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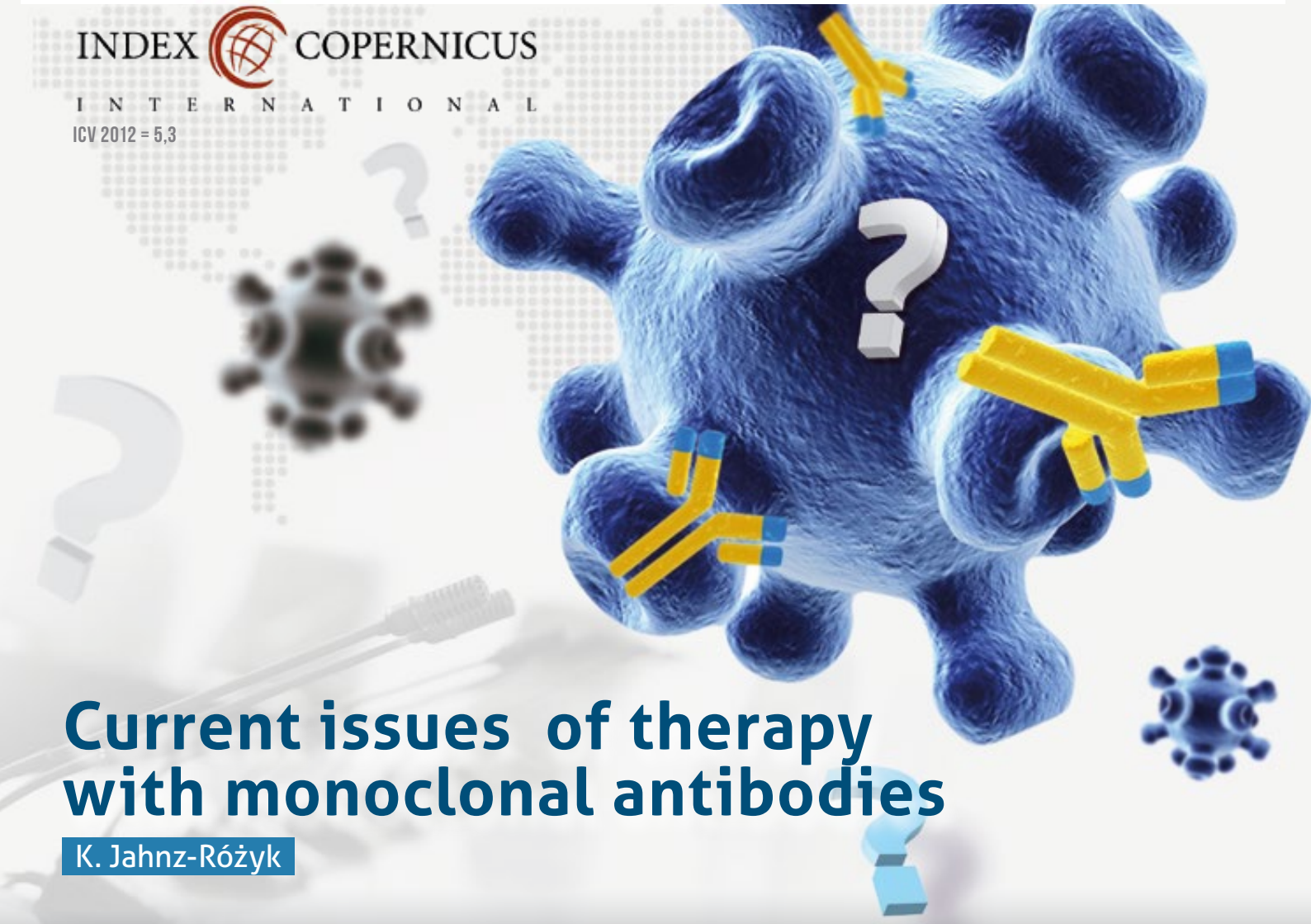
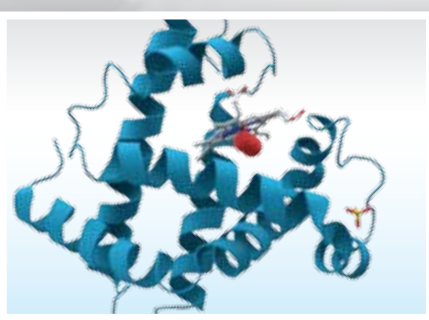


Current issues of therapy with monoclonal antibodies

K. Jahnz-Różyk



S. Albrecht et al:

Therapeutic proteins: facing the challenges of glycobiology.

E. Więsik-Szewczyk:

Belimumab therapy in systemic lupus erythematosus - the clinical expectations and burdens.

I. Skrzekowska-Baran & B. Podgórny:

„Pay-back" mechanism in the Polish reimbursement system - analysis and appraisal.

Dear Colleagues

IN THE FIFTH ISSUE OF JHPOR, CURRENT PROBLEMS OF TREATMENT WITH MONOCLONAL ANTIBODIES AND FUSION PROTEINS ARE SHOWED. FIRST JHPOR CONFERENCE, HELD ON 15TH MARCH 2014 IN WARSAW, WAS DEVOTED TO THIS TOPIC. YOU CAN FIND AN AUDIO-VIDEO REPORT OF THIS CONFERENCE ON OUR WEBSITE.

Recently many biological drugs have lost or will lose patent protection soon- hence biosimilars will be introduced to the market.

In Poland, a group of experts from various fields of medicine has developed a position paper, which could be helpful in making therapeutic decisions for doctors who use biological drugs in everyday practice.

This position paper has been published in "Polski Merkuriusz Lekarski" (Pol. Merk. Lek., 2014, XXXVII, 217) and you can find a translation of this article in the current JHPOR issue.

Experts are in agreement in their opinion that the complex and dynamic problem of using innovative and biosimilar biological drugs places a duty on all health care professionals to systematically monitor this process.

We also recommend the articles concerning the reimbursement system and actions of NHF in Poland and many other.

We wish you an interesting read of the fifth JHPOR issue!

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Prof. K. Jahnz-Różyk

Deputy Editor-in-Chief
Dr J. Lis

General Editorial Policies

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Journal of Health Policy & Outcomes Research (JHPOR) is pre-reviewed, international scientific journal, publishing the work of an important contribution to the development of pharmacoeconomics and outcomes research in Poland and worldwide. The journal is issued under the auspices of the Polish Society of Pharmacoeconomics. The journal is published twice a year in electronic form, optionally in the paper version.

Topics of publications include the following issues:

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Patient-Reported Outcomes (PRO)
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Comparative Effectiveness Research
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Current issues of therapy with monoclonal antibodies

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Keywords:
Biosimilars, Drug Program, Monoclonal antibodies

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ABSTRACT

The paper presents the most important aspects of treatment with monoclonal antibodies (MABs). Clinical and economic consequences of MABs biosimilars were shown. Access to MABs treatment in drug programs in Poland has been also presented.

SOME TERMS AND DEFINITIONS OF BIOPROCESSING AND BIOLOGIC MEDICINES [1]

Biotechnology is a technological application that uses biological systems, living organisms or derivatives of, to make or modify products or processes.

Bioprocessing uses organisms or biologically derived macromolecules to carry out enzymatic reactions or to manufacture products.

Biopharmaceutical is a therapeutic product created trough the genetic manipulation of living things, including but not limited to proteins and monoclonal antibodies, peptides, and other molecules that are not chemically synthesized, along with gene therapies, cell therapies, and engineered tissues.

Biopharmaceuticals involve the incorporation of foreign DNA into an organism's genetic material to generate a genetically modified organism (GMO) producing elevated amounts of therapeutic protein.

Majority of biopharmaceuticalas are therapeutic proteins or glycoproteins (i.e. proteins with sugar attached).

Protein therapeutics can more effectively interact with a large number of target receptors; small molecule drugs do not.

The interaction is more effective in triggering the desired biological response.

Production of biopharmaceuticals is a complex and costly process and involves the following steps:

1. Upstream processing (batch, fed batch and perfusion)
2. Primary Capture & Recovery (harvest and product separation)
3. Downstream processing and purification (chromatography and virus removal filtration, concentration and diafiltration)
4. Formulation and filling (sterile filtration).

Early biopharmaceuticals included simple proteins which were typically replacement proteins for existing natural products e.g. insulin.

Current biologics are most complex proteins with tertiary structure and post-translational modifications e.g. monoclonal antibodies.

Monoclonal antibodies (MABs) are a special class of proteins, known as immunoglobulins,

MODULAR CONSTRUCTION OF THE GENOME OF INFLUENZA VIRUS IS ALSO RESPONSIBLE FOR THE HUGE VARIATION IN BOTH GENOTYPE AND PHENOTYPE.

or Igs. All proteins are made up of amino acids. Anti-bodies are used by the immune system to identify and neutralize foreign objects.

Biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. Biosimilars must be shown on the basis of analytical, non-clinical and clinical data to be similar to an original biologic in terms of structural characteristic, and safety and efficacy. Biosimilar cannot be more potent or efficacious than innovator.

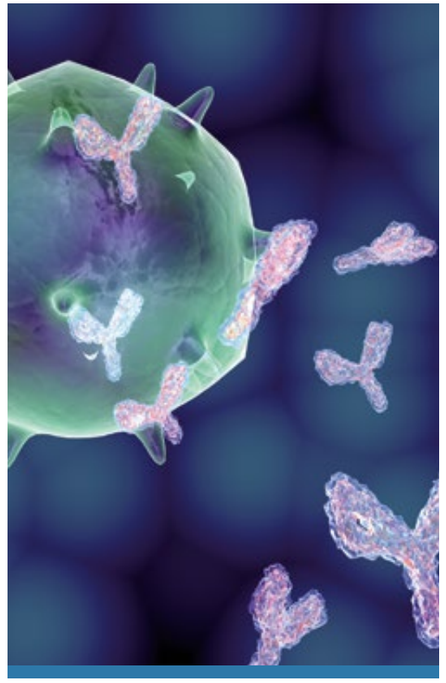
Differences across European Member States in national healthcare systems, structures and processes impact biosimilar uptake. Such differences may be any or all of the following:

- Physicians' perception of biosimilars (willingness to prescribe)
- Patients' acceptance of biosimilars (willingness to accept)
- Local pricing and reimbursement regulation (willingness to pay)
- Procurement policies and terms (willingness to buy).

MONOCLONAL ANTIBODIES [1]

Monoclonal antibodies (MABs) were first invented by Kohler & Milstein (1975) in Cambridge, UK. MABs are antibodies that are produced by one type of immune cell and are all clones of a single parent cell. Initially, the development of MABs therapy was slower because of rejection problems of mouse proteins in humans.

Monoclonal antibody therapy is the use of MABs to specifically bind to target cells or proteins. This may then stimulate the patient's immune system to attack those cells. It is possible to create a MAB specific to almost any extracelular/ cell surface target, and thus there is a large amount of research and development currently being undertaken to create MABs for numerous serious diseases (such as rheumatoid arthritis, multiple sclerosis, Alzheimer's disease and different types of cancers). There are a number of ways that MABs can be used for therapy. For example: MABs therapy can be used to destroy



malignant tumor cells and prevent tumor growth by blocking specific cell receptors.

ACCESS TO MABS AND FUSION PROTEINS IN POLAND – DRUG PROGRAMS [2]

MABs in Poland are reimbursed under the drug programs. Drug Program is a guaranteed benefit. Treatment of the program is done with the use of innovative, expensive active ingredients. Treatment is carried out in selected disease and includes strictly defined group of patients.

The content of each drug program is published as an annex to the notice of the Minister of Health on the list of the Reimbursement of Drugs, Food Products for Special Dietary Purposes and Medical Devices. Description of the program include: patient eligibility for the treatment, exclusion and inclusion criteria of the program, drug regimen, method administration, a list of diagnostic tests performed at the patient's eligibility for the program and necessary to monitor treatment.

Eligible patients for drug programs are treated free of charge.

Currently 14 antibodies are available (Tab.1) in 16 drug programs, especially in cancer, and chronic autoimmune diseases (Tab.2).

Table 1. Available MABs in drug programs in Poland (as of June 2014)

Adalimumab	B32, B33, B35, B37
Bevacizumab	B4, B50
Cetrolizumabum pegol (Cimzia)	B45
Cetuximabum (Erbitux)	B4, B5
Entanerceptum (Enbrel)	B33, B35, B36
Golimumabum (Simponi)	B33, B35, B36
Infliximabum (Inflectra, Remicade, Remsima)	B33, B35, B36, B55
Implimumabum (Yervoy)	B59
Natalimumabum (Tysabri)	B46
Omalizumabum (Xolair)	B44
Palvizumabum (Synagis)	B40
Pantimumabum (Vectibix)	B4
Rituximabum (MabThera)	B12, B33
Ustekinumabum (Stelara)	B47

Table 2. Drug Programs in Poland

B4	Colorectal cancer
B5	Hepatocellular carcinoma
B12	Lymphomas
B32	Crohn Disease
B33, B34, B35	Rheumatoid arthritis
B35,B36, B47	Psoriasis
B36	Ankylosing spondylitis
B40	RSV infections
B44	Severe allergic asthma (omalizumabum)
B46	Multiple sclerosis
B50	Ovarian cancer
B55	Colitis ulcerosa
B59	Melanoma

PHARMACOVIGILANCE [3]

Immune responses to therapeutic protein products may pose problems for both patient safety and product efficacy. Immunologically based adverse events, such as anaphylaxis, cytokine release syndrome, so-called "infusion reactions," and non-acute immune reactions such as immune complex disease could cause termination of the development of therapeutic protein products or limit the use of otherwise effective therapies. Unwanted immune responses to therapeutic proteins may also neutralize the biological activity of therapeutic proteins and may result in adverse events not only by inhibiting the efficacy of the therapeutic protein product, but by cross-reacting to an endogenous protein counterpart, if present. Because most of the adverse effects resulting from elicitation of an immune response to a therapeutic protein product appear to be mediated by humoral mechanisms, circulating antibody (to the therapeutic protein product) has been the chief criterion for defining an immune response to this class of products.

THE CONTENT OF EACH DRUG PROGRAM IS PUBLISHED AS AN ANNEX TO THE NOTICE OF THE MINISTER OF HEALTH ON THE LIST OF THE REIMBURSEMENT OF DRUGS, FOOD PRODUCTS FOR SPECIAL DIETARY PURPOSES AND MEDICAL DEVICES.

Both patient-related and product-related factors may affect immunogenicity of therapeutic protein products. These factors provide the starting point for an immunogenicity risk assessment. Ideally, these factors should be taken into consideration in the early stages of therapeutic protein product development.

MABs are now established as targeted therapies for malignancies, transplant rejection, autoimmune and infectious diseases, as well as a range of new indications. However, administration of MABs carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. In addition, there are numerous adverse effects of MABs that are related to their specific targets, including infections and cancer, autoimmune disease, and organ-specific adverse events such as cardotoxicity.

The most frequently reported in the medical literature adverse effects of treatment with MAB include:

1. Immune reactions: acute anaphylactic, anaphylactoid reactions against the MAB, serum sickness, tumor lysis syndrome, cytokine release syndrome. An example is rituximab or cetuximab, which has been attributed to the development of Ig-E antibodies against galactose- alfa-1,3 – galactose.
2. Infections (e.g reactivation of tuberculosis). This complication has been described most often after infliximab treatment.
3. Progressive multifocal leukoencephalopathy (PML). Based on clinical data it has been estimated that risk of PML corresponds to about 1 in 1000 patients treated with natalizumab. Additionally, PML was also observed after rituximab and efalizumab therapy.
4. Platelet and thrombotic disorders. An acute, severe, self-limiting thrombocytopaenia can be caused by infliximab (TNFα-specific), efalizumab (CD11aspecific) and rituximab (CD20-specific); however the mechanisms of action remain not clear. Moreover, the serious side effects: thrombocytopaenia has occurred in around 3% of subjects receiving alemtuzumab for early multiple sclerosis and can be fatal.
5. Autoimmuno diseases (e.g lupus-like syndromes, thyroid diseases, autoimmuno colitis). This can be exemplified by the development of anti-nuclear antibodies and antibodies to double-stranded DNA, and also with lupus-like syndromes in patients treated TNF-specific MABs for rheumatic diseases.
6. Cancer. There are theoretical concerns over potential tumorigenicity of TNF specific MABs and IL-12.
7. Dermatitis. The EGFR-specific mAbs cetuximab (a chimeric mAb) and panitumumab (vectibix; Amgen) (a fully humanized mAb) commonly cause a skin rash on the face and upper torso, although dermatitis can present as dry skin, pruritus and erythema. The rash is generally mild to moderate, and usually occurs in the first fortnight of therapy.
8. Cytokine storm. In March 2006, a life-threatening cytokine release syndrome occurred during a first-in-human study with TGN1412 (a CD28-specific superagonist MAB), resulting in a range of recommendations to improve the safety of initial human clinical studies with mAbs.
9. Cardiotoxicity. This can be exemplified by cardiac dysfunction caused by trastuzumab, which is most commonly an asymptomatic decrease in left ventricular ejection fraction that tends to be reversible.

