 year's time horizon was considered the ICUR ratio value jumped to 206 793 PLN (growth of 243% compared to the basic value). Changes of the remaining parameters have a minor influence on the result of analysis (maximal deviation is 19%). In each of the cases under consideration (except 1 year's time horizon) in the sensitivity analysis, the ITB therapy remained a cost-effective technology. The multi-way sensitivity analysis demonstrated that the biggest changes of the ICUR from the basic value occurred when the minimal (maximal) utility value for baclofen pump therapy and simultaneously the maximal (minimal) utility value for standard therapy (changes respectively of +67,5% and -28,7%) are supposed.

Table 3. Results of one-way sensitivity analysis

No.	Parameter	Notes	ICUR [PLN/QALY]
1.	Basic value		60 224
2.	Increased cost of baclofen test	Diagnostic stay longer than 2 days	61 630
3.	Frequency of visits in order to refill the pump – once per 3 months		35 705
4.	Minimal costs of rehabilitation	Based on questionnaires	64 604
5.	Maximal costs of rehabilitation		54 533
6.	Minimal costs of focal treatment		63 855
7.	Maximal costs of focal treatment		49 843
8.	Complications of ITB treatment costs -30%		60 103
9.	Complications of ITB treatment costs +30%		60 345
10.	Lack of standard treatment complications		61 323
11.	No botulinum toxin treatment in baclofen pump treatment patients group		59 110
12.	No botulinum toxin treatment in standard treatment patients group		71 564
13.	Equal costs of orthopaedic treatment in both groups		61 986
14.	Costs of orthopaedic treatment -50% in both groups		61 105

No.	Parameter	Notes	ICUR [PLN/QALY]
15.	Costs of orthopaedic treatment +50% in both groups		59 343
16.	No necessity of orthopaedic surgeries in patients cured with baclofen pump therapy		59 245
17.	No necessity of orthopaedic surgeries in patients cured with standard therapy		62 965
18.	Lower probability of ITB pump therapy withdrawal	Based on Gilmartin 2000	56 876
19.	Higher probability of ITB pump therapy withdrawal	Based on Murphy 2002	76 180
20.	No costs and health effects discounting		56 468
21.	1 year's time horizon		206 793
22.	Minimal utility values	Based on de Lissovoy 2007	67 712
23.	Maximal utility values		54 227
24.	5% discount rate for costs and 0% for health effects		51 948
25.	5% discount rate for costs and 3,5% for health effects		57 696

Discussion

No other economical analysis estimating profitability of using ITB therapy in spastic cerebral palsy in Poland were identified, hence an external validation was conducted on basis of analyses performed for other countries, and so for other health care systems. As a result of search of economical analyses (databases: PubMed, Cochrane Library, CRD Database, NICE) two analyses estimating the profitability of baclofen pump treatment of spasticity in children were found (Hoving 2008 [15], de Lissovoy 2007 [6]). In the analysis of Hoving 2008 [15] standard therapy was defined to include physiotherapy, speech therapy, occupational therapy, while in the analysis of de Lissovoy 2007 [6] – as a conventional medical and surgical care. Present analysis in concordance with the currently used clinical practice in Poland, defines standard treatment of major spasticity as an entirety of activities serving to improve the functional conditions. The calculations were made for 6 years' time horizon, whereas in both abovementioned foreign analyses the results were presented for shorter periods: 1 year – Hoving 2008 [15] and 5 years – de Lissovoy 2007 [6].

The analysis of de Lissovoy 2007 [6] seems to be the most similar with regard to the method applied (similar time horizon, health state utilities in the model were evaluated on the basis of the analysis of de Lissovoy [6]). Results presented in de Lissovoy [6] are consistent with the results of present analysis with respect to the health effects obtained. Using ITB therapy in comparison to standard therapy one gains 1,19 QALYs in a 5 years' time horizon. In this analysis ITB therapy in 6 years' time horizon together with concomitant therapy compared to standard therapy, allows to gain 1,30 QALYs.