Evaluation of the efficacy of biological treatment must be linked to its safety. Meanwhile, only 3% of publications in pubmed database refer to the safety aspects of these drugs.

BIOSIMILARS [4,5,6,7,8,9]

Biosimilar is a biological product which is highly similar to the reference product notwithstanding minor differences in clinically inactive components. There are not clinically meaningful differences between the biological product and the innovator product in terms of the safety, purity, and potency of the product. Although the terminology varies by jurisdiction in highly regulated markets, the term always refers to a biologic product that is similar to an already approved reference medicine.

Biosimilars are used in many diseases because they allow for the treatment of more patients, are cheaper by up to 30% and allow for the extension of the therapeutic indications.

A wide variety of biosimilars is available, from relatively small molecules such as human insulin or erythropoietin, to complex molecules such as MABs. The EU has led the way in establishing a regulatory framework for the approval of biosimilars. Under this framework, a total of 16 biosimilars have been approved for use in the EU.

It should be stressed that biosimilars approved to date have been relatively simple biologics to re-create, whereas emerging biosimilars such MABs drugs have extensive post-translational modifications and therefore show greater variation, presenting a challenge in terms of their assessment of comparability with the respective reference products. The European Medicines Agency ("EMA") has produced guidelines on the requirements for MABs-based biosimilars. Two MABs therapies – Inflectra and Remsima (Infliximab) have been approved in 2013.

On 22 May 2014, the EMA published a finalised version of its guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. The revised EMA Guideline is expected to come into force in December 2014 and will replace the current guideline which came into effect in June 2006 [5].

The revised EMA Guideline outlines the general principles concerning the quality aspects of biosimilars containing recombinant proteins and derivatives as active substance(s).

Furthermore, the revised EMA Guideline provides guidance concerning the quality requirements that are to be assessed as part of an application for marketing authorisation of a biosimilar which claims to be similar to an authorised biological product in the European Union ("EU").

The EMA Guideline outlines the quality requirements for biosimilars in the following areas:

- MANUFACTURING PROCESSES;
- THE BIOSIMILAR COMPARABILITY EXERCISE FOR QUALITY;
- THE CHOICE OF REFERENCE MEDICINAL PRODUCT;
- ANALYTICAL METHODS;
- PHYSICOCHEMICAL CHARACTERISATION;
- BIOLOGICAL ACTIVITY; AND
- PURITY AND QUALITY ATTRIBUTES FOR RELEVANT SPECIFICATIONS OF THE SIMILAR BIOLOGICAL MEDICINAL PRODUCT.

According to the EMA Guideline, an extensive comparability exercise between the reference medicinal product and the biosimilar will be required to demonstrate that the biosimilar has a similar profile in terms of quality, safety and efficacy to the reference medicinal product. This should include a comprehensive analysis of the proposed biosimilar and the reference medicinal product using sensitive and orthogonal methods to determine any similarities or potential differences in quality attributes.

This analysis should include comparative studies unless otherwise justified. Any detected differences in the quality attributes must be appropriately justified with regard to their potential impact on safety and efficacy.

Furthermore, the EMA Guideline requires extensive state-of-the-art characterisation studies to be performed in parallel on both the reference medicinal product and the biosimilar. These studies will demonstrate that the quality of the biosimilar is comparable to the reference medicinal product.

From 2014 Inflectra and Remsima are included in the reimbursement system in Poland. Main issues related to MABs biosimilars treatment include [6,7,8,9]:

- COMPLEXITY AND VARIABILITY OF BIOLOGIC MANUFACTURING
- REGULATORY ENVIRONMENT
- CLINICAL TESTING AND APPROVAL OF BIOSIMILARS, INCLUDING INDICATION EXTRAPOLATION
- INTERCHANGEABILITY AND AUTOMATIC SUBSTITUTION
- PHARMACOVIGILANCE AND NAMING

ECONOMIC CONSEQUENCES OF BIOSIMILARS [10]

Since 2000, the therapeutic market for monoclonal antibodies has grown exponentially. The current "big 5" therapeutic MABs on the market are bevacizumab, trastuzumab (both oncology), adalimumab, infliximab (both autoimmune and inflammatory disorders, 'AIID') and rituximab (oncology and AIID) accounted for 80% of revenues. In 2009-2012, the market size of MABs grew at a CAGR (Compound Annual Growth Rate) of 13%, far higher than the overall growth rate of biopharmaceuticals in the same period. However, we're now mid-way through the long anticipated decade of patent expiry. A total of around $255bn worth of products are expected to have come off patent by 2016 and patent expiry offers a golden opportunity for the companies looking towards generic and biosimilar development. Patent protection presents differently in different countries of the world.

Below are examples of Erbitux, Remicade and Enbrel.

And so:

1. Erbitux (cetuximab)

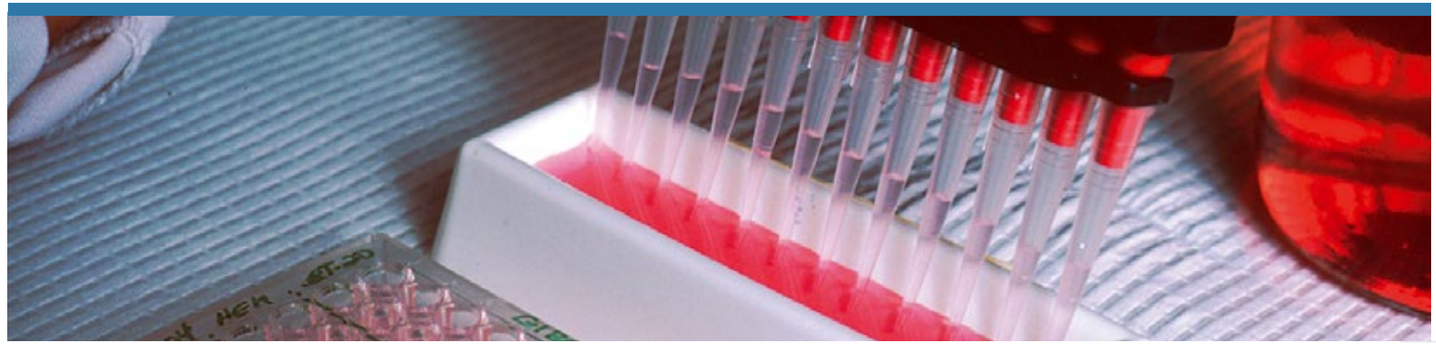
Erbitux is a chimeric monoclonal antibody rather confusingly distributed by BMS and Eli Lilly in the United States and by Merck KGaG in Europe. It is a EGFR inhibitor used for treatment of metastatic colon cancer, metastatic non-small cell lung cancer and head and neck cancer. In the US, having generated BMS over $700 million sales in 2012, it was granted a recent patent extension until November 2028.

2. Remicade (Inflixmab)

In 2013 Remicade generated a tremendous $8.9bn in global sales for distributors Janssen Biotech (USA), Mitsubishi Tanabe Pharma (Japan) and Merck & Co (rest of the world). It's a chimeric monoclonal antibody against TNF-α which is used to treat autoimmune diseases such as psoriasis, Crohn's disease and rheumatoid arthritis. Remicade's patent has already expired in Europe, but has until September 2018 in the United States.

3. Enbrel (Etanercept)

Another TNF-inhibitor co-marketed by Amgen, Pfizer and Takeda, Enbrel has a particularly interesting patent story. It was originally set to expire in the United States in October 2012, but a sixteen year extension was granted. However



a biosimilar version has been launched by Indian pharmaceutical company Cipla which claims to be thirty percent cheaper than the innovator. This has raised some concern and serious consideration by the global health sector, and it will be interesting to track Cipla's progress in this area.

Driven by enhanced economic level, expanded scope of medical insurance reimbursement, as well as lower prices incurred by intensified competition, Chinese MABs market is expected to continue to grow significantly. In 2013-2017, Chinese monoclonal antibody market will grow at 35%, sharing 21.5% of the global monoclonal antibody market in 2017 (9.5% in 2012).

CONCLUSIONS

MABs treatment is a significant medical and financial problem of each country. The loss of patent protection for referential drugs will allow the introduction of cheaper biosimilars. The introduction of biosimilars in chronic diseases must also take into account the wider aspects of safety of such therapy. ■

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Therapeutic proteins: facing the challenges of glycobiology

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ABSTRACT

The biologics sector is experiencing tremendous growth worldwide and is fuelled by the launch of a vast product range targeting mainly cancer, autoimmune diseases and hormone/enzyme disorders. However, biologics are one of the most expensive therapeutics to produce, due to both their inherent structural complexity and variability which challenges their manufacturing process and requires a thorough understanding of the product characteristics. More than one third of therapeutic proteins are glycoproteins such as monoclonal antibodies, cytokines, hormones, growth factors, clotting factors, enzymes as well as fusion proteins. Glycosylation is a major post-translational modification (PTM) and a tightly regulated critical quality parameter in the production of therapeutic proteins. This review includes a comprehensive overview on critical glycosylation and production parameters of different classes of therapeutic glycoproteins. It highlights the significance of protein glycosylation in product efficacy, stability and immunogenicity as well as in the development and regulation of follow-on biosimilar products which are set to vastly transform the biologics market in the coming decade.

INTRODUCTION

Since the introduction of recombinant DNA technologies in the 1980's the biologics market has experienced rapid growth including the successful launch of a vast variety of products such as cytokines, hormones, enzymes, fusion proteins and monoclonal antibodies (mAbs). By 2018 biologics are forecasted to account for one quarter of all drug expenses worldwide [1]. However, despite their growing demand, biologics are one of the most expensive pharmaceutical drugs. Biopharmaceuticals are structurally complex molecules and more than one third of approved biopharmaceuticals are glycoproteins. Glycosylation is the most abundant and most structurally diverse post translational modification (PTM). Other features include amidation, sulfation, hydroxylation and carboxylation in proteins [2]. Protein glycosylation in the ER and Golgi results in a complex set of N- and/or O-glycans conferring significant micro- and macro-heterogeneity to the molecule [3]. Representative N- and O-glycans are represented in Figure 1.

GLYCOSYLATION IS THE MOST ABUNDANT AND MOST STRUCTURALLY DIVERSE POST TRANSLATIONAL MODIFICATION (PTM). OTHER FEATURES INCLUDE AMIDATION, SULFATION, HYDROXYLATION AND CARBOXYLATION IN PROTEINS.

Keywords:
production parameters, sialylation, Biologics, biosimilars, cell culture, immunogenicity, monoclonal antibodies, N- and O-glycosylation

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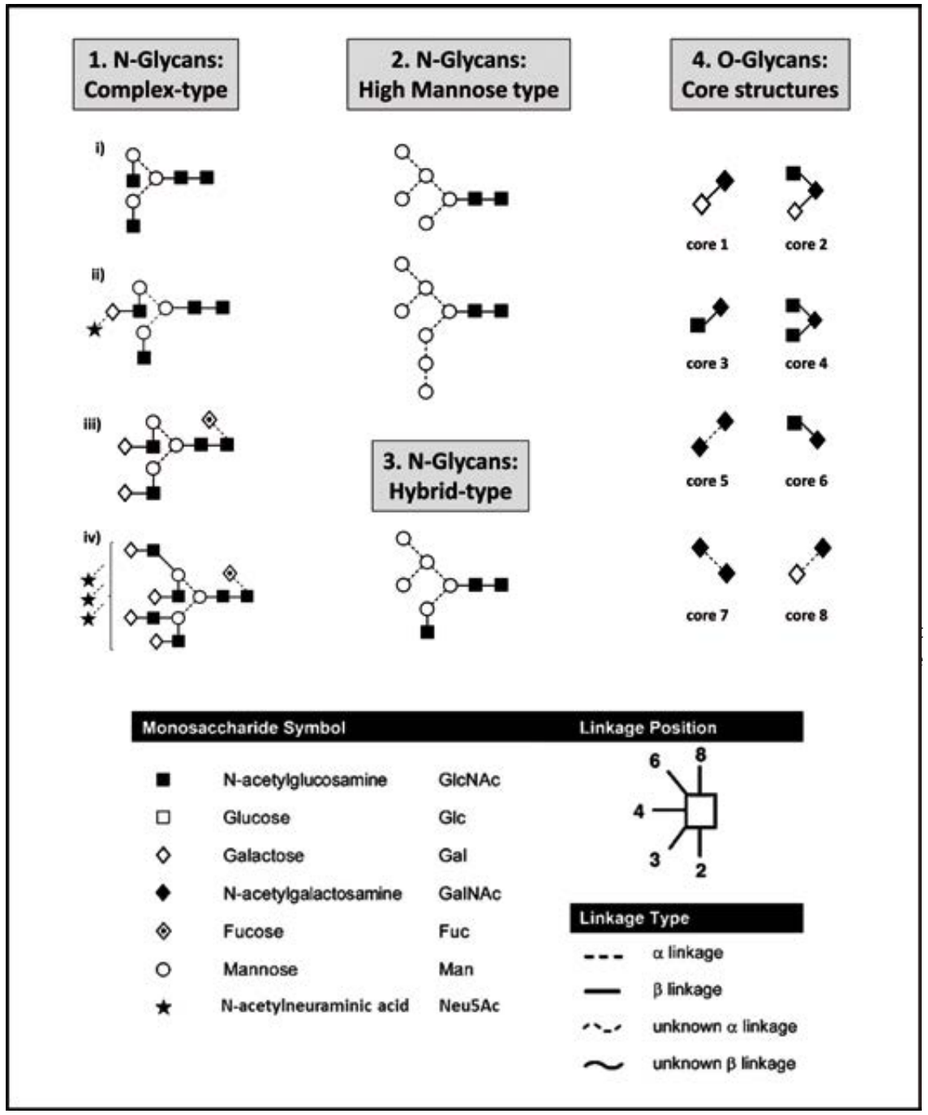

Figure 1. Representative N- and O-glycan structures. Complex-type N-glycans (1) are the most abundantly present N-glycan type on therapeutic glycoproteins.

Figure 1. Representative N- and O-glycan structures. Complex-type N-glycans (1) are the most abundantly present N-glycan type on therapeutic glycoproteins. These N-glycans can be a-galactosylated [G0] (i), mono-galactosylated [G1] (ii), di-galactosylated [G2] (iii), tri-galactosylated [G3] (not shown) and tetra-galactosylated [G4] (iv), core-fucosylated (iii, iv) and sialylated (ii, iv) and can carry up to four antennas (iv). N-glycans of high-mannose type (2) and hybrid type (3) are generally less frequent. O-glycans on therapeutic proteins are mainly of the core 1 type (4). O-glycans can be additionally extended by Gal-GlcNAc repeats and modified by sialylation, fucosylation, sulphatation, methylation, or acetylation.Glycans are represented using the Oxford symbol nomenclature [113]

N-glycans are typically composed of a core pentasaccharide unit (Man3GlcNAc2) which is linked via a chitobiose (GlcNAc2) to an asparagine (Asn) residue on the Asn-X-Ser/Thr-protein (serine/threonine) consensus sequence. Pharmaceutical glycoproteins produced in mammalian cell expression systems predominantly carry multi-antennary complex-type N-glycans which can be core-fucosylated and sialylated [4]. O-glycans on pharmaceutical glycoproteins are mainly of the core 1 type [Gal(β1,3) GalNAc] and are attached to the glycoprotein via a Ser/Thr residue [5,6]. The glycosylations macro- and micro-heterogeneity of proteins can significantly influence product efficacy and immunogenicity and is highly dependent on cell culture and manufacturing conditions and thus, the glycosylation of biopharmaceuticals presents an important quality and safety parameter. The manufacturing process of biologics is therefore challenging, expensive and time-consuming and can take up to 15 years from the pre-clinical phase until final market approval. Regulatory frameworks require the demonstration of proper glycosylation within acceptable variation limits and require the integration of strict and detailed quality control parameters into the manufacturing process [7,8].