The ICUR ratio obtained in the analysis of de Lissovoy [6] (42 000 $/QALY) does not exceed profitability threshold for a unit of effect in American conditions (it is a cost-effective technology). The difference of final ICUR result compared to present analysis may stem from different discount rate assumed in the analysis of de Lissovoy [6] (3% for costs and health effects), shorter time horizon (5 years) and, presumably, distinct cost data (there was no detailed information about it, only the total cost calculated on the basis of resource use in a group of a dozen or so of children; in both compared groups therapy costs were significantly higher than in Polish conditions).

An additional difference between the discussed analyses is the approach to possible complications connected with ITB treatment. Merely, in the analysis of de Lissovoy [6] the treatment costs of adverse effects were not taken into account in basic variant (these costs were considered in an extra scenario, in which the final result was observed to reach 45 700 $/QALY). Moreover, patients' withdrawal from baclofen pump therapy was not entertained, while in present analysis both the costs of adverse effects treatment (in both of compared groups) and costs of possible baclofen pump removal – and of repeated implantation in some circumstances – together with decrease of the health state utility which follows side-effects, were all considered. In the Dutch analysis of Hoving 2008 [15] effectiveness of baclofen pump therapy was measured in the VAS (Visual Analogue Score) scale, still the life quality was estimated using the EQ-5D questionnaire. In the analysis of Hoving 2008 [15] gaining one additional QALY costs 32 737 € in 1 year's time horizon. Authors of the analysis did not gave the results in a form of QALY and it complicates a comparison of the difference of health effects to those from the present analysis. The ICUR ratio obtained in the Dutch analysis does not surpass profitability threshold (80 000 €) for a unit of effect – the infusion pump therapy is a cost-effective technology.

Acknowledgements

The analysis was prepared on request of the Medtronic Poland Sp. z o.o. company. We are especially indebted to prof. UM dr hab. med. Jarosław Sławek and lek. med. Anna Świerczyńska for their help.

[1] €=3,1566 PLN; mean echange rate in 2008

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Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 89-92
DOI: 10.7365/JHPOR.2012.1.13

Time and Motion Study of Anaemia Management with Erythropoiesis Stimulating Agents in Haemodialysis Units in Poland

Wiesław Klatko M.D., Ph.D.
Head of Nephrology Department, Specialist Voivodeship Hospital , Ciechanów
(Specjalistyczny Szpital Wojewódzki, Ciechanów)

Jacek Felisiak M.D.
Head of Nephrology Department with Dialyses Center, Voivodeship Hospital ,Zielona Góra
(Szpital Wojewódzki, Zielona Góra)

Abstract

Anaemia is a common complication of chronic kidney disease (CKD) contributing to morbidity, mortality and reduced quality of life of patients. Anaemia management is time consuming for healthcare professionals and patients. A major challenge for haemodialysis centers is to improve efficiency while maintaining high standards of care. The objective of our study was to compare time spent by healthcare professionals for routine renal anaemia treatment in haemodialysis centers with short acting erythropoiesis stimulating agents (ESA),which are administered 1-3 times a week vs. long acting agent, administered once a month – methoxy polyethylene-glycol epoetin beta (Mircera®). The study was a multicentre, prospective, observational study using time and motion methodology and conducted in Poland, France and Italy. Here we present the results from the Polish centers only (three Polish centers participated in the study). The observed annual time per patient receiving short-acting ESAs ranged from 176 to 380 minutes, while for Mircera® once per month, the expected time per patient per year ranged from 21 to 68 minutes (from 54 to 111 injections avoided per patient per year; from 82% to 88% reduction of time vs traditional ESAs). Our study showed that a substantial reduction in time spent on ESA administration may be achieved by converting from shortacting ESAs to once monthly treatment with Mircera. Such savings may allow healthcare resources to be reallocated to other aspects of patient management, thereby enhancing the overall quality of dialysis care, and potentially enabling improvements in clinical outcomes.

Key words: Time and Motion, haemodialyses, renal anaemia, erythropoiesis stimulating agents

Background and rationale

Anaemia is an important and frequently occurring complication of chronic kidney disease (CKD). Erythropoiesis-stimulating agents (ESAs) are standard treatment for renal anaemia1. Effective treatment of anaemia using ESAs such as epoetin alpha and its biosimiliars, epoetin beta or darbepoetin alpha requires injections ranging from 3 times weekly to once every 1-2 weeks [2-5]. Mircera® (methoxy polyethylene glycol-epoetin beta) is approved by the European Medicines Agency for the treatment of symptomatic anaemia in patients with CKD. In Phase II and III trials once-monthly Mircera® had similar efficacy to the traditional ESAs [6]. In view of the increasing health care costs it is desirable to improve cost-effectiveness while maintaining high standards of care. A reduction of the frequency of ESA injections may lead to the hospital staff workload savings, thus allowing more time to perform other necessary tasks. A recent study assessing the personnel time and supplies for anaemia management with currently available ESAs in haemodialysis centres showed, that with the use of once-monthly Mircera® the time necessary for anaemia management activities was 79% to 84% shorter vs mix of other ESAs, and additional savings could be generated with respect to nonobservable tasks [7]. The current study compared the time spent by health care personnel in haemodialysis centres on anaemia-related tasks in patients treated with Mircera® vs other ESAs in real-life setting.

Objectives

The primary objective was to document health care personnel time for anaemia management-related tasks when using various ESAs, including Mircera®, in patients with end-stage renal disease (ESRD) undergoing haemodialysis. The secondary objective was to obtain qualitative information on changes in practice patterns observed and/or expected as a result of the introduction of once-monthly Mircera® maintenance therapy.

Methods

Prospective, observational study conducted in several centres in 5 European countries. The time used for ESA-treatment related activities was assessed using the time and motion methodology and qualitative information on less frequent activities was obtained through interviews. The study was conducted in various centrs in Germany, France, Italy, Spain and Poland. This report presents the data and results from the three Polish hemodialysis centres that participated in the study. The time and motion methodology includes dividing a process (i.e. anaemia management) into key tasks, and repeated observations of each task to assess the average time needed to perform it. The sum of the average times spent on each activity yields total average time for the complete process. This study focused on frequent and observable activities related to the management of anaemia using ESA. The time and motion data were collected during haemodialysis sessions during which at least one patient received ESAs (defined as any ESA except for Mircera®) and/or Mircera®. The dialysis sessions when an ESA or Mircera® were administered were classified as "ESA session" or "Mircera® session", respectively. The anaemia management tasks suitable for time and motion observations were the activities related to the preparation, distribution, injection, record-keeping, and inventory/ordering of ESAs. Two types of activities were distinguished: the activities performed in a group of patients called "per group" activities, and the activities performed in an individual patient called "per patient" activities.

Endpoints

The primary study endpoints were: 1) Observed health care personnel time (total and by type of professional) per patient using ESAs vs. Mircera® per session;
2) Time per patient using ESAs vs. Mircera® per year (including average time per session for ESAs multiplied by average number of ESA sessions per patient per year and average time per session for Mircera® multiplied by 12 injections per patient per year);
3) observed time for all patients in the centre per year using ESAs and Mircera®. The secondary endpoints included the extrapolation of the Mircera® uptake for the entire centre from 0% to 100% using estimated time per patient per year for ESAs vs. Mircera. This allowed to calculate time savings obtained by the switch from ESAs to Mircera®.

Statistical analyses

For each sample, descriptive statistics were calculated (N, mean, min, max, standard error). For each activity, 95% confidence intervals (CI) were calculated. For each per group activity, a Generalised Linear model was used to determine if group size was a predictor or time or not. If group size mattered (p value < 0.1), the analysis used the adjusted coefficients for the Mircera sample. If group size did not matter, the unadjusted coefficients were used instead.

Regulatory and ethical considerations

The study did not affect the treatment that patients would have received anyway, so patient informed consent was not required. Patient demographics were not collected.

Description of Polish centres

The centres that participated in this study were Ciechanów (C01), Zielona Góra (C02) and Łódź (C03). The number the treated patients with ESRD ranged from 60 (C01) to 136 (C03).