The recent approval of the first biosimilar antibodies in Europe represents a major landmark in the young history of biologic therapeutics [9]. Additionally, more than 70 mAbs are in pre-clinical development [10] which are expected to have comprehensive market implications such as a significant price reduction in the range of 20-30% [11,12]. To date, a total of 18 biosimilars within the product classes of human growth hormone, granulocyte colony-stimulating factor (GCSF), erythropoietin (EPO) and TNF-inhibitor have already been approved for use in the EU [13]. Biosimilars can be defined as follow-on products of an innovator biopharmaceutical for which the patent has expired. The approval of biosimilars follows an abbreviated regulatory pathway but comprehensive comparability studies are required as laid out in guidelines issued by the FDA and EMA [14,15]. Due to the complex nature of biologics and the manifold influences during the production process an absolute similarity cannot be reached. Therefore an extensive dataset derived from pharmacokinetic bioequivalence testing and biophysical characterization is required in order to guarantee safety and efficacy of the biosimilar.

This review includes a comprehensive introduction to the different classes of therapeutic glycoproteins and includes details of the associated critical glycosylation parameters and critical production parameters, such as cell lines and culture conditions. Through our own research activities in the development of high-throughput glycotechnology for quantitative, detailed structural analysis of protein N- and O-glycosylation we have gained a solid insight into the complexity of post-translation glycosylation and the concomitant challenges of their analytical characterization. We also relay interesting case-studies on the glycosylation variability of therapeutic proteins which show that altered glycosylation does not automatically implicate changes in product quality and regulatory rejection. The understanding of the structure-function relationship is therefore a key requirement in the production of biologics.

THERAPEUTIC PROTEINS CLASSES

Pharmaceutical glycoproteins can be sub-divided into different product classes, the largest and best selling of which are the monoclonal antibodies. Other important biologics product classes include glyco-engineered Fc IgG fusion proteins, cytokines, growth factors, hormones and enzymes.

The glycosylation heterogeneity of proteins largely determines their therapeutic effector function and should closely resemble human protein glycosylation. In order to obtain a human-like glycosylation pattern most therapeutic glycoproteins are produced in eukaryotic cell lines, such as Chinese Hamster Ovary (CHO), myeloma (NS0) or hybridoma (SP2/0) [16].

Monoclonal antibodies (mAbs)

Therapeutic mAbs are recombinant immunoglobulins (IgG) mainly of the IgG1 subtype which have a monovalent epitope affinity to specific antigens. Antibodies utilised in the treatment of cancer and autoimmune diseases form the main therapeutic areas and constitute about 80% of the total antibody sales in the US [1]. A comprehensive overview on mAbs and their therapeutic use is given in Table 1.

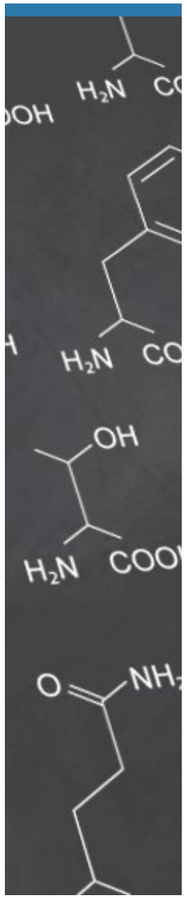

Table 1. Commercial EMA- and FDA-approved glycosylated monoclonal antibodies for therapeutic use [114]

	TARGET	APPLICATIONS (EXAMPLES)	PROPRIETARY (COMMERCIAL) NAME	CELL LINE
ANTI-INFLAMMATORY	TNFα	RheumatoidarthritisCrohn's diseaseUlcerative colitis	Adalimumab (Humira®)	CHO
			Golimumab (Simpoli®)	SP2/0
			Infliximab (Remicade®)	SP2/0
	BLys	Systemic lupus erythematosus	Belimumab (Benlysta®)	NS0
	CD3	Transplant rejection	Muromonab (Orthoclone-OKT3®)	Hybridoma
			Basiliximab (Simulect®)	NSO
	IL1β	Cryopyrin-associated periodic syndroms	Canakinumab (Ilaris®)	SP2/0
	IL6R	Rheumatoid arthritisJuvenile idiopathic arthritis	Tocilizumab (Actemra®)	CHO
	IL12/IL23	Plaque psoriasis	Ustekinumab (Stelara®)	SP2/0
	α4-integrin	Multiple sclerosisRheumatoid arthritis	Natalizumab (Tysabri®)	NS/0
	IgE	Asthma	Omalizumab (Xolair®)	CHO
ANTI-CANCER	CD20	Non-Hodgkin'S lymphomaChronic lymphocytic leukemiaRheumatoid arthritis	Rituximab (Rituxan®, MabThera®)	CHO
			Obinutuzumab* (Gazyva®)	CHO
			Ofatumumab (Arzerra®)	NS0
	CD52	Leukemia	Alemtuzumab (Campath®, Mabcampath®)	CHO
	CTLA-4	Melanoma	Ipilimumab (Yervoy®)	CHO
	Her2	Breast cancer	Trastuzumab (Herceptin®)	CHO
			Pertuzumab (Perjeta®)	CHO
	EGFR	Colorectal cancer	Cetuximab (Erbitux®)	SP2/0
			Panitumumab (Vectibix®)	CHO
	VEGF		Bevacizumab (Avastin®)	CHO
	CD3/EpCAM	Malignant ascites	Catumaxomab# (Removab®)	CHO
ANTI-VIRAL	A-epitope of viral fusion protein	Respiratory-Syncytial-Virus	Palivizumab (Synagis®)	CHO
	B. anthracis protective antigen	Anthrax	Raxibacumab* (ABthrax®)	NS0
ANTI-CANCER	C5 complement	Paroxysomal nocturnal hemoglobinuria	Eculizumab (Soliris®)	NS0

*Not approved by *EMA/#FDA. mAbs withdrawn from the market are not included*

Most therapeutic antibodies are chimeric (suffix –ximab; 70% human), humanized (suffix –zumab: 85-90% human) or human antibodies (suffix –umab: 100% human). These are less immunogenic compared with the initially used murine antibodies (suffix –omab: 100% mouse) [18]. IgGs are Y-shaped molecules and have a molecular weight of approx. 150kDa. They are composed of two "heavy" (approx. 50 kDa) and two "light" (approx. 25 kDa) polypeptide chains interconnected by disulfide bonds. The CH2 constant domain located on each heavy chain in the Fc region (= dimeric base of the antibody) has a conserved N-glycosylation consensus sequence at Asn297 (Figure 2). N-glycosylation is mandatory for Fc-effector functions of IgG which are mainly of anti-inflammatory nature such as the modulation of T- and NK (natural killer cell) activity [19]. One of the key immunogenic mechanisms of antibodies and a key element of antibodies used in cancer therapy is their ability for Fc-receptor binding. This antibody-receptor interaction can mediate compliment-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) and can finally result in the lysis of the target cell. Alpha-1,6-core-fucosylation of Fc N-glycans is a characteristic glycosylation feature of CHO cells and largely decreases the ability of the antibody to mediate ADCC [20]. Fucosyltransferase FUT 8 is responsible for the transfer of α1,6-linked fucose to the chitobiose core. The production of non-core-fucosylated anti-CD20 antibodies in CHO cells by FUT8 gene knockout resulted in a 100 fold increased ADCC [21].

The antigen-binding sites of the antibody are located in its Fab region (i.e. arms of the antibody) which is composed of one constant and one variable domain from each heavy and light chain, respectively. Antibodies against a variety of target-antigens have been approved for therapeutic use. Most therapeutic antibodies lack Fab glycosylation. In a recent study six therapeutic mAbs (cetuximab, infliximab, basiliximab, palivizumab, panitumumab and zalutumumab) were investigated for glycosylation in the Fab region. However, glycosylation could only be confirmed for cetuximab [22]. Interestingly, hypersensitivity against cetuximab has been connected to the presence of the immunogenic α(1,3)-linked galactose residues in the Fab region of the antibody. This was mainly explained by the exposed nature of the Fab N-glycans as binding of IgE to α(1,3)-linked galactose in the Fc region of rituximab was absent [22]. Likewise, the increased complexity of Fab-glycosylation such as sialylation, galactosylation and the presence of Lewis-terminal structures can be explained by the exposure of this glycoprotein region during Golgi processing [23]. In therapeutic approaches which do not depend on Fc effector functions, antibody Fab fragments have been recognized as an attractive alternative [24]. Due to the lack of glycosylation these can be more cost-efficiently produced using bacterial expression systems. However, the absence of glycosylation results in a short serum half-life. Conversely, conjugation with polyethylene glycol (PEG) is a common strategy to prolong serum half-life [25]. The addition of 40kDa of PEG to a Fab fragment conferred a serum half-life similar to IgG [26]. Certolizumab pegol (Cimzia®) is an example of a PEGylated therapeutic mAb-Fab to tumor necrosis factor alpha (TNF-α) utilized in the treatment of Crohn's disease and rheumatoid arthritis.

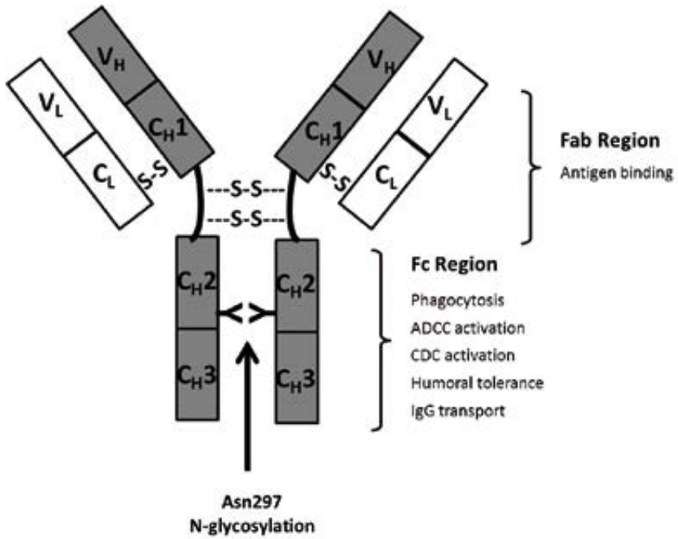

Figure 2. Schematic of immunoglobulin G (IgG) indicating the two N-glycosylation sites at Asn297 in the CH2 of the Fc region of the molecule as well as the therapeutic functions mediated by the Fab and Fc of the molecule. C: constant domain; V: variable domain; H: heavy chain; L: light chain; S-S: disulfide bond; bended line: hinge region

Fc IgG fusion proteins

Therapeutic fusion proteins are created through joining genes from different proteins by recombinant DNA technology. This results in polypeptides which combine the properties of the originator proteins and often contain an additional linker peptide.

Examples of therapeutic Fc IgG fusion proteins include Alefacept (Amevive®), Abtacept (Orenci®), Belatacept (Nulojix®), Etanercept (Enbrel®) and Rilonacept (Arcalyst®) [27]. The most commercially successful fusion protein is the TNFα inhibitor Etanercept with global sales reaching $7.3 billion (USD) in 2010 [27]. Etanercept is a dimeric glycoprotein with a mass of approx. 150kDa and is used in the treatment of autoimmune diseases such as rheumatoid arthritis. It is composed of a human TNFα receptor part linked to an IgG1 Fc portion through an O-glycopeptide. Each part of the dimeric molecule carries one N-glycosylation site on its Fc part and two N-glycosylation sites on its TNFα unit. Figure 3 shows the total N-glycosylation profile of Etanercept (Enbrel®) as analyzed in our laboratory [5]. It includes a complex mixture of mono- to tetra-antennary core- and non-core-fucosylated structures which can carry up to two sialic acid residues. The glycan structures were identified by exo-enzymatic sequencing and confirmed by mass spectrometry as described in a later paragraph on glycan characterization [5]. By studying the N-glycosylation site heterogeneity of Etanercept (Enbrel®) we observed that the small biantennary neutral N-glycans were predominantly localized on the Fc part whereas larger tri- and tetra-antennary structures are attached to the TNFα unit [5]. Additionally, 12 occupied O-glycosylation sites carrying neutral, mono- and di-sialylated core 1 type structures were localized in the linker region of the fusion protein [5].

Erythropoietin

Erythropoietin (EPO) is a glycopeptide cytokine which controls and stimulates the production of red blood cells (termed erythropoiesis). The therapeutic use of EPO focusses on the restoration of blood haemoglobin concentration upon renal failure as well as the prevention of anemia in cancer patients undergoing treatement. Recombinantly produced therapeutic EPO is a glycopeptide with a mass of approx. 30kDa. It

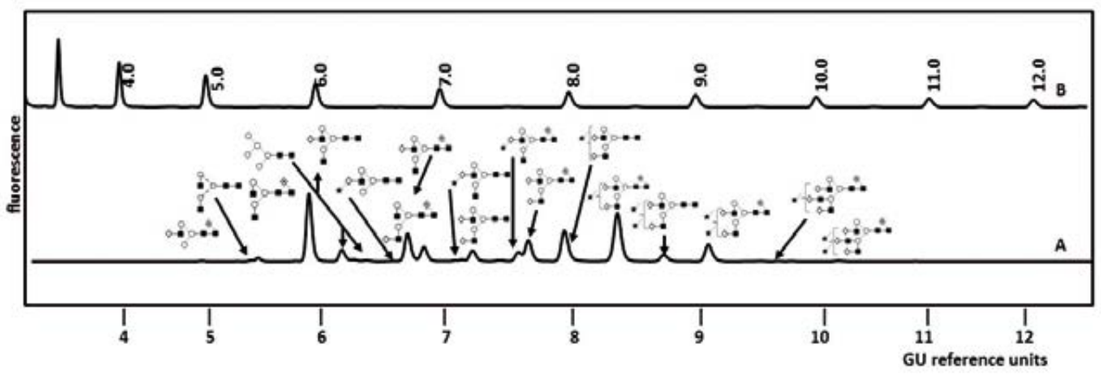

Figure 3.UPLC analysis of total N-linked glycans from Etanercept (Enbrel®) by HILIC-FLR as performed in our laboratory (A). The glycans were released from the fusion protein by PNGase F and fluorescently labelled. For an instrument-independent comparison, the retention times of peaks are transformed to standardized glucose unit values (GU) by comparing the profile to a dextran hydrolysate ladder (B). Structures were identified by sequential enzymatic digestion as exemplified in Figure 4 for the monosialylated N-glycan fraction from Etanercept (Enbrel®). Adapted from Houel et al 5, with permission from the American Chemical Society.

contains three N-linked glycosylation sites (Asn 24, 38, 83) which carry sialylated tetra-antennary structures and one O-glycosylation site (Ser 126) which carries mono- and disalylated core-1 structures [6]. The impact of glycosylation on EPO secretion, stability, half-life and effector functions has been extensively studied [28,29]. Full N-deglycosylation resulted in a total loss of EPO biological activity and a loss in resistance to thermal stress [28]. Sialylation plays an important role in serum half-life. De-sialylated EPO has a half-life of only 2 min and is subsequently rapidly cleared in the liver via galactosyl receptors of the hepatocytes [30]. Pharmaceutical EPO preparations form a large product family and are sub-divided into different classes based on their glycosylation characteristics. Epoetin-α (i.e. Epogen® and Eprex®) and epoetin-β (i.e. Recormon® and NeoRecormon®) are both produced in CHO cell systems but differ in their glycosylation characteristics [31]. It was shown that Eprex® (epoetin-α) has a higher degree of O-acetylation and a higher relative amount of immunogenic Neu5Gc per total sialic acid than NeoRecommon® (epoetin-β) [32,33]. Epoetin-δ (Dynepo®, withdrawn from the market in 2008) is most similar to human EPO due to its production in human cell lines (HT-1080). Dynepo® has neither any Neu5Gc nor O-acetylation but is the only isoform which contains sialyl-Lewis x epitopes (SLex; [Fuc(α1-3)[Neu5Ac(α 2-3)Gal(β1-4)]GlcNAc(β-)]) [32].

Darbepoetin (Aranesp®) is a hypergalactosylated EPO-analogue for which two additional glycosylation sites (Asn 30, 88) have been introduced by glyco-engineering [34]. A comparison of darbepoetin alpha to conventional epoetin-α/-β is given in Table 2. Darbepoetin can carry up to 22 sialic acid residues compared to just 14 in conventionally produced EPO. This results in an up to four times increased serum half-life and 2.2-fold higher in vivo activity [35-37]. However, the in vivo activity does not correlate with the receptor binding potential. The receptor binding correlates inversely with glycosylation and therefore requires the application of a six to 14-fold higher concentration of darbepoetin to achieve similar half-maximal receptor binding activity as EPO but allows longer dosing intervals due to its lower clearance rate [36,37].