Quantitative results

In all three centres the average time for observed anaemia management tasks per patient per session was 3.25 minutes for ESAs and 3.03 minutes for Mircera®. In C01 and C02, activities were performed for each patient individually, so average times per ESA vs. Mircera® patient were directly comparable. In C03, preparation and distribution activities were performed per group of patients. The average size of groups varied substantially in the two samples: average of 10

patients per session received ESAs while average 2 patients received Mircera®. Based on the current average number of ESA sessions per patient in each centre, a patient switched to Mircera® would generate time savings from 82% (C01) to 88% (C02 and C03). Based on expected time per patient per year for ESAs vs. Mircera, and the number of patients treated with ESAs vs. Mircera, the annual time spent on anaemia management was extrapolated per centre. Total time per centre ranged from 170 hours or 21 working days (C02) to 397 hours or 50 working days (C03). Results cannot be compared across centres because of differences in numbers of patients in each centre, percentage uptake of Mircera, and the expected annual number of ESA sessions per patient.

Efficiency gains were obtained by avoiding injections, and the time used for the observed activities. The number of injections avoided per patient per year ranged from 55 (C01) to 112 (C02). Potential additional time savings could be due to less frequent anaemia management activities, such as inventory, ordering, and storage. In order to compare efficiency gains across centres, time savings (hours) for the extreme scenarios of 100% Mircera® and 0% Mircera® uptake were calculated. Time savings ranged from 221 hours in C02 to 477 hours in C03, translating into reductions ranging from 82% (C01) to 88% (Centres 2 and 3).

Qualitative results

Questionnaire 1 (answered by the head nurse and a nephrologist) included blood sampling, inventory, ordering, storage at the ward and physician visits. Two centres expected a decrease in the frequency of ad hoc tests with a switch to Mircera®. All centrs expected overall time savings for inventory and ordering, and only about half of the refrigerator space needed for ESAs would be used in case of the complete switch to Mircera®. Physician visits for assessment of anaemia status would be reduced from daily/weekly to monthly.

Questionnaire 1 (answered by a pharmacist at the centre pharmacy) included time of inventory or ordering activities. The pharmacy in one centre reported no reduction in time of inventory or ordering activities after the switch to Mircera®, while a pharmacy in another center believed that up to 50% of time dedicated to receiving orders from the ward and ordering ESAs from wholesalers could be saved. Pharmacy in the third center did not respond. Questionnaire 2 (answered by the head nurse) included several questions concerning functional aspects of the switch from ESAs to Mircera® with respect to various personnel activities. All three centers observed/expected functional changes in the unit, including lower frequency and/or less total time required for the inventory of ESA at the pharmacy and at the ward, ordering of ESA at the pharmacy and at the ward, less refrigerator space necessary for ESAs at the pharmacy and at the ward as well as less time spent on the preparation and injections of ESAs.

Conclusions

The results of the study show that 100% conversion to once-monthly maintenance therapy with Mircera® would offer annual time savings on frequent anaemia management tasks in the range of 82% to 88% compared to a scenario where only traditional ESAs are used (absolute time savings with 100% conversion in the range of 221 to 477 hours). These results confirm the findings from the previous study assessing the use of Mircera® administered once per month in Germany and the UK [7]. Total observed annual time per centre ranged from 175 to 397 hours. Comparison of the times in respective centers is difficult due to variations of percentage uptake of Mircera® (from 22% to 34%; average 29%) expected annual number of ESA injections per patient (from 68 to 124; average 93 sessions) and the number of patients treated in the centre (from 60 to 136; average 94 patients). The observed annual time per patient receiving traditional ESAs ranged from 176 to 380 minutes, while for Mircera® once-monthly the expected time per patient per year ranged from 21 to 68 minutes (from 54 to 111 injections avoided per patient per year; from 82% to 88% reduction of time vs traditional ESAs). Information on other less frequent and/or nonobservable anaemia management related activities was assessed qualitatively through interviews with one key centre healthcare staff member (the head nurse). Inventory/ordering frequency for Mircera® was expected to be reduced in all centers. All centers expect that substantially less refrigerator space would be needed if only Mircera® was used. With respect to scheduled blood testing the results varied by center but the conversion to once-

monthly Mircera® maintenance therapy may have some impact on reducing the frequency of blood testing. Two centers expected the frequency of the nephrologist assessment of anaemia status during a daily ward round to be reduced. The pharmacies in all three centres reported less total time needed for inventory, ordering and refrigerator space due to introduction of Mircera®. The analysis has shown that once-monthly Mircera® (12 injections per year) maintenance therapy results in substantial time savings, allowing healthcare resources to be allocated to other important ESRD related healthcare needs. The respondents believed that once-monthly Mircera® leads to significant benefits to the center as a whole and for nursing staff, with somewhat lower benefits perceived for nephrologists and patients. Centers believed that the time freed up from converting to Mircera® would lead to overall improved anaemia management. The respondents believed that this time could be spent on a wide range of activities, but in particular "improving overall CKD care", "instructions on AV-shunt care", and "documenting patient parameters".

In conclusion, with traditional ESAs, hemodialysis centers spend a substantial amount of time per year on tasks related to anaemia management. Our study showed that a substantial reduction in time spent on ESA administration and associated costs may be achieved by converting from traditional ESA regimens to once monthly treatment with Mircera. Such savings may allow healthcare resources to be reallocated to other aspects of patient management, thereby enhancing the overall quality of dialysis care, and potentially enabling improvements in clinical outcomes.

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The study was sponsored by Roche Polska. Medical writing of this article was provided by Roche Polska and performed by Mikołaj Kobielski M.D., Ph.D.; Quality Audit House. House.

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 93-94
DOI: 10.7365/JHPOR.2012.1.14

Nowoczesne narzędzia informatyczne w procesie monitoringu refundacyjnego

lek.stom. Norbert Wilk
Instytut Arcana

mgr Krzysztof Kloc
Instytut Arcana

Abstrakt

Tło: Działalność w obszarze refundacji, ze względu na silne otoczenie konkurencyjne oraz uwarunkowania prawne, wymaga doskonałej wiedzy na temat wszystkich szans i zagrożeń refundacyjnych.

Metoda: W tym celu opracowano narzędzie umożliwiające sprawne i kosztowo-efektywne identyfikowanie oraz przekazywanie wszelkich informacji związanych z finansowaniem technologii medycznych ze środków publicznych. W ramach monitoringu obserwacją objęte jest ponad 150 różnorodnych źródeł informacji, w tym czasopisma naukowe, agencje rejestracyjne, instytucje wydające wytyczne kliniczne oraz rekomendacje refundacyjne a także internetowe wydania prasy branżowej oraz codziennej. Monitoring prowadzony jest z wykorzystaniem specjalistycznych narzędzi informatycznych.

Wyniki: Odnalezione i przeselekcjonowane informacje, w postaci codziennego newslettera, przekazywane są odbiorcom za pośrednictwem zaprojektowanej w tym celu bazy komputerowej.

Wnioski: Monitoring refundacyjny to użyteczne narzędzie umożliwiające identyfikację istotnych informacji związanych z refundacją oraz sprawne codzienne ich przekazywanie do określonych odbiorców.

Słowa kluczowe: monitoring, newsletter, market access, refundacja

Abstract

Background: Activities in the field of reimbursement, due to strong competitiveness and legal constraints, require great knowledge on every funding opportunities and threats.

Methods: For this purpose a tool has been developed which enables efficient and cost-effective identification and forwarding of any information related to financing of health technologies with public funds. During the monitoring process over 150 different sources of information are being observed, including scientific journals, regulatory agencies, institutions developing clinical guidelines and reimbursement recommendations and also on-line versions of specialist and daily press. Monitoring process is conducted using specialized computer tools.

Results: Information which has been found and selected is forwarded to the recipients in a form of a daily newsletter using a computer database designed for that purpose.

Conclusions: Reimbursement monitoring is a useful tool for identification of significant information related to reimbursement and for effective, daily transmission of this information to specified recipients.

Keywords: monitoring, newsletter, market access, reimbursement

Tło

Decyzje związane z finansowaniem ze źródeł publicznych wymagają danych z różnych źródeł i dziedzin wiedzy. Aktualnych informacji potrzebują zarówno przedstawiciele administracji zarządzający środkami publicznymi, jak i producenci leków starający się o uzyskanie finansowania. Nierzadko kluczem jest czas – im szybciej wiadomość dotrze do odbiorców, tym więcej mają czasu na odpowiednią reakcję.