Other cytokines, growth factors, hormones, clotting factors and enzymes

Therapeutic interferons (IFNs) are glycoproteins of the cytokine family. Approved glycosylated IFNs include IFN-α (Alferon®/Avonex®) and IFN-β (Rebif®). IFN-α contains one potential glycosylation site. Upon introduction of an O-glycosylation site reduced thermal stability was observed whereas the introduction of four N-glycosylation sites resulted in improved serum half-life [38,39]. Likewise, a higher stability and in vitro availability were observed for glycosylated IFN-β (one N-glycosylation site) compared to non-glycosylated IFN-β [40].

Table 2. Comparison of the structural and pharmacokinetic properties of epoetin-α/-β and hypergalactosylated darbepoetin-α [31, 32, 35, 36]

	EPOETIN-α/-β	DARBEPOETIN-α
Number amino acids	165	165
Glycosylation sites	3x N-glycans (Asn 24, 38, 83) 1x O-glycan (Ser 83)	5x N-glycans (Asn 24, 30, 38, 83, 88) 1x O-glycan (Ser 83)
Number sialic acid residues per molecule	up to 14	up to 22
Sialic acid O-acetylation	+	+++
Glycan content per molecule	up to 40%	up to 51%
Molecular weight	30.4 kDa	37.1 kDa
Half-life (intravenous administration)	6-9 h	25 h
Half-life (subcutaneous administration)	19-24 h	48 h
In vivo activity		2.2 fold higher than epoetin-α/-β
Dose requirement for half-maximalreceptor binding activity		6-14x higher than epoetin-α/-β

+++ major abundance + minor abundance

Similar to IFNs, the haematopoietic growth factor granulocyte colony-stimulating factor (G-CSF) is available in its glycosylated (Lenograstim®) and non-glycosylated (Filgrastim®) form. G-CSF is a peptide hormone used in cancer therapy to reduce the risk of neutropenia. Glycosylated G-CSF is produced in CHO cells and carries one O-glycosylation site whereas non-glycosylated G-CSF is produced in E coli. Although in vitro studies depicted an up to 20-fold increase in activity of the glycosylated analog no differences were observed in vivo [41,42].

Therapeutic hormones, clotting factors and enzymes form large classes of therapeutic glycoproteins. The effects of glycosylation on the stability, in vivo efficacy and serum half-life of these glycoprotein classes were carefully reviewed by Sola et al. [43]. In additional studies, the introduction of four additional N-glycosylation sites on follitropin (Follistim® / Gonal F®), increased both the in vivo bioactivity and the serum half-life of the follicle-stimulating hormone up to twofold [44,45]. The introduction of N-glycosylation sites resulted in a higher biopotency compared to the introduction of O-glycosylation sites [45]. On the contrary, the affinity of the antithrombotic serine protease drotrecogin-α (Xigris®) to thrombin increased upon selective removal of one of the four N-glycosylation sites (Asn 313) [46]. Enzyme replacement therapy is applied in rare lysosomal storage diseases such as Fabry disease in which agalsidase-α (Replagal®) and agalsidase-β (Fabrazyme®) are used successfully. In this case the exposure of mannose/mannose-6-phosphate at the terminals of the six N-glycosylation sites on the glycoproteins are of great importance for the mannose-6-phosphate receptor mediated cellular internalisation of the enzyme [47].

SIGNIFICANCE OF PROTEIN GLYCOSYLATION

Glycosylation can modulate the immunogenicity, efficacy, solubility and pharmacokinetic behavior of biopharmaceuticals and was extensively reviewed by Hossler et al and Walsh et al [2,4]. Multiple relations were reported between N-glycosylation and the therapeutic efficacy and immunogenicity of therapeutic proteins, while much less is known about the influence of O-glycans mainly attributed to their in-homogenous chemical nature.

Total N- and O-glycosylation

Glycan macro- and micro-heterogeneity can influence the folding, biological activity, kinetics and stability of therapeutic proteins. As observed for EPO, the total removal of N-glycans resulted in a significant decrease in product secretion, catabolic half-life and in vivo biological activity whereas the removal of the O-linked glycan did not have any effect [29]. Conversely, the glycoengineering of additional N-glycosylation sites on EPO, IFN-α and follitropin resulted in increased biological activity as well as increased serum half-life [38,44,45,48]. The lack of O-glycosylation on recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) resulted in antigenicity and highlighted the role of O-glycans in masking potentially antigenic sites on the protein backbone [49].

Sialylation

Terminal N-glycan sialylation is an important quality parameter which determines the serum half-life of a protein. A 200-fold or more decrease in serum half-life of completely de-sialylated EPO compared to the sialylated reference EPO was observed when injected intravenously in rats [50]. Sialylation masks structural determinants such as mannose which are otherwise prone to ligand interaction and thus clearance of the molecule. Sialic acids on the Fc portion of intravenous gamma globulins have been shown to play an important role in the anti-inflammatory properties of the molecules as was demonstrated in a mouse model for serum arthritis [51]. The induction of inhibitory FcγRIIB by macrophages which

consequently leads to the therapeutically desired FcγRIII activation in autoimmune diseases such as rheumatoid arthritis showed to be mediated by sialic acids on human intravenous γ globuline [52].

Sialic acid O-acetylation

O-acetylation of sialic acids has been recognized as an important quality parameter for erythropoiesis stimulating agents such as Eprex® and NeoRecormon® [32]. Due to the increased hydrophobicity and decreased susceptibility to sialidases conferred through O-acetylation an extension in the serum half-life can be assumed [32,53].

Galactosylation

The proportion of a-galactosylated (G0), mono-galactosylated (G1) and di-galactosylated (G2) N-glycans is dependent on cell culture conditions. CHO cells generally result in low galactosylation rates [54]. The assessment of terminal galactosylation is required by regulatory authorities. Terminal N-glycan galactosylation is directly related to N-glycan sialylation. The possible impact on CDC activity through involvement in complement C1q binding was shown for rituximab but, overall, variations in Fc galactosylation are not considered to adversely influence product stability or safety [54,55].

Mannosylation and terminal GlcNAc

Recognition of high mannose type N-glycans by mannose receptors and mannose binding lectins as well as the induction of endocytosis of the reticulo-endothelial system by terminal Man and GlcNAc promotes an accelerated serum clearance of the respective glycoproteins [56-58]. On the other hand it has been shown in vitro that antibodies carrying high-mannose structures (Man5, Man8/9) potentially enhance ADCC, decrease CDC and increase the binding affinity to FcγRIIIa [59].

Core-fucosylation and bi-secting GlcNAc

Antibody-dependent cell-mediated cytotoxiticy (ADCC) is triggered by communication between IgG-Fc and natural killer (NK) cells and is mediated through the receptor FcγRIIIa expressed on NK. Core α(1,6)-fucosylation of Fc N-glycans negatively affects this effector function [20]. The presence of core α(1,6)-fucosylation is inversely linked to the presence of the glycosyl transferase GnT-III, which is responsible for the addition of bisecting GlcNAc. Cell-engineering approaches which aim to inactivate core-fucosylation and simultaneously introduce GnT-III succeeded in increasing ADCC by almost 100 fold and thus is an essential step in the manufacturing of ADCC-mediating therapeutic proteins utilized in cancer therapy [60,61].

Non-human glycan epitopes

Non-human sugars on therapeutic proteins are a result of the production cell-line used and can lead to an immunological response. N-glycolyl-neuraminic acid (Neu5Gc) and terminal α1,3-linked galactose are xenoreactive sugars from mammalian cell-lines [62]. Candidate cell lines from yeasts, insects and transgenic plants contain additional immunogenic sugars such as α(1,3) core-fucose and β(1,6) xylose [62]. The pre-clinical assessment of xenoreactive sugars is complicated by their non-immunogenicity in animals. This requires the development of alternative test models such as CMAH (cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein) knockout mice [63] which eliminate the biosynthesis of Neu5Gc from all cells mimicking the normal human lack of functional CMAH.

Neu5Gc is considered as an oncofetal antigen [64] and anti-Neu5Gc antibodies in humans have been shown to induce complement-mediated cytotoxiticy in the presence of Neu5Gc [65]. In the case of EPO, low levels of Neu5Gc (i.e. 1%), induced a negligible immunogenic response whereas levels of 7% of Neu5Gc showed a considerable response [66]. Additionally, up to 1% of total human circulating antibodies are directed against α(1,3)-linked galactose [67]. Cetuximab-induced anaphylaxis in some areas of the United States could be related to IgE specific for α(1,3)-linked galactose in patient sera [68].

FACTORS INFLUENCING PROTEIN GLYCOSYLATION IN BIOLOGICS PRODUCTION

The glycosylation characteristics of therapeutic proteins are largely determined by culture systems and conditions. A detailed understanding of the production process and the monitoring of glycosylation during manufacturing is therefore required in order to assure product safety and efficiency.

Cell culture systems

Cellular expression systems which are capable of producing human-like N-glycosylation are essential for the manufacture of biopharmaceutical glycoproteins. Since bacterial expression systems (such as E.coli) lack the necessary enzymatic glycosylation machineries, the use of mammalian cell lines is common practice in glycoprotein production. Most frequently used are Chinese hamster ovary cells (CHO) followed by

Table 3. Glycosylation characteristics of standard and alternative production cell lines. According to [16, 70-73] and research performed in our laboratory

	CHO	BHK	NSO, SP2/0	HUMAN	ANIMAL&MILK	PLANT	YEAST	INSECT	BACTERIAL
GLYCOSYLATION	+	+	+	+	+	+	+	+	-
SIALYLATION	++	+	+++	++	++	-	-	-	-
α2,6-SIALYL	-	-	+	+	+/-	-	-	-	-
NEU5GC	++	+++	+++	+	+/- *	+++	-	-	-
α1,3-GAL	+	+	++	-	++	-	-	-	-
BISECT. GLCNAC	-	-	-	+	-/+	-	-	-	-
α1,6-CORE FUC	+	+	++	+	+	+/-	-	+	-
α1,3-CORE FUC	+	+	++	+	+	+/-	-	+	-
β1,6-XYLOSE	-	-	-	-	-	+	-	+	-
HIGH-MANNOSE	+	+	+	+	+	+	+++	++	-
PAUCI-MANNOSE	-	-	-	-	-	-	-	+++	-
ADDITIONAL CHARACTERISTICS	-	-	-	outer-armfucosylation (Le^x/SLe^x)	-	outer-armfucosylation(Le^a)	Phosphorylation	-	-
ADDITIONAL APPROVEDTHERAPEUTICS(EXAMPLES)	Enbrel® (Etanercept)	Helixate® (FS Factor VIII)	Arzerra ® (Ofatumumab)[a]	Elaprase® (idursulfase)	ATryn® (antithrombin)	-	-	-	Neupogen® (filgrastim)
	Rituxan® (Rituximab)	NovoSeven® (Factor VIIa)	Remicade® (Infliximab)[b]	Xigris® (Drotrecogina)	Creon® (pancrelipase)	-	-	-	Humalog® (insulin)

*+++ abundant presence ++ presence + low presence – not present +/- both, presence and absence reported. *presence of Neu5Gc from exogenous sources possible; aNS0; bSP2/0. Lex: Lewis x epitope [Fuc(α1-3)[Gal(β1-4)] GlcNAc(β-)]. SLex: sialyl-Lewis x epitope [Fuc(α1-3)[Neu5Ac(α 2-3)Gal(β1-4)]GlcNAc(β-)]. Lea: Lewis a epitope [Gal(β1-3) [Fuc(α1-4)]GlcNAc(β-)]*

baby hamster kidney cells (BHK), murine myeloma (NS0) and hybridoma (SP2/0) cells, human cell lines, transgenic animals and milks (e.g. pig, goat). As mammalian cell expression systems are complex, often difficult to scale up and expensive, alternative production platforms based on plants, yeasts, and insects are currently under investigation. An overview on the glycosylation characteristics of cellular expression systems is given in Table 3 and has been extensively reviewed and studied [16,69,73]. The main disadvantages of CHO, NS0, SP2/0 and transgenic animals/milks is the presence of non-human Neu5Gc and α(1,3) Gal epitope [62,74] which can evoke immunogenic responses in humans. Another critical point is the presence of core-(α1,6) fucosylation which reduces the ADCC effector function of mAbs. CHO cells lack GNT-III which is responsible for the addition of bi-secting GlcNAc and results in the increased presence of core-(α1,6) fucosylation instead. Glyco-engineering approaches aimed at decreasing the glycoprotein immunogenicity and the overexpression of GNT-III are ongoing [75,76]. The use of human cell lines (e.g. Per.C6, Hek293, HT-1080) is of special interest because their glycosylation machinery closest resembles that of humans. Additionally, a tenfold increased productivity was observed in the human cell line Per. C6 compared to conventional cell lines [77]. However, their application for commercial manufacturing is still limited as the risk of pathogenic infection presents an additional hurdle for regulatory approval.

No therapeutic proteins produced by plants, yeasts or insects have been approved thus far despite their high productivity, low costs and ease of scaling up to industrial production levels [62]. Reasons for this include the presence of immunogenic sugars such as α(1,3) core-fucosylation and β(1,6) xylose. Additionally, the overall lack of sialylation and the presence of highly mannosylated structures ranging up to Man100GlcNAc2 for yeasts and paucimannosic structures (i.e. Man3GlcNAc2) lead to an accelerated clearance of these glycoproteins [62]. Significant efforts have been made in glycoengineering of alternative production cell lines resulting for example in the successful production of complex N-glycans in Drosophila S2 cells or the purification of rMAbs carrying human N-glycosylation from yeast cells [78,79].

Cell culture conditions

During the development and production of biopharmaceuticals a continuous scaling- up of the manufacturing process is required. Scaling up the production of biopharmaceuticals is a complex task as the increase of protein quantity might affect and compromise product quality [80]. Changes in process therefore require thorough comparability studies which need to be performed according to comparability protocols defined by the regulatory authorities [81]. Due to concerns in concomitant changes in glycan structures the FDA recently banned the application of up-scaling in the production of aglucosidase α (Myozyme®) from 160 L scale to 2000 L scale and required a new biologic license for the application [82].

The manufacturing mode and processing variables such as pH, temperature, oxygen level and media composition have a significant effect on protein glycosylation which was extensively reviewed by Hossler et al and is briefly summarized in the following paragraph [4]. Production methods applying low shear force (i.e. perfusion mode) generally result in slower cell growth but more complete glycosylation and overall sialylation [83,84]. A pH range of 6.8-7.2 was considered optimal for appropriate galactosylation and sialylation of EPO production in CHO cells [85,86]. Increased ammonia levels result in an increased culture pH and has been shown to have adverse effects on protein sialylation [87]. Similarly, a decrease in process temperature (i.e. from 37°C to 30°C) has been shown to negatively affect EPO sialylation although it resulted in an increased cell viability [85]. However, a synergistic effect between temperature and pH was observed since the loss of sialylation efficiency during lowered temperatures could be prevented by a simultaneous decrease in pH [85]. For a consistent glycosylation level, the degree of dissolved oxygen should be kept between 10 and 100% [88]. Critical media components include monosaccharides, nucleotide sugar precursors, small molecules such as sodium butyrate, ammonia and amino acids as well as lipids and metal ions. Cultures limited in monosaccharide supply show lowered glycosylation and sialylation whereas product- and culture-dependent trends were observed with nucleotide sugar supplementation [89-91]. Appropriate supplementation of amino acids, manganese and lipids were shown to have a positive impact on sialylation and N-glycan site occupancy for both recombinant human EPO and IFN-ɣ [92,93].

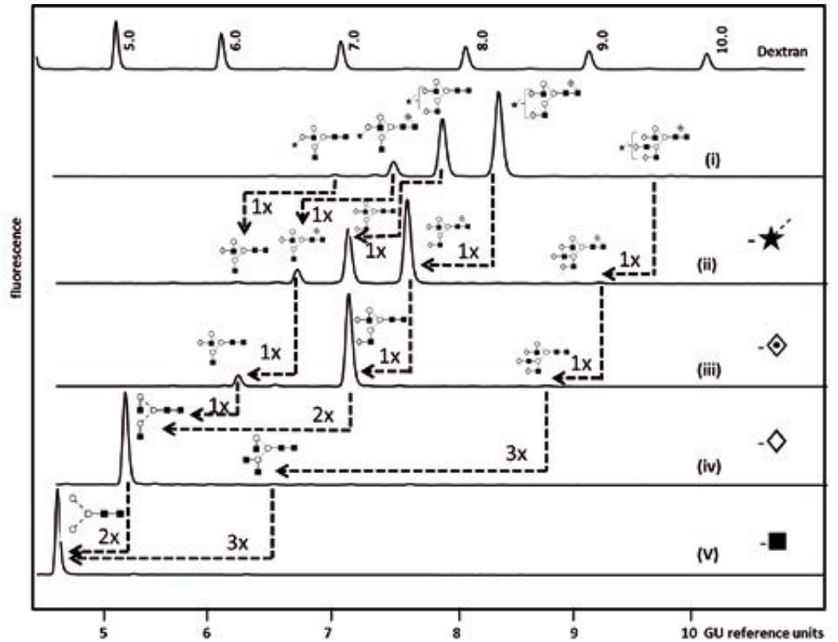

Figure 4. Exoglycosidase array analysis of fluorescently labelled mono-sialylated WAX fraction from Etanercept (Enbel®) by HILIC-fluorescence to determine N glycans structures. (i) Whole N-glycan pool released by PNGase F (ii) ABS (Athrobacter ureafaciens Sialidase) releases α2-3/6/8 sialic acids. (iii) BFK (Fucosidase from bovine kidney) releases α1-2/6 fucose. (iv) BTG (Bovine testes ß-galactosidase) releases galactose ß1-3/4 linkages and (v) GUH (hexosaminidase) release ß-GlcNAc but not GlcNAc linked to ß1-4 Man.Dashed arrows indicate the enzymatic removal of one (1x), two (2x) or three (3x) sugar units. For an instrument-independent comparison, the retention times of peaks are transformed to standardized glucose unit values (GU) by comparing the profile to a dextran hydrolysate ladder. Adapted from Houel et al 5, with permission from the American Chemical Society.

Glycan characterization

The complexity of protein glycosylation means their analytical characterization is hugely challenging and usually requires the use of orthogonal techniques. N-glycans are most commonly analyzed after the enzymatic release by peptide N-glycosidase F (PNGaseF) using high- and ultra-performance liquid chromatography (HPLC/UPLC) or capillary electrophoresis (CE) coupled to a fluorescent detector and/or mass spectrometer (MS) [5,95,96]. Hydrophilic interaction liquid chromatography (HILIC) and reversed phase (RP) are stationary phases which can be used for complimentary chromatographic glycan separation whereas weak anion exchange (WAX) chromatography allows the separation of glycans according to their charge [97]. Fluores-

cent detection enables structural quantification but requires glycan derivatization by fluorescent labels (2-aminobenzamide [2-AB] and 2-aminobenzoic acid [2-AA] for HPLC/UPLC and 1-aminopyrene-3,6,8-trisulfonic acid [APTS] for CE-LIF) [97]. Matrix-assisted laser desorption-ionization (MALDI-TOF MS) and electrospray ionization (ESI) are routinely used for compositional glycan analysis [98]. Combined with mass fragmentation (MS/MS) these methods result in glycan sequence information based on the formation of diagnostic ions. Another powerful tool for glycan sequence and linkage identification which is routinely used in our laboratory is the enzymatic panel digestion of 2-AB labelled glycans using an array of linkage-specific sialidases, fucosidases, galactosidases, N-acetylhexosaminidases and mannosidase [97]. Figure 4 exemplifies our analytical workflow for the exo-enzymatic sequencing of mono-sialylated N-glycans obtained by WAX fractionation of Etanercept (Enbrel®) (see Figure 3 for the total N-glycan profile) which allowed the confident assignment of the structures present [5].

Proteolytic cleavage of IgG by using the enzyme IdeS FabRICATIOR facilitates the identification of glycan heterogeneity in the Fab and Fc region of monoclonal antibodies [5]. GlycoBase and UniCarbDB are two powerful structural databases which have been implemented for the efficient interpretation of LC and MS data [99, 100]. Furthermore, a low-cost robotic sample preparation platform has recently been established for the high-throughput IgG N-glycan analysis which results in highly reproducible data and considerably reduces manual sample handling errors [101]. The identification of O-glycans is more challenging due to the lack of a single consensus sequence for glycan attachment and the lack of a common core structure. The combination of Collision Induced Dissociation (CID), which results in glycan sequence information and Electron Transfer Dissociation (ETD), which enables the identification of the amino acid residue at the glycosylation site presents a powerful MS glycan characterization approach for simple O-glycans as present on therapeutic glycoproteins [5]. Similarly, peptide mapping is used to confirm glycosylation site occupancy in N-glycan analysis while reduced CE-SDS is used as a tool for assessing total glycosylation of protein sub-units [102].

Alterations in PTMs, and thus glycosylation, can affect the higher-order structure of proteins and was reviewed by Berkowitz et al [103]. This can, for example, result in protein aggregation. Global information on protein structure can be obtained by classical analytical techniques such as circular dichorism (CD), differential scanning calorimetry, analytical ultracentrifugation (AUC) and size exclusion chromatography [103]. Hydrogen-deuterium exchange (HDX) is a new and powerful MS based method which even enables the localization of these structural changes in biopharmaceuticals [104].

ASSESSMENT OF PROTEIN GLYCOSYLATION IN BIOLOGICS AND BIOSIMILAR MANUFACTURING

The characterization of protein glycosylation plays an important role during the production process of biologics and biosimilars. In biosimilar production the demonstration of similarity to the innovator product is a key regular requirement. Similarly, the manufacturer of biologics has to prove a reproducible and consistent production process and ensure that the desired glycosylation is present and immunogenic epitopes are reduced to a minimum. An example of the importance of controlled production are the “epidemic” incidences of Eprex®-induced antibody-induced red blood cell aplasia (PRCA) which was, amongst other factors, deduced to production-related changes in the carbohydrate profile [105,106]. Glycosylation changes between different producers, different production charges and biosimilar versus originator products were repeatedly observed [102,107-110]. Differences were observed between the abundance of non-core-fucosylated N-glycans of rituximab and proposed biosimilar Rituximab GP2013 [102]. However, complementary CDC-, ADCC- and receptor binding assays of innovator and biosimilar product showed very comparable results. Differences in N-glycan galactosylation levels were observed between trastuzumab and a candidate biosimilar and changes in N-glycosylation site occupancy were observed between tenecteplase tissue plasminogen activator (TNK-tPA) and a follow-on product [107,110]. Despite the probable effect of the significantly decreased site-occupancy on the bioactivity of the biosimilar the follow-on TNK-tPa was considered acceptable for marketing [107,110].

Interesting observations were made by Kawasaki et al when comparing three epoetin α and one epoetin β products from two different countries [108]. Although for all products tetra-sialylated tetra-antennary structure were most abundant, significant intra-class differences were observed in the acetylation pattern and presence of smaller structures for epoetin α.

The pre- and post-production change variability of glycosylation attributes was recently studied for darbepoetin-α (Aranesp®), rituximab (Rituxan®/Mabthera®) and etanercept (Enbrel®) [109]. Significant decreases in darbepoetin-α sialylation by 10%, a 3-fold increase in non-core-fucosylated G0 for rituximab or a 20% decrease in the di-galactosylated structure G2F for etanercept did not result in a market withdrawal of the products.

The question as to which changes in glycosylation attributes are acceptable can thus only be answered on a case-by-case basis and should be done in combination with complimentary data.

CONCLUSION

The inherent variability of biological systems challenges the manufacturing process of biologics and biosimilars. The requirements of manufacturing biologics are complex and a thorough understanding of the product is crucial. It is therefore of importance that biomanufacturing follows quality-by-design (QbD) principles. QbD defines the critical quality attributes (CQAs) of a product and requires the understanding of the association between CQAs and clinical properties [111]. Glycosylation is a key quality attribute as it can influence production rate, efficacy and safety of pharmaceutical proteins. The approval of biosimilars and the approval of changes in the manufacturing process of biologics are strictly regulated. However, the decision of comparability is difficult and cannot be generalized. A state-of-the art analytical toolbox is a key requirement for the establishment of a more targeted development process. However, the availability and extent of reference-product batches might be limited to the manufacturer. The assessment of comparability and the refining of regulatory guidelines would therefore be greatly facilitated by the existence of data collections on commercialized biologics. The establishment of defined reference standards which integrate knowledge on structural characteristics and structure-function relationships is still a matter of debate [112] but will definitely move forward the quality of biologics and biosimilar legislation and production.

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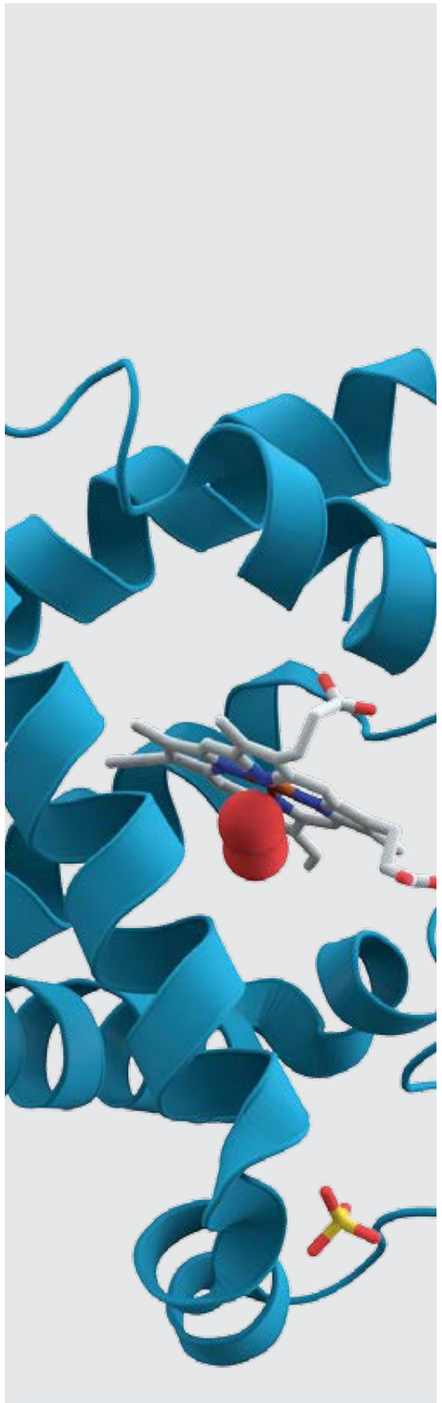
ABBREVIATIONS

ADCC, antibody-dependent cellular cytotoxicity; Asn, asparagine; BHK, baby hamster kidney; BLys, B-lymphocyte stimulator; CD, cluster of differentiation; CDC, complement dependent cytotoxicity; CHO, Chinese hamster ovary; CTLA, cytotoxic T-lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; EMA, European medicines agency; EpCAM, epithelial cell adhesion molecule; EPO, erythropoietin; FDA, food and drug administration; Fuc, fucose; Gal, galactose; G-CSF, growth factor granulocyte colony-stimulating factor;Glc, glucose; GlcNAc, N-acetyl-glucosamine; Her, human epidermal growth factor; HILIC-FLR, hydrophilic interaction liquid chromatography with fluorescence detection; IL, interleukin; IgG/E, immunoglobulin G/E; mAb, monoclonal antibody; Man, mannose; Neu5Ac, N-acetyl-neuraminic acid; Neu5Gc, N-glycolyl-neuraminic acid; PNGaseF, peptide N-glycosidase F; RANKL, receptor activator of nuclear factor-kappa B; Ser, serine; Thr, threonine; (S)Lea/x, (sialyl) Lewis a/x epitope; TNF, tumor necrosis factor; UPLC, ultra-performance liquid chromatography; VEGF, vascular endothelial growth factor; WAX, weak anion exchange chromatography. ■



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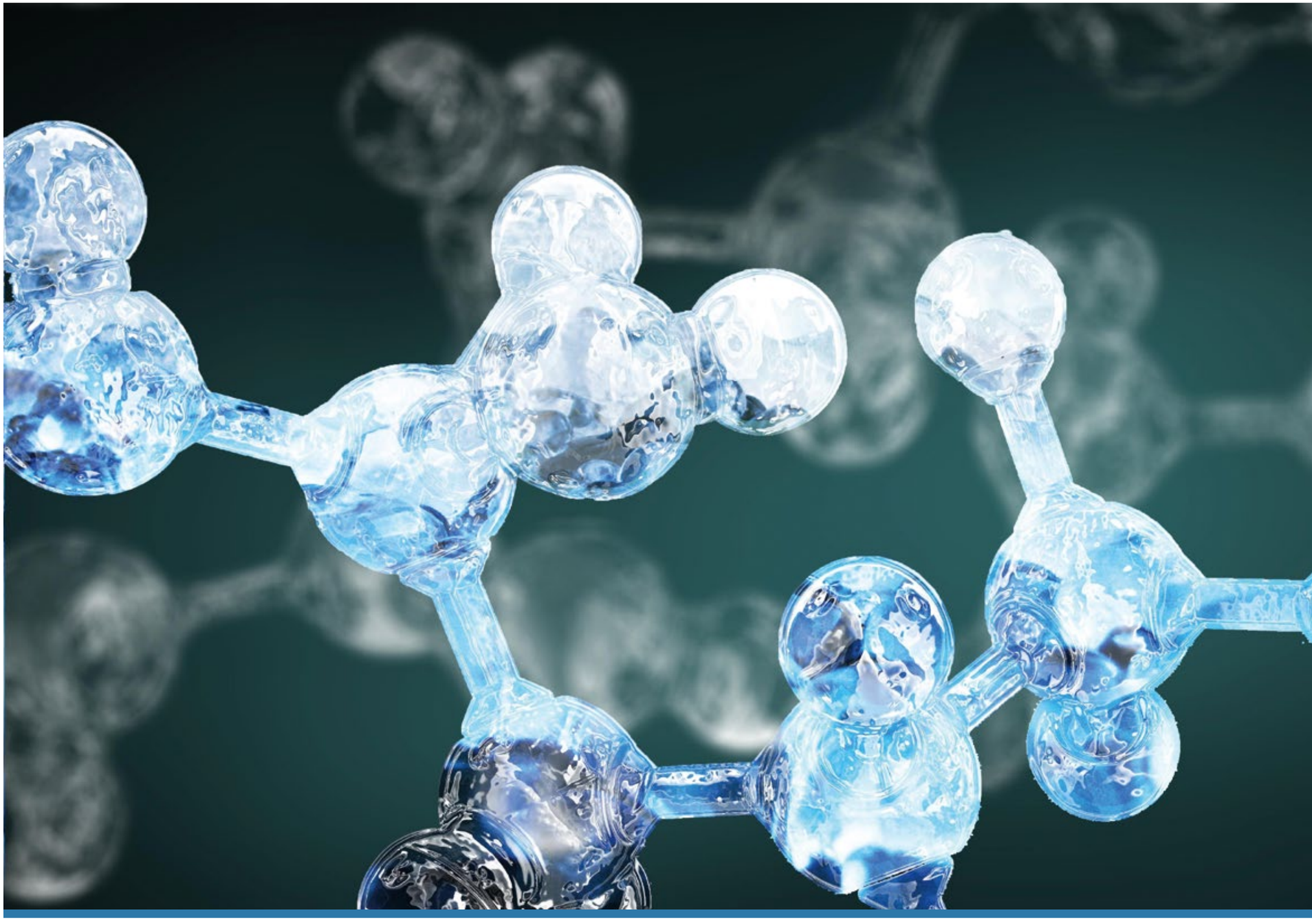

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Immunomodulation as the desired therapy in some cases of allergic diseases

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ABSTRACT

There has been a strong belief for many years that there is no pathogenic connection between allergy and autoimmunity. Academic books usually describe the disparate immune mechanisms playing pivotal role in pathogenesis of allergic and autoimmune diseases. A simplified hypothesis of Th1/Th2 balance disorder represents an accepted model of the diseases. Recent findings have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. The systematic review of the literature was performed searching electronic databases for the pathologic and clinical intersection of allergic a autoimmune conditions. Research is currently focused on the key elements that regulate the immune response. Mast cells, which play important role in allergic inflammation, make it likely that they have profound effects on numerous autoimmune conditions. Environmental stress and proinflammatory cytokines may activate the protein kinases in both conditions. The presence of autoantibodies in some allergic conditions such asthma or atopic dermatitis may point out an autoimmune background in some cases. Genetic factors lead the development and process of immunologic diseases. Data suggest a close relation between genepolymorphism of HLA and cytokines and development of autoimmunity and allergy. The infection also may play an important role in the induction of the diseases. Despite the use of more effective anti-inflammatory drugs, the progressionof many allergic and autoimmune diseases may not be halted. Better knowledge about the considerable communication between complex signalling pathways pointout immunomodulation as the key to successful therapy of both allergic and autoimmune conditions.