Cel

Opracowanie narzędzia umożliwiającego sprawne i kosztowo-efektywne wyszukiwanie oraz identyfikowanie wszelkich informacji mogących mieć istotny wpływ na sytuację refundacyjną wybranych leków lub na system finansowania leków w Polsce.

Metoda

W ramach monitoringu gromadzone i przekazywane do odbiorców są informacje bezpośrednio związane z określonymi lekami oraz informacje dotyczące systemu refundacji leków lub potencjalnie mogące mieć w pływ na ten system. Aby zapewnić wysoką skuteczność monitoringu,

obserwacją objęte jest ponad 150 różnorodnych źródeł informacji.

Pod kątem nowych pierwotnych i wtórnych dowodów naukowych w zakresie efektywności klinicznej oraz kosztowej leków oraz wszelkich opracowań dotyczących organizacji systemu opieki zdrowotnej monitorowane są czasopisma naukowe tj. The New England Journal of Medicine (NEJM), British Medical Journal (BMJ), The Lancet oraz bazy publikacji naukowych tj. PubMed i Cochrane Library. W zakresie informacji związanych z bezpieczeństwem, wskazaniami do stosowania oraz obrotem leków monitorowane są instytucje wydające decyzje rejestracyjne w kraju jak i na świecie czyli Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Europejska Agencja Leków (EMA), Amerykańska Agencja ds. Żywności i Leków (FDA) oraz urzędy rejestracyjne z Wielkiej Brytanii, Kanady, Nowej Zelandii oraz Australii.

Doniesienia na temat nowych lub zaktualizowanych wytycznych i rekomendacji klinicznych identyfikowane dzięki ciągłej obserwacji stron internetowych wydających je towarzystw i organizacji naukowych tj. National Guideline Clearinghouse (NGC), American Cancer Society (ACS), National Cancer Instutute (NCI), European Cancer Organisation (ECCO), Institute for Clinical Evaluative Sciences (ICES).

Pod kątem rekomendacji refundacyjnych oraz decyzji refundacyjnych monitorowane są krajowe i zagraniczne ministerstwa ds. zdrowia oraz rządowe agencje i instytucje HTA, m.in. Agencja Oceny Technologii Medycznych (AOTM), National Institute for Health and Clinical Excellence (NICE), Scottish Medicines Consortium (SMC), Pharmaceutical Benefits Advisory Committee (PBAC), Pharmacology and Therapeutics Advisory Committee (PTAC) oraz Canadian Agency for Drugs and Technologies in Health (CADTH).

Monitoringiem objęte są również mass-media czyli popularne portale informacyjne, internetowe wydania prasy codziennej oraz stacji radiowych i telewizyjnych. Źródła te są monitorowane pod kątem wszelkich informacji istotnych z punku widzenia sytuacji refundacyjnej wybranych leków oraz całego systemu opieki zdrowotnej w Polsce i wybranych krajach. Równoległe monitorowanie wielu źródeł przy zachowaniu odpowiednio wysokiego poziomu czułości jest możliwe dzięki zastosowaniu nowoczesnych narzędzi informatycznych. Podstawę stanowi oprogramowanie sygnalizujące zmiany na stronach internetowych oraz czytniki kanałów RSS. W przypadku serwisów dostarczających duże ilości wiadomości ogólnych, z których tylko niewielka część wchodzi w zakres objęty monitoringiem, stosuje się dodatkową funkcję oprogramowania monitorującego, polegającą na informowaniu o zmianach tylko w momencie pojawienia się co najmniej jednego z 40 słów kluczowych oraz zaznaczania tych słów w treści widomości. Funkcja ta w znacznym stopniu przyśpiesza proces wstępnej selekcji informacji umożliwiając tym samym monitorowanie źródeł, w przypadku których, analiza wszystkich doniesień byłaby bardzo czasochłonna, a przez to nieefektywna. Wstępnie wyselekcjonowane informacje zostają poddane ocenie analitycznej i sklasyfikowane jako potencjalnie istotne lub nieistotne z punktu widzenia sytuacji refundacyjnej leków objętych monitoringiem bądź ogólnej sytuacji refundacyjnej w Polsce lub innym kraju. Informacje sklasyfikowane jako istotne zostają umieszczone w specjalnie skonstruowanej bazie komputerowej. Wszystkie informacje odnalezione w danym dniu są grupowane i wysyłane o określonej godzinie w formie automatycznie generowanej wiadomości poczty elektronicznej.

Wyniki

W monitoringu refundacyjnym dzięki zautomatyzowanemu procesowi gromadzenia i selekcji informacji praktycznie każda informacja dotycząca refundacji konkretnego leku lub tylko potencjalnie związana z finansowaniem ze środków publicznych, znajdująca się w internecie, może zostać zidentyfikowana zaraz po jej opublikowaniu. Wykorzystanie bazy komputerowej umożliwia sprawne zarządzanie odnalezionymi informacjami, redukując jednocześnie nakłady pracy i minimalizując ryzyko przypisania wiadomości do nieprawidłowego odbiorcy. Każdy adresat znajdujący się w bazie otrzymuje codziennie za pośrednictwem poczty elektronicznej powiadomienie zawierające pogrupowane na odpowiednie kategorie zestawienie wszystkich wiadomości, które danego dnia zostały odnalezione. Zestawienie zawiera datę odnalezienia wiadomości, krótki jej opis oraz bezpośredni link do źródła w którym ta wiadomość została odnaleziona.

Wnioski

Monitoring refundacyjny to użyteczne narzędzie umożliwiające identyfikację istotnych informacji związanych z refundacją oraz sprawne codzienne ich przekazywanie do określonych odbiorców.

Journal of Health Policy & Outcomes Research
ISSN 2299-1247
jhpor, 2012, 1, 95-97

Polish Pharmacoeconomic Society activities review

Monika Szkultecka -Dębek
Roche Polska Sp. z o.o.

The Polish Pharmacoeconomic Society was created in 2001 by 26 founding members. Since January 20, 2006 Polish Society has been a Chapter of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

The mission of the Polish Pharmacoeconomical Society is to promote the development of theoretical knowledge and practical application of pharmacoeconomics and to popularize best practices in the evaluation of the effectiveness of treatments. It is also important for the Society to promote initiatives, attitudes and activities leading to the development of pharmacoeconomics and the assessment of the effectiveness of treatments and research results utilization in order to shape the social and health policy.

According to its mission the Society aims at translating the results of scientific research in the field of pharmacoeconomics and treatment effectiveness studies into practice to ensure fair and effective use of limited resources allocated by the society for health care. Last year among others, the Society's activities centered on organizing pharmacoeconomic conferences, workshops, competitions for students, working on the Polish pharmacoeconomical guidelines update. In 2010 the Society established 5 sections or task forces in order to fulfill its mission and to create a platform for close cooperation of the society members in the fields they are particularly interested in.

Those sections were:

- Epidemiology and cost of disease
- Health Technology Assessment
- Health Related Quality of Life
- Methodology of pharmacoeconomical analysis
- Therapeutic Programs and Pharmaceutical Care

Finally, four started their activities and during the General Meeting in December 2011 it was decided that the Methodology of pharmacoeconomical analysis task force will become part of the Health Technology Assessment section. Members of all of the task forces meet regularly (usually once a month) and work on the areas agreed, according to a pre-specified plan. Every year each section should present the yearly report of activities to the General Meeting. The reports from each section's meetings are available on the Polish Pharmacoeconomical Society website.

The Therapeutic Programs and Pharmaceutical Care section (TPPC), since it was established by the Polish Pharmacoeconomical Society in 2010, has had 16 members involved in the task force activities. The scope of interest has been the therapeutic programs area and the pharmaceutical care issues. The Therapeutic Programs constituted one of the possible ways of drug reimbursement in the Polish health care system by the end of 2011. Predefined inclusion criteria of the programs allowed qualified patients to be treated according to the program description and it was one of the ways to reimburse drugs assuring good efficacy and safety monitoring. The treatment was delivered to those patients for whom certain treatment would be really beneficial, it was frequently a targeted therapy. The eligible patients' population was possible to define due to clear inclusion and exclusion criteria, also including diagnostic procedures. The public payer could plan and control spending from the health care budget in an efficient way. Apart from those positive results there are still areas for improvement in order to facilitate better access to treatment within those Programs for patients especially with innovative therapies.