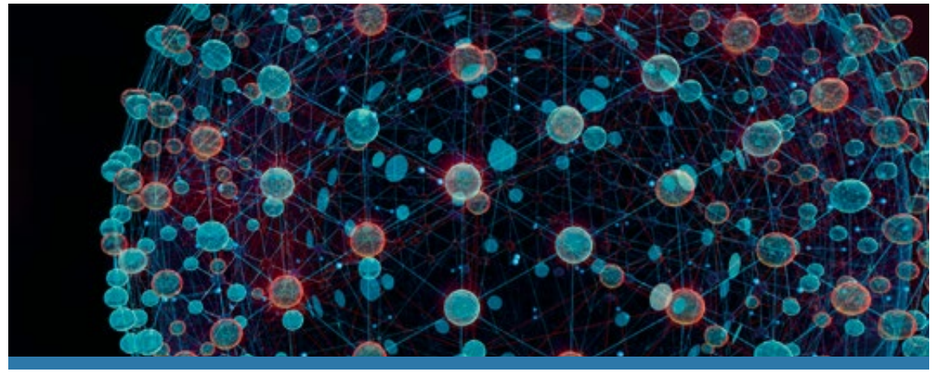
INTRODUCTION

Allergic diseases are very common and represent a major health problem worldwide. There has been observed an epidemic increase in prevalence of allergy in the last decades in some countries. It is estimated that 10 – 30% of the population is affected [1,2]. Because of their chronic, incurable, and sometimes life-threatening course, these diseases may be a significant socioeconomic burden. In many cases the diagnosis and treatment of affected individuals is insufficient and/or inadequate. In spite of great progress in research into the pathogenesis and treatment of allergy in the last few decades, there are still many problems to be resolved. Allergic diseases show a wide heterogeneity involving different organs such eyes, skin, respiratory and digestive tract. Allergic problems present variability in severity and clinical course which are at the present time only poorly defined. More precise definition of the clinical subtypes (phenotypes) of allergic patients appears important and necessary to address the right therapy to the right patient [1]. Some authors of academic books underline clear border between allergy and autoimmunity. The typical pathologic pictures would not suggest a similarity in pathogenesis of allergic and autoimmune disorders. Most cases of rhino-conjunctivitis or asthma are characterised by activity of Th2 (T-helper type 2) lymphocytes and Th2-derived cytokines as interleukins: IL-4, IL-5, IL-13 and stimulation of and eosinophil-predominant inflammation. On the contrary putative autoimmune disorders such as rheumatoid arthritis or type 1 of diabetes mellitus are thought to be mediated by Th1 (T-helper type 1) lymphocytes and Th1-derived cytokines as interleukins: IL-2, IFNγ. The most popular simplified hypothesis of Th1/Th2 imbalance attempts to explain ethiopathology of certain diseases [3,4]. However, in recent years, findings of some studies have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. In recent years interest of investigators is focused on the key elements that regulate the immune response in many allergic and autoimmune diseases: mast cells, autoantibodies, T-cells, cytokines and genetic determinants [5,6,7,8,9,10]. It is obvious that mast cells play important role in allergic inflammation. But they may have also profound effects on numerous autoimmune conditions. Another factors such as environmental stress and proinflammatory cytokines may activate the protein kinases in both allergic and autoimmune diseases. There are studies in which autoantibodies have been found in some allergic conditions such asthma or atopic dermatitis and they may point out an autoimmune background in some cases. Some recent discoveries have provided additional insight into roles of Th17 cells and T regulatory cells [9,11,12]. It is obvious that genetic factors play an important role in the development and process of immunologic diseases. The studies from recent years suggest a close relation between gene polymorphism of HLA and cytokines and development of autoimmunity and allergy. The gene polymorphisms may act as risk or as protective factors [13,14,15]. The role of the infection also may be important in the induction of allergy and autoimmunity [16,17,18]. In some cases similar clinical manifestations of both immunopathologies are observed and may result sometimes in diagnostic problems. Ever-expanding knowledge about the considerable communication between complex signalling pathways point out immunomodulation as the key to successful therapy of both allergic and autoimmune conditions [12]. It also helps to identify promising areas for future research.

RELATIONSHIPS BETWEEN AUTOIMMUNITY AND MAST CELL-RELATED DISEASES

Epidemiological data

Epidemiological data on the coexistence of both types of these mentioned disorders are scarce. Studies of the possible association between allergy and autoimmunity at the population level have come to varying conclusions. For



example in the last few decades, a positive correlation between the prevalence of asthma and the incidence of type-1 diabetes has been found at the population level, but not in the individual. Both of these immune-mediated disorders are positively associated with the gross national product [7]. In another study Tirosh et al. analyzed data from nearly 3-years of follow up of about 450 000 population of Israeli soldiers aged from 18 to 21 years. Studies have shown an inverse correlation between the occurrence of asthma and autoimmune disorders. Autoimmune diseases are often related to women. The inflammatory bowel diseases, vasculitis, arthritis, and autoimmune thrombocytopenia occurred more frequently in women who have not suffered from asthma while type-1 of diabetes in men without a history of asthma [19]. According to some experts opinions, extrapolating the results of this study to the general population can lead to erroneous conclusions [5]. In the Medline database one can find a few publications that prove a lower incidence of autoimmune diseases in patients with allergy or atopy, or indicate a negligible difference in the appearance of autoimmune disorders in patients with previously diagnosed allergic disease in contrast to controls without allergy [10]. Conversely, there are also reports arguing that there may be risk of developing autoimmune disease in allergic patients. In children with allergic diseases, more frequently than in the control group, the elevated antibody titers against peroxidase [20,21] and anticardiolipin antibodies [22] were found. Similar results were obtained in the group of 200 Iranian women. Half of them was suffering from asthma. A significant percent of asthmatic women had increased levels of anti-thyroid autoantibodies, but in the majority without clinical evidence of thyroid disease [23]. Agache et al. observed a frequent incidence of antinuclear antibodies in patients with severe asthma [24]. Similar reports were presented by Canadian researchers. The study included 3 groups of patients: patients with atopic asthma, patients with non-atopic asthma and patients with asthma and concomitant systemic lupus (SLE). Antinuclear antibodies in significance number of patients with non-atopic asthma were found in contrary to atopic asthma group but in lower titers compared to the group suffering from asthma and coexistent SLE. Moreover, the positive skin test to autologous serum in patients with non-atopic asthma and asthmatic patients with SLE was observed. It may suggest participation in the pathogenesis of autoimmune inflammation in non-atopic asthma [25]. Analysis of adult data from one of large American national studies demonstrated that common allergic disorders diagnosed by doctors were positively associated with incidence of physician-diagnosed autoimmune diseases. An interesting issue is a quite common occurrence of respiratory symptoms and bronchial hyperreactivity (BHR) in patients suffering from autoimmune diseases. Researchers emphasize that BHR in these patients is likely to be a consequence of structural changes and infiltration of inflammatory cells [7]. On the basis of previous studies we can say that the coexistence of both types of disease is still considered uncommon, although possible phenomenon.

Pathophysiological background

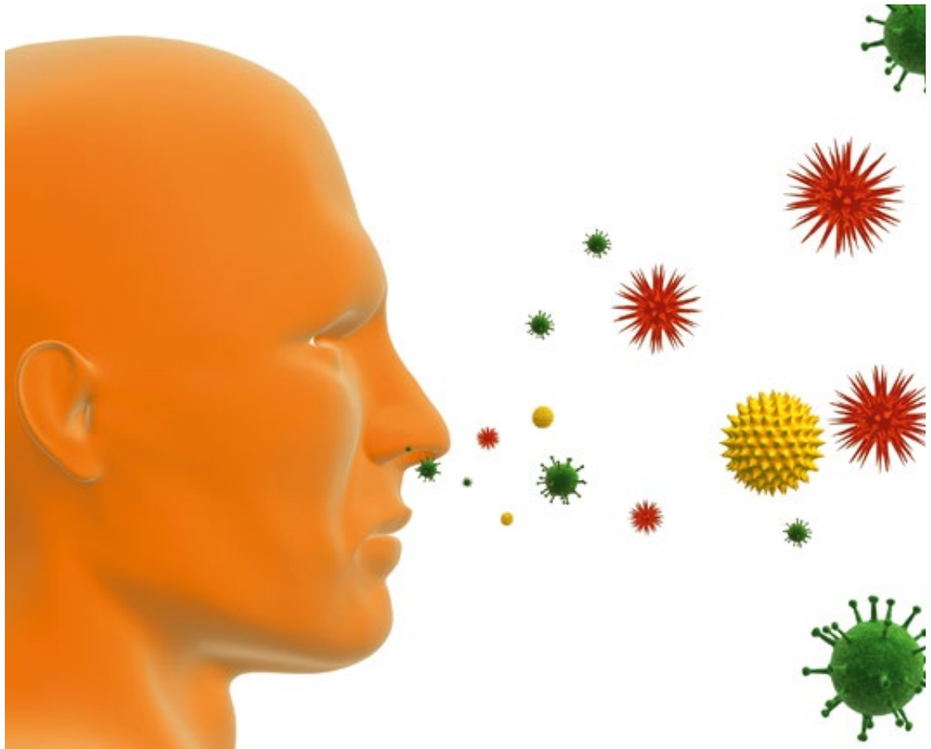
Both processes allergy and autoimmunity may show some similarities in their clinical course. Mast cell related conditions and autoimmune syndromes are inflammatory processes caused by dysregulated immune response. Both disorders are complex and result from the interaction between several factors: enviromental, genetic and individual. But the immune mechanisms involve similar types of cells, cytokines, antibodies, and mediators [7,8,9,12]. Recent studies have also shown close proximity of the certain genes regulating the occurrence and course of the two types of diseases [15].

Mast cell is associated mainly with the early phase of the allergic reaction. Antigens interact with the specific IgE molecules already bound to high affinity Fc receptors on the surface of mast cells to induce degranulation. The mast cell releases a mixture of compounds, including histamine, heparin, chymase, tryptase from its cytoplasmic granules. Releasing of mediators determines the course of the early phase of an allergic reaction. But contact with the allergen also provides for the production of a number of mediators and cytokines (prostaglandins, leukotrienes, TNF-a), which will be gradually released and determine the development of the so-called late phase of allergic inflammation, which is very complicated and dependent on the number of cells receptors, cytokines and mediators. The role of mast cells in the pathogenesis of allergic diseases has been well established [2,3,4]. However, recent studies have shown the possible involvement of mast cells in the disease as: multiple sclerosis, rheumatoid arthritis, bullous pemphigoid, Sjögren's syndrome, autoimmune thyroiditis and systemic sclerosis [5,8,12,26,27]. In previous studies it was found that not only exogenous factors can activate mast cells. For example contact with other cells such as T lymphocytes may result in degranulation of mast cells [26,27]. Other IgE-independent signals can lead to mast cell activation, including the interaction some molecules with the surface receptors Fcg I and III, anaphylatoxins, low molecular weight peptides such as substance P or a calcitonin gene-dependent peptide [12,26,27]. Mast cells and B-limfocytes have been found in the increased number in the synovial fluid of patients with rheumatoid arthritis. The increase in mast cell number is strongly correlated with activity of the disease. The studies of a murine model of inflammation demonstrated that transgenic mast cell-deficient mice were resistant to erosive arthritis induced by the arthritogenic antibodies [12]. It is widely known that mast cells are a source of TNF - a, which is the main mediator of inflammation. TNF - a is also the major cytokine present in the rheumatoid joints. TNF - a stimulates the production and release of inflammatory factors such as the matrix-damaging proteases, prostanoids, IL - 6 and GM- CSF. Similarly, an increased number of mast cells and elevated levels of tryptase and other mast-cell derived mediators were detected in cerebrospinal fluid obtained from individuals with multiple sclerosis. Mast cells were also observed in plaques and sites of demyelination. Although their presence in tissues affected by an autoimmune process seems to be obvious, there is still debate of their direct participation in the pathogenesis of this type of inflammation [12,30].

BOTH PROCESSES ALLERGY AND AUTOIMMUNITY MAY SHOW SOME SIMILARITIES IN THEIR CLINICAL COURSE. MAST CELL RELATED CONDITIONS AND AUTOIMMUNE SYNDROMES ARE INFLAMMATORY PROCESSES CAUSED BY DYSREGULATED IMMUNE RESPONSE.

T lymphocytes may be another link between the two processes. Autoreactive Th1 lymphocytes play a crucial role in autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune type 1 diabetes melitus, multiple sclerosis and autoimmune thyroid disease [4]. However many studies have shown that Th1 and Th2 are not the only cells that pave the directions of inflammation. More recently several different types of Th lymphocytes have been described: Th17, Th22 and Th9. The researchers focused their attention on the Th17 lymphocytes that are involved in chronic inflammation. They differentiate under the influence of strong pro-inflammatory cytokines such as IL-6, IL-21, IL-13 or TGF-β. Th17 cells are the source of IL-17 group of cytokines, which may have different functions in the inflammatory response. While the IL- 17F is correlated positively with the severity of asthma , IL-17A in an answer to allergen rechallenge decreases airway inflammation, which suggests a regulatory role of this cytokine in the lungs [13,28,29]. The role of Th17 and IL -17 is also emphasized in diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, psoriasis, SLE [31]. Increased activity of these cells was observed also in patients with allergic rhinitis and the presence of nose polyps, atopic dermatitis (AD). In patients with AD, number of Th17 cells positively correlated with the severity of the disease, perhaps by reducing the effect on the expression of mRNA for filaggrin, as shown by other studies [9,3]. An interesting issue is of plasticity of some T lymphocytes. Under the influence of different environmental factors, the nature and function of cells may be converted. Observations have shown that during the environmental allergen challenge, transformation of cells releasing IL- 17 in Th1 cells may occur [13]. An important recent finding (in studies of animal inflammation models) is that initiate Toll-like receptors (particularly- TLR4/inflammasome) activation can increase Th1- and Th17- types of immune response, which are frequently associated with autoimmune diseases. Recent reviews underlines the role of pathogen in activating of Toll-like receptors and inflammasome. Many adjuvants such as alum or Pertussis toxin may induce autoimmunity disorder in this way in animal models of inflammation [16].

Regulatory T cells - Treg - (CD4+ CD25 + FoxP3+) appear to be responsible for the homeostasis of immune system in the healthy subjects. It is a heterogeneous group of cells. Augmentation of Treg cell function might control Th2 mediated inflammation. Downregulation of these cells



function may give serious effects. The classical theory of autoimmune disorders is the loss of the ability to distinguish between their own and foreign antigens [3]. However it seems likely that the activation of the process of autoimmunity is due to specific stimulus- a so called “danger signal”, which makes an antigen presenting cell recognize an antigen as a stranger, requiring elimination. These signals can be either exogenous or endogenous , it can be caused by inflammatory process [33,34].

Previous research underline the crucial role of B cells in both types of inflammation. They may act as antigen presenting cells in the early phase of the reaction, and after differentiating into plasma cells become a source of various antibodies (IgG, IgM, IgA, IgD, IgE), depending on the type of the immune reaction. Thus B lymphocytes seem to play an important role in the pathophysiology of both allergic and autoimmune disease. B cells have numerous roles in these two types of inflammation, most notably differentiating into plasma cells and producing autoantibodies. Autoantibodies activate immune cells and the secretion of proinflammatory cytokines such as IL-6, IL-10, and TNFα, which may lead to tissue damage. There are also subpopulations of lymphocytes called Breg cells (B regulatory cells) that produce IL- 10, which has been involved in the control and limitation of inflammation. There is also evidence that these cells may have the influence on of Treg differentiation and Th17 and Th1 suppression. Recent studies have shown that there are several subpopulations of these lymphocytes, which indicates the complexity of their role in the process of inflammation. Breg cells were selected on the presence of the cell surface markers CD19 and CD20. There is the interesting question of the potential effects of B cell depleting therapy (rituximab - monoclonal antibodiy directed against the specific B cell surface markers CD20 or CD22) that may exert on Breg [9,29].

The presence of increased levels of autoanibodies, sometimes specific for a single tissue, is perceived as a hallmark of autoimmunity. However, several reports suggest a possible role for autoantibodies in allergic diseases [35]. Some patients with asthma, allergic rhinitis or atopic dermatitis have impaired sensitivity to β-adrenergic agents. Autoantibodies directed toward the β-adrenergic receptor were found in the serum of some patients with asthma. These antibodies can block the biologic function of the β2-adrenergic receptor in vitro [5,12]. Previous studies have shown that the levels of IgG autoantibodies to cytokeratin 18, a bronchial epithelial cell antigen, were significantly higher in patients with asthma compared with healthy controls [36]. Also IgG autoantibodies and T-cell reactivity against a common 55-kD antigen shared by platelets and endothelial cells have been found in group of asthmatics. These autoantibodies were mainly restricted to individuals with more severe, glucocorticoids-dependent, non-allergic asthma [7]. Nahm et al reported antibody reactivity against enzyme a-enolase, which is component of bronchial cells. The presence of serum anti-enolase autoantibodies significantly distinguished patients with severe course of the disease and aspirin-induced asthma [37]. Szczeklik et al. found the incidence of antinuclear antibodies in 55 % of patients on aspirin-induced asthma, 39 % of patients with allergic asthma, 41 % of patients with non-allergic asthma in contrast to 11% of the control group [38]. There is theory that antinuclear antibodies do not have a direct role in asthma pathogenesis, but indicate a susceptibility only towards autoimmune processes due to dysregulation of immune system, for example via reducing efficiency of Treg cells, which usually inhibits immune response against autoantibodies [7]. The presence of autoantibodies to β-adrenergic receptors and bronchial epithelium in patients with asthma may demonstrate autoimmune phenomena in allergic conditions, although a causal link between allergy and autoimmunity has not yet been established. It means that a mechanistic link between these antibodies and an allergic condition is yet to be proven [9].

The role of IgE antibodies in the allergic process is obvious. Some investigation showed that the presence of IgE antibodies, however, is not exclusive to atopic disease. Specific IgE antibodies have been observed in autoimmunity: anti-cyclic citrillunated peptides in rheumatoid arthritis, anti-GAD65 antibodies in type 1 diabetes, anti-TSH receptor antibodies in Grave’s disease, and anti-myelin peptides in multiple sclerosis, although the direct pathogenic role is largely unknown [9].

The genetic background of allergic and autoimmune disorders is represented by a complex network of interacting genes. Genome-wide screen studies of asthma have identified a several main regions of genome where genetic variants or disease-causing mutation are placed. Moreover genome-wide screen in families with rheumatoid arthritis has similarly shown linkage near the asthma locus on chromosome 2 and the TCR-α locus on chromosome 14. Some findings suggest that important genes or gene families may be common to several inflammatory and immune disorders. The genes are responsible for the production of specific cytokines and mediators what determines the directions of immune response. Previous studies point out toward the transcription factors such as STAT1, STAT4, GATA3, which expression is associated with production of specific cytokines. While STAT1, and STAT4, ultimately lead to release of interferon gamma (IFN-γ), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and other cytokines of Th1 response, the transcription factor GATA3 is expressed and promotes further expression of Il-4, Il-5, and Il-10, and B cell-mediated humoral immunity. GATA3 activation also serves to repress IFN-γ secretion [9,13]. Recent report published in Nature in 2013 indicates possible polymorphisms in a single gene of transcription factor BACH2. Genetic polymorphisms within a single locus encoding the transcription factor BACH2 may be associated with numerous autoimmune and allergic diseases. Assessment of the genome-wide function of BACH2, revealed that it represses genes associated with differentiation of effector cell. These findings identify BACH2 as a key regulator of CD4 T-cell differentiation that prevents inflammatory disease by controlling the balance between tolerance and immunity. BACH2 is expressed in B cells. Thus, at both cellu-

lar and molecular level, BACH2 functions to limit immune activation, enabling it to play a critical role in the maintenance of immune homeostasis. These findings help explain the role of BACH2 as a key node in human autoimmunity [14].

Although other findings of gene-wide screen study showed that the single mutation may determine only one specific type of immune response [15]. However, the proximity of location of the genes of determining the course of the inflammatory response may be considered as another link between these two processes. Is it a protective mechanism against the development of both types of reaction, or rather may it predispose to their coexistence? - The answer may be revealed in further research.

Allergic inflammation as a target to immunomodulation

Despite remarkable advances in diagnosis and use of potent anti-inflammatory drugs, asthma and many other allergic diseases are still incurable. It seems that progression of airway inflammation may not be halted. Understanding of pathological features of allergic inflammation showed that the process is highly complex with multiple features that include infiltration of the airways mucosa or skin by activated lymphocytes, eosinophils, and neutrophils, degranulated mast cells, and activated epithelium cells. Asthmatic epithelium exhibits sloughing and denudation, and cilia dysfunction together with collagen deposition in the epithelial sub-basement membrane area [2]. Allergic pathology is associated with the release of pro-inflammatory substances including inflammatory peptides, chemokines, lipid mediators, cytokines, and growth factors. In addition to infiltrating leukocytes, structural cells in the affected tissue, including smooth muscle cells in airways, endothelial cells, fibroblasts, and airway epithelial cells, are all important sources of symptoms of the diseases causing or enhancing mediators. Leukocyte migration and cellular activation are controlled by cell adhesion molecules, such as selectins, integrins, and members of the immunoglobulin superfamily.

The expression and function of these adhesion molecules and the subsequent chemotactic attraction and activation of infiltrating pro-inflammatory cells are controlled by a numerous of cytokines, chemokines, and mediators. Moreover structural cells may play important roles in the inflammatory processes. These inflammatory processes are coordinated by a complex cytokine network [2,3,4,12]. However, depending on the inflammatory context, cytokines often exert opposing actions and they often exhibit redundancy in their functions. Modulating the cytokine network in allergic diseases, sometimes with severe course, such as asthma or atopic dermatitis with biological therapy presents a new but challenging paradigm for treatment of these disorders. The basis for immunomodulation therapy of allergic diseases was initiated by the development of Th2 predominant response. It is associated with unique cytokine profile: IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33. Therapy based on this hypothesis concentrates on changing the balance of the immune system towards Th1 response. This can be done in two ways: blocking Th2 derived cytokines with antagonists (monoclonal antibodies, soluble receptors) or by stimulating Th1 response, boosting by addition of recombinant cytokines for example [39,40]. Some studies showed that IFN-g had potent local and systemic effects on the airway epithelium. This cytokine plays role in activation of antigen-presenting cells, IL-12 production and differentiation of naive T lymphocytes into Th1 [41,42]. IL -12 was considered as the additional target of immunomodulation, because mouse studies revealed that administration of this cytokine suppresses antigen-induced tissue eosinophilia and inhibits IgE production. Unfortunately due to significant toxicity IFN-g and IL-12 did not come to general use [41,43].

There are promising results of studies on unmethylated cytosine-guanine dinucleotides, known as CpG motifs. These motifs, as the adjuvant to immunotherapy, promote Th1 response, preventing tissue eosinophylia and reducing IgE production, and bronchial hyperresponsivenes. Il-18 also appears to play complex role in up-regulating Th1 response [41]. Although there is no certainty whether stimulating of Th1 response is beneficial in any case of allergic disease.

Recently most research is focused on down-regulation of Th2 immune response. The inhibition of eosinophil accumulation in asthma therefore represents a potential therapeutic strategy. Evidence from research showing IL-5 tissue localization in allergic diseases together with studies in IL-5-knockout, transgenic mice, suggest IL-5 is crucial to the development and release of eosinophils from the bone marrow and their enhanced adhesion to endothelial cells and their activation and secretion in the tissues. The presence of tissue eosinophils is evident feature of several allergic diseases including asthma, rhinitis, eosinophilic esophagitis and idiopathic hypereosinophilic syndrome [43,49].

DESPITE REMARKABLE ADVANCES IN DIAGNOSIS AND USE OF POTENT ANTI-INFLAMMATORY DRUGS, ASTHMA AND MANY OTHER ALLERGIC DISEASES ARE STILL INCURABLE.

Both Il-4 and IL-13 are very important cytokines for the tissue accumulation of eosinophils and they are main factors of IgE synthesis by B lymphocytes. Both exert its effects through the special receptor complex (IL-4Rα/IL-13Rα1) which then activates the transcription factor STAT-6. It has an important role in activating genes associated with the differentiation of naive T-cells into Th2 cells, airway inflammation, and bronchial hyperreactivity. Studies with soluble IL-4R given in a nebulized form demonstrated an improvement in the course of moderate asthma. However, despite these promising findings subsequent trials have not been as successful and consequently this treatment is no longer being developed [41,44,45]. Airway hyperresponsivenes, mucous hyperproduction, up-regulation of eotaxin and IgE production and eosinophilis recruitment are regulated by Il-13. Many recent studies are focused on blocking action of IL-13 with promising results [41,45]. IL-33 belongs to the IL-1 superfamily. IL-33 and its receptor ST2 promote various activities related to the up-regulation of TH2 response. This cytokine is released predominantly by damaged cells. It suggests that IL-33 function as an endogenous danger signal particularly in epithelial and endothelial cells is directly exposed to environmental challenge. The experimental models of asthma revealed that the blockade of IL-33 and its receptors reduces the severity of the disease [46].

TNF-α is one of the most important cytokines in innate immune response that has been implicated in several chronic inflammatory diseases including also autoimmune disorders. Anti-TNF-α therapy proving useful in these conditions. TNF-α is produced by macrophages and other pro-inflammatory cells including dendritic cells, monocytes, B and T lymphocytes, neutrophils, and what important for pathogenesis of allergic diseases by mast cells and eosinophils, which together with the structural cells including fibroblasts, epithelial cells, and smooth muscle cells represent significant sources of this mediator. TNF-α exerts pro-inflammatory effects on various cells and may play a key role in amplifying airway inflammation through activation of transcription factors: NF-κB and AP-1. Because TNF-α is thought to be the main mediator contributed to bronchial hyperreactivity, airway remodeling, and resistance to steroids in asthma and atopic dermatitis therefore represents a potential target for therapy [2,7,45].

Receptor for IL-17 (very important proinflammatory cytokine) has become the newest target for immunomodulatory drugs [47,48]. For recent years attention of researchers is focused on the chemokine receptors, especially CCR3. Chemokines are a family of small, secreted proteins that control migration of many cells. Eotaxin is an inducible chemokine secreted in asthma that promotes selective recruitment of eosinophils from the blood into inflammatory tissues via CCR3, a seven-transmembrane-spanning Gprotein-coupled receptor.

Another approach to immunomodulation is targering transcription factors. Attempting to modulate STAT-6 or GATA-3 and the signaling pathways may be essential to modification of the course of inflammation. But it presents serious challenge to researchers because these molecules are intracellular [41].

IgE plays a very important role in the pathogenesis of diseases associated with immediate hypersensitivity reactions, including allergic asthma, atopic dermatitis, urticaria, food allergies and others. IgE-dependent symptoms are a result of it binding to high-affinity receptors (FcεRI) on mast cells and basophils and to low-affinity receptors (FcεRII) on macrophages, dendritic cells, and B lymphocytes. Allergen mole-

cules join to the Fab components of IgE binding on the cell surface thereby activating intracellular signal transduction. In mast cells, this leads to the degranulation and release of preformed mediators and the rapid synthesis and release of other mediators responsible for allergic inflammation. Therefore, blocking the action of IgE using antibodies that do not result in cell activation is an attractive therapy approach [2,3,4,49].

Immunomodulatory drugs in treatment of allergic disorders

There is a group of patients with severe course of asthma or/and atopic dermatitis who does not respond to standard therapy despite the use of maximal dose. Moreover it is well known that steroid therapy does not prevent the airway remodeling in asthmatic patients and does not influence the natural course of the diseases as well as topical steroids in atopic dermatitis [2,32,50]. In allergic asthma due to exogenous allergens efficacy of immunotherapy has been confirmed in numerous clinical studies [2]. Whereas in non-allergic, intrinsic asthma the airway inflammation is triggered by complex mechanisms, probably also involving IgE and perhaps, autoimmunity [7,8]. In the past, various, potentially immunosuppressive drugs such as methotrexate, ciclosporin, gold salts and troleandomycin, have been used in patients with severe steroid-dependent or steroid-resistant asthma. Most of these drugs gave significant steroid-sparing effects. However numerous adverse events during the therapies were observed. Many studies have failed to demonstrate an unacceptable risk-benefit ratio [7]. GINA report does not recommend these drugs as the standard therapies as well as macrolides nad anti-TNF-a agents. As a novel therapy omalizumab is recommended as add-on therapy in very severe atopic asthma [2]. Cyclosporine has been still used in chronic urticaria refractory to other therapies [51]. Several studies have examined the therapeutic efficacy of macrolides in patients with asthma. Because of their pleiotropic effects: anti-inflammatory and immunomodulatory in addition to antibacterial there were trials of maintenance treatment with low-dose macrolides. The Azithromycin in Severe Asthma Trial has demonstrated efficacy and safety of this therapy. A significant reduction in number of exacerbations was observed in patients with severe, non-eosinophilic asthma. Although chronic therapy with macrolides is associated with the risk of population antimicrobial resistance, than it should be reserved to special selected cases [52].

Humanized murine anti-TNF-α antibody - infliximab and soluble TNF-α receptor linked to human IgG1-etanercept have been developed and preliminary clinical studies in asthma showed significant improvements in lung function, reduction of airway hyperreactivity, and number of exacerbations, particularly in patients with severe asthma refractory to treatment with glucocorticosteroids [53]. There were few attempts of treatment with both of these drugs the patients with atopic dermatitis, but without the expected success [32]. However, a following clinical trial with the anti-TNF-α biologic golimumab in patients with severe, uncontrolled asthma reported negative clinical findings. Moreover, this study was terminated early due to unacceptable adverse events including frequent serious infections and eight cases of malignancies in the active-treatment group compared with the placebo group [45].

Omalizumab is a humanized monoclonal antibody directed to the FcεRI binding domain of human IgE resulting in a rapid decline in circulating levels of unbound IgE. Omalizumab does not bind to IgE bound to specific receptors on cells but down-regulates expression of high-affinity receptors by these cells. Omalizumab inhibited early-phase and late-phase allergen-induced asthmatic reactions and reduced serum free IgE concentrations and has progressed through clinical development [49]. In several studies omalizumab has been shown to be beneficial as an add-on therapy in severe persistent asthmatics with inadequately controlled symptoms while a pooled analysis of six controlled clinical trials that evaluated the effect of add-on omalizumab in patients with severe persistent allergic asthma reported significant improvements in quality of life indices. Omalizumab reduced the frequency of exacerbations and improved symptom control while allowing a reduction in the use of glucocorticoids and β2-agonists. It also improved patients' quality of life and produced a significant improvement in lung function. Moreover, in patients with severe asthma, omalizumab significantly reduced disease exacerbations and hospital admissions compared with control subjects. It appears to be well tolerated but more long-term studies are needed to fully demonstrate the benefit and safety of anti-IgE therapy in asthma. A number of studies have also examined the use of omalizumab as a treatment for other allergic diseases including food-allergy, mastocytosis, allergic rhino-conjunctivitis, chronic idiopathic urticaria, atopic dermatitis, hymenoptera venom allergy, and Churg-Strauss syndrome. But these conditions have not become still indications for this biologic agent [7,9]. Omalizumab has not been yet tested in patients with non-allergic asthma, but there are some findings provide the rationale for use in these group of patients. Elevation of total serum IgE was found in some of these individuals, supporting the role of this immunoglobulin, independent of allergy for developing of asthma symptom. In some patients with non-allergic asthma local production of IgE in bronchial biopsies has been demonstrated [7]. Previous observations revealed that the response to omalizumab is variable and difficult to predict. It seems that some biomarkers may help to predict the response to anti-IgE therapy and can identify potential responders. Among these biomarkers

were fractional excretion of nitric oxide (FENO), peripheral blood eosinophil count, and the novel one - serum periostin (a matricellular protein which is secreted by bronchial epithelial cells when stimulated by Th2 cytokines). Omalizumab as well as lebrikizumab, pitrakinra, dupilumab and tralokinumab were associated with greater effects in specific high-biomarker groups. Similarly the proof of the need for personalized medicine in asthma and other allergic diseases was provided by study with lebrikizumab (humanized IgG4 monoclonal IL-13 neutralizing antibody administered intravenously). In the study, pre-treatment measurements of th2 inflammation (serum IgE and ostepontin - biomarker from epithelial cells for IL-13 action). Although the response of the overall population was minimal, the high-biomarker group showed a rapid and sustained increase in pre-bronchodilator FEV1 after 12 weeks therapy. A major advance in personalized medicine will be the identification of particular endotypes of diseases and help to guide the use of specific biologics in the appropriate patients. It may allow to modify the activity of the innate immune response in individuals who manifest specific pathway activation [54]. With the exception of omalizumab and dupilumab the majority of biologics have proven inadequate in the clinical setting in asthma even though they were highly effective in animal models of asthma. Conflicting evidence exists regarding efficacy of omalizumab as well as rituximab in atopic dermatitis [32,55].