In Poland, until the third quarter of 2011 there were 39 defined, diligently described and operating Therapeutic Programs. According to the Polish law the Minister of Health announced implementation of a new Program after the AHTAPol President issued a positive recommendation for the reimbursement of a newly introduced drug and, if applicable, for the whole amended Therapeutic Program. Due to the changes in the legal regulations in the health care sector, the project of the new Reimbursement Legal Act was presented for public consultations at the beginning of 2011. Immediately the TPPC task force initiated work on the comments to the new Reimbursement Legal Act. Those comments and proposals for new solutions were submitted to the Polish ISPOR Chapter Board as one of the voices in the public discussion. The hurdles that the new law could cause for patients' access to treatments were pointed out. Also a need to set up registries for different disease areas was underlined.

Among other changes, according to the new act, since 2012 the Therapeutic Programs have been to be replaced by the Drug Programs which could result in significant changes, that were seen as needing further discussions. One of the major changes is that drug manufacturers will be involved in the process of creating Programs and now will have possibility or even obligation to submit proposals of new Drug Programs to the Ministry of Health. The new approach to Programs provoked a discussion within the TPPC task force about the future approach to biosimilar drugs, on how they will be defined, what requirements there will need to be fulfilled to form part of a Drug Program. The TPPC task force investigated the approach to the biosimilar drugs in the European Union and at the EMA. Among other aspects discussed, the task force concentrated on the production process of original drugs and a biosimilar drug seeking differences. Finally an agreement was reached that there is a need to define a biosimilar drug in the Polish legal environment. The TPPC task force agreed on the following definition: A biosimilar drug is a drug produced using biotechnological methodology and it is similar in terms of medicinal product design, pharmacological and pharmacokinetic properties, safety and efficacy, but not identical with the original registered and an authorized reference biological medicinal product. This definition was presented to the Board at the Polish ISPOR Chapter meeting in December 2011 as the proposals to be included in the future acts regarding reimbursement and HTA assessments.

Concurrently, the TPPC task force worked on the pharmaceutical care issues such as financing. The current financing model was discussed and activities were initiated to look for possibilities of financing pharmaceutical care from health care budget. A special meeting to learn from others and to share experience with an invited nurse (an experienced educator in diabetology) was organized. Further steps are planned for 2012. In November 2011 the TPPC section was the factual patron of the Polish National Pharmaceutical Care Competition organized by the Students Chapter "Social Pharmacy" and the students' Scientific Association from the Medical University in Lublin. The competition was addressed to Pharmacy students in Poland.

The Health Technology Assessment section (HTA) concentrates its activities on broad aspects of HTA. The main aim of the HTA Section is to review the official HTA guidelines issued by AHTAPol in 2009. The task force plans to provide AHTAPol with constructive and detailed comments and to propose solutions on how to improve and to adapt the guidelines into real life setting after several years of experience with HTA reports preparations.

Among other activities, a lecture about pharmacovigilance was presented in February 2012 and the safety issues were discussed as being a requirement in the guidelines part of the health technology assessment report. The members of the HTA Section considered the possible sources of data about drugs safety and discussed the possibility of using data such as Eudravigilance and documents like SPC, PSUR in the safety assessments. One of the issues discussed by HTA section members was the newly implemented by the Reimbursement Legal Act rationalization analysis. It is an addendum to the previously established HTA requirements, but without any specified details on how it should be carried out or what the expectations towards it are. As a result of the discussion the HTA section has prepared a list of questions that need to be answered and clarified by the decision maker.

The Health Related Quality of Life section (HRQoL) started its activity in 2012 and there are two main objectives for 2012. Firstly the Section

will work on a dictionary of quality of life and utility related terms. The other objective is to review the part of the HTA guidelines that are related to the quality of life (clinical efficacy analysis) and utilities (economic analysis) and to prepare a statement on it. The epidemiology and the cost of a disease section has taken up activities in the epidemiology area as well as aims at preparing the basis for the assessment of the cost of a disease

The sections' activities presented above are ambitious and require special dedication of all the teams working on the projects. The results of the annual work of each section will be presented at the following General Meeting scheduled for December 2012.