The immunotherapy is the oldest and the most widely used method of immunomodulation in allergic diseases. It was first developed at St Mary's Hospital in London at the end of the 19th century. The basic principles were described by Freeman and Noon, and many of them remain valid today. This form of treatment involves the subcutaneous or sublingual administration of gradually increasing quantities of allergens until a dose is reached that is effective in inducing immunologic tolerance. The primary objectives of allergen-specific immunotherapy are to decrease the symptoms triggered by allergens and to prevent recurrence of the disease in the long-term. Several mechanisms have been proposed to explain the beneficial effects of immunotherapy. First of all the reduction in specific IgE levels is observed

during long-term therapy, although they can increase temporarily pending the initial phase of SIT. But the inhibition of the recruitment and activation of effector cells including mast cells, eosinophils, and basophils in the allergic respiratory mucosa of the nose and bronchi seems to be more important. Data strongly suggest that these mechanisms are modified as a consequence of altered T-lymphocyte responses following high dose allergen exposure during immunotherapy. Immunotherapy also has been shown to induce a subset of T-regulatory cells with allergen-specific increases in the production of IL-10 and TGFβ. These cytokines inhibit T responses and reverse antibody production in favour of IgG4 and, possibly, IgA synthesis with downregulation of IgE responses. These events are accompanied by suppression of allergen-induced T cell-dependent late responses in the skin and lung and long term disease suppression which is apparent following discontinuation. Immunotherapy is the only treatment that has the potential to modify the course of allergic disease, which is in contrast to usual pharmacotherapy [56]. However, there is some concern about the use of immunotherapy as immunomodulatory treatment in patients with autoimmune disorders- although there is no hard evidence that SIT is actually harmful to these patients. Also, the results of long term observational study do not indicate the increased prevalence of new cases of autoimmune diseases in the group of patients treated with SIT [57].

CONCLUSIONS

Available data indicate the complexity of the allergic inflammation and the possibility of participation of the same components in both allergic and autoimmune diseases. Both types of disorders result from dysregulation of the immune system. Not only genetic factors but also environmental factors (eg, infections) have an impact for their development and course. The imbalance of Th1/Th2 pathways is one of the aspects of pathogenic mechanisms only. Recent studies revealed that the same types of cells (Treg, Breg) regulate both types of inflammation There are involved also similar cytokines, antibodies and mediators. The newest studies have provided additional insight into the roles of Th17 cells, B cells and Treg cells as well as the considerable communication and commonalities between the complex signaling pathways. In addition, external factors may have influence to the immune response. Taking into account pathogenesis mosaic, major task in the future of allergic diseases research should be to identify phenotypes that will ultimately lead to individualized medicine and patient-tailored treatment.

The results of previous in vitro studies and animal models have indicated the promising development of novel compounds targeted at diverse aspects of the inflammatory cascade underlying pathogenesis of allergic diseases such as asthma, atopic dermatitis, chronic urticaria. The development of novel anti-inflammatory therapies for these disorders has proven to be for the most part disappointing; in particular, results from animal-based studies have been very misleading. Despite significant benefit and few adverse effects, the blockade of action of single cytokine or mediator, or receptor often result in partial efficacy only, and does not addresses all allergic population. Future investigations of alternative pathways of inflammation are needed. Moreover identification of specific endotype of disease seems to be essential for adequate treatment. ■

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Belimumab therapy in systemic lupus erythematosus – the clinical expectations and burdens

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with serious organ involvement and unpredictable outcome. In 1990s B-cell activating factor (BAFF), which induces B cell maturation, survival, switch-class recombination and high-affinity antibodies production was discovered. The intensive research proven the importance of BAFF in SLE pathogenesis in both murine models and humans. In 2011 belimumab, human monoclonal antibody specific for soluble BLyS (B-lymphocyte stimulator) was approved for active, seropositive SLE treatment in add to standard of care therapy. Belimumab is the first target, biologic therapy formally approved for SLE. To overcome the complexity and heterogeneity of SLE the new rules in clinical trial design were done: restrict inclusion criteria involving only seropositive patients with active disease and implementation of a novel, composed responder index. Despite the success, new medication rises some efficacy concerns: modest clinical effect, no data provided for treatment of lupus nephritis or central nervous system involvement and very high cost.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, with the wide range internal organ involvement, that cause significant morbidity, increased mortality rate and diminished quality of life. Due to its heterogeneity, lack of universal biomarkers and unpredictable course of flares and remissions, it is difficult to construct and to achieve primary end-points in SLE clinical trials. After 50 years of failures in 2011 US Food and Drug Administration (FDA) approved first new, target therapy in SLE – belimumab, which is monoclonal antibody neutralizing BAFF (B-cell activating factor). This review paper presents arguments advocating this therapy from pathogenic and clinical point of view and on the other hands explains its limitations.

LYMPHOCYTES B, BAFF AND APRIL SYSTEM IN SLE

B cells play a critical role in autoimmunity and SLE pathogenesis. Under normal conditions B cells develope in the bone marrow and in the peripheral lymphoid organs. Their differentiation into memory cells and antibody secreting plasma cells is mainly antigen-dependent and needs both co-stimulation from T cells, cytokine environment and B-cells survival factors [1]. One of them is BAFF also commonly known as BLyS (B-lymphocyte stimulator). It is a 285 amino-acid type-II transmembrane protein member of tumor necrosis factor (TNF) superfamily, subsequently cleaved a soluble 17-kD biologically active protein (also known as TNF superfamily member 17 – TNFSF17). BAFF was first described

PRIMARY CERVICAL CANCER CONSTITUTES A VAST MAJORITY OF CASES OF UTERINE CANCER AND DEVELOPS OVER MANY YEARS FROM PRECANCEROUS LESIONS KNOWN AS CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

in 1999 by three independent groups, and since the very first descriptions was suspected to play a critical role in human B-cells immunity, both in physiology and pathology [2-5]. BAFF binds to three receptors on B cells: BCMA (B cell maturation), TACI [transmembrane activator and CALM (calcium modulator and cyclophilin ligand) interactor] and BAFFR (BAFF receptor also known as BR3).

The major source of systemic BAFF are myeloid-lineage cells: monocytes, dendritic cells, macrophages and neutrophils and bone-marrow–derived radiation-resistant stromal cells. Also expression of BAFF by follicular Th cells in germinal centers, is necessary for the development of antigen-specific high affinity B cells [6]. BAFF mainly circulates in trimeric forms. As well multimeric forms of BAFF were described (in ex. clusters of 60-merics), however their influence on in vivo immune response remains to be elucidated. The main importance is now related to function of soluble, trimeric forms. Both, in humans and mouse, BAFF contributes in B cell survival, differentiation of immature B cells to mature B cells, to Ig class switch and antigen specific antibody production, leading to generation of high affinity antibodies [7-10]. Moreover some studies on mouse models suggest that autoreactive B cells have a greater dependency on BAFF then non-autoreactive B-cells populations [11].

The other important player in B cells homeostasis is a proliferation inducing ligand known as APRIL. It is a 250-amino acid member of the TNF ligand super family (TNFSF13), which shares homology with BAFF. APRIL is released only in soluble form and binds to two receptors, TACI and BCMA, but not to BAFFR, leading to more pronounced influence of APRIL on plasma cells [12]. From practical point of view it is important to remember that soluble BAFF inhibition does not influence on APRIL function by TACI and BCMA.

Due to its properties it is not surprising that BAFF is associated with SLE. In animal models Baff-transgenic mice developed severe B cell hyperplasia, hypergammaglobulinemia, multiple autoantibodies, immune-complexes and immune deposition in kidneys [13-16]. An association of BAFF levels and human SLE also has been documented. The preliminary results indicated that serum BAFF level was elevated in the patients with SLE, and the increased BAFF in SLE existed in the soluble form, which is cleaved from cell surface [17, 18]. The serum BAFF level correlated with serologic abnormalities, including dsDNA titer, however did not correlate with disease activity and severity. However there was a suggestion that the disease activity tools and small number of patients were not sufficient to confirm relation. In the study which included over 200 SLE subjects association between a greater increase in the BLyS level from the previous visit

and a greater increase in the SELENA-SLEDAI (SLE Diseases Activity Index) score at the subsequent visit, and between an elevated BLyS level at the previous visit and a greater SELENA-SLEDAI score at the subsequent visit, demonstrate a relationship between circulating BLyS levels and SLE disease activity [19]. Almost 50% and 61% of patients have manifested persistently or intermittently elevated serum BLyS and blood BLyS mRNA phenotypes, respectively in longitudinal observation [20]. In Cheema at al. study BLyS levels correlated inversely with nephrotic-range proteinuria in SLE patients [18]. This results lend support to the notion that inhibition of BAFF/APRIL axis is therapeutic targeting in SLE and lead to further progress in the area. Despite belimumab, monoclonal antibody that inhibits soluble BAFF, three other type of molecules are in clinical development – atacicept, fusion protein which targets BAFF and APRIL, blisibimod (peptibody) and tabalumab, monoclonal antibody, both target membrane and soluble BAFF [21].

BELIMUMAB IN SLE

Belimumab (Benlysta) is a first BAFF antagonist approved by FDA. It is a human IgG1 mAb that neutralizes soluble BAFF [21]. However its way from bench to bedside was somehow bumpy [23]. In 2003 a phase I clinical trial (70 lupus patients enrolled) documented safety of the drug [24]. A phase II clinical trial in SLE with mild and moderate disease activity confirmed that therapy was safe, but the efficacy end-points were not met. Belimumab was administered intravenously initially at day 0, 14, 28 and then every 28 days. SELENA SLEDAI and SELENA SLEDAI Flare Index were used for the activity assessment. There was no significant improvement in the disease activity except of patients who were ANA (antinuclear antibodies) or dsDNA positive on study entry [25]. In 2009 novel evidence-based systemic lupus erythematosus responder index (SRI) was described, based on belimumab phase II SLE trial and demonstrated its potential utility. It demonstrated the ability to define a responder index based on improvement in diseases activity without worsening in overall condition or the development of significant disease activity in new organ system [26]. Subsequently SRI was implemented as an outcome measure in both pivotal belimumab studies. In a phase III study which was conducted in 90 centers in Latin America, Asia Pacific and Eastern Europe (Romania and Russia), only unequivocally seropositive patients, with active disease (score ≥ 6 at screening on SELENA SLEDAI) were included. They have to be on a stable treatment regimen with fixed doses of prednisolone or standard of care therapy (SOC): non-steroidal anti-inflammatory, antimalarials or immunosuppressive, at least 30 days before the first study dose. It is necessary to underscore that on study design the changes to SOC therapy was restricted after 16 weeks for immunosuppressant medications and after 24 weeks for antimalarials.

The main clinical exclusion criteria were severe lupus nephritis and central nervous system involvement. To the BLISS-52 study 1266 patients were screened and 847 randomly assigned in 1:1:1 ratio to placebo, or belimumab 1 mg/kg, or 10 mg/kg. The study drug was administered by iv infusion on days 0, 14, 28 and then every 28 days until week 48. The primary efficacy endpoint was the response rate at week 52, assessed by SRI [27]. A responder was defined as having a reduction of at least 4 points in the SELENA SLEDAI score, no new British Isles Lupus Assessment Group index A organ domain score (BILAG), no more than 1 new BILAG B organ domain score and no worsening in Physician Global Assessment (PGA) score (increase<0.3) at week 52 compared with the baseline. At week 52 primary end-point was achieved. Significantly greater responses were noted starting from week 16 for dose 10 mg/kg (except week 20) and from week 28 for dose 1 mg/kg. Moreover the proportions of patients with at least a 50% reduction in prednisone dose were significantly greater with belimumab 10 mg/kg at every visit from weeks 24 to 52. Use of prednisone was significantly greater in the placebo group then in the belimumab group (10 mg/kg) from week 12 to 52. The reduction in risk of flares was shown by the increase of median time to flare, and the risk of moderate to severe flares was significantly reduced in the belimumab group. Early in the study, starting form week 4 and 8 belimumab improved serum complement concentration and decreased dsDNA titer.

MOREOVER THE CLINICAL RESPONSE ASSESSED BY SRI IS A COMPOSITE INDEX INCLUDING SEVERAL INDEPENDENT TOOLS OF ACTIVITY ASSESSMENT WHICH ARE NOT ROUTINELY USED IN THE REAL LIFE. IT MAKES DIFFICULT FOR CLINICIANS TO ASSESS RESPONSE AND MAKE DECISIONS FOR TREATMENT CONTINUATION OR DISCONTINUATION.

The BLISS-76 study, the second study which led to belimumab approval for SLE, included 826 patients from US and Europe. Similarly to BLISS-52 primary end-points were achieved by week 52, but SRI did not differ significantly between groups in week 76 [28].

The safety profile of belimumab was similar to that of placebo, with no differences between trial arms in any studies.

Pooled analysis of this trials revealed benefits of belimumab (10 mg/kg) in the mucocutaneus, musculoskeletal, CNS and vascular organ domains [29]. Also at the post-hoc analisys among the 267 patients with renal involvement at baseline from BLISS-52 and BLISS-76, those receiving mycophenolate mofetil or with serologic activity at baseline had greater renal organ disease improvement with belimumab than with placebo [30]. It seems that the most important predictors for benefits from belimumab treatment are high disease activity at baseline, dsDNA positivity, hipocomplementemia and high dose of steroids [31].

Lately data of the total belimumab exposure over 7 years (double-blind and open-label periods) and 1746 patient-years were published. SLE response rates at week 52 in autoantibody-positive patients: was in placebo, 29%; and in belimumab, 46% ($p < 0.05$). In the continuation study, 57% of auto-antibody-positive patients had an SRI response by year 2 and 65% by year 7; severe flares occurred in 19% with placebo and 17% with belimumab during the first year, with the annual rate declining to 2%-9% during years 2-7. Anti-dsDNA autoantibodies in patients positive for them at baseline had a progressive decline of 40%-60% from baseline over 2-7 years with belimumab. Corticosteroid use decreased over time with ≥ 50-55% reduction in median dose during years 5-7. Serious and overall annual adverse events rates, including infections, were generally stable or decreased during 7-year treatment [32].

Finally belimumab (Benlysta) is approved only as an add-on therapy for SLE in adults with a positive auto-antibody test whose disease is still highly active despite standard treatment. Despite the hopes for approval of new drug, some practical concerns have been raised, limiting the clinicians enthusiasm.

LIMITATIONS OF BELIMUMAB THERAPY IN SLE

A first area of concern is the limited target group- only patients with seropositive SLE but with exclusion of more severe and debilitating organ involvement: active lupus nephritis and central nervous system. All the completed and published studies with belimumab excluded such patients.

The second problem is the prolonged time for the response assessment. The time necessary for initial treatment is as long as 6-12 months, both for responders and non-responders. In the latter it means at least 6 month of really expensive, biologic treatment that does not give any clinically significant benefits. In case of responders there are another issues – doubts if there is no loss of efficacy on prolonged treatment, as response from 52 weeks, was no longer present 24 week later in BLISS-76 study [33]. It can be due to the BAFF independent autoimmunity pathogenic pathway that can occurre in patients with the prolonged BAFF inhibition.

Moreover the clinical response assessed by SRI is a composite index including several independent tools of activity assessment which are not routinely used in the real life. It makes difficult for clinicians to assess response and make decisions for treatment continuation or discontinuation. Another aspect is a clear explanation for patients what benefits can be expected from this chronic treatment in their health status or particular, specific symptoms. It seems to be mostly intuitive. On the other hand in the real life possibility to reduce glicocorticosteroids dose, and to avoid glicocorticosteroid-related damage, can be important argument for treatment, for both, the patient and the clinician. The next argument, important for remitting-relapsing patients can be prolong time between moderate or severe flares, which lead to hospitalization and cytotoxic treatment induction.

On the other hand if any benefits for belimumab treatment is achieved the next concern is the time of discontinuation. There are no any available data to support this decision but on the it is not reasonable to continue belimumab life-long.

Taking all of this into consideration due to unfavorable estimates of cost effectiveness belimumab is still not recommended by NICE for SLE treatment [34]. Additional economic studies involving the real cost of SLE treatment and clinical data regarding belimumab treatment and discontinuation are needed to change this recommendation. Future research may define the specific clinical manifestations related to abnormalities in BAFF/APRIL system, what might help to stratify patients with SLE into subgroups that are more likely to respond for anty-BAFF therapy [35]. ■

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Biosimilar drugs – automatic substitution regulations review. Polish ISPOR chapter's Therapeutic Programs and Pharmaceutical Care (TPPC) task force report

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ABSTRACT

Objectives: **Review of the EU regulations concerning substitution of biological products with biosimilar products .**

Methods: **The TPPC task force has checked the approach to automatic substitution by WHO, at the EMA level and in countries across European Union. An internet search was performed checking the regulations and direct contact to Regulatory Agencies in all European Union member states.**

Results: **Based on the research we have obtained directly information from 23 EU Member States and Switzerland. Most of the EU countries do not allow for automatic substitution of the reference biological medicinal product by a biosimilar. Currently some EU countries already have local legal regulations towards automatic substitution of medicinal products in place.**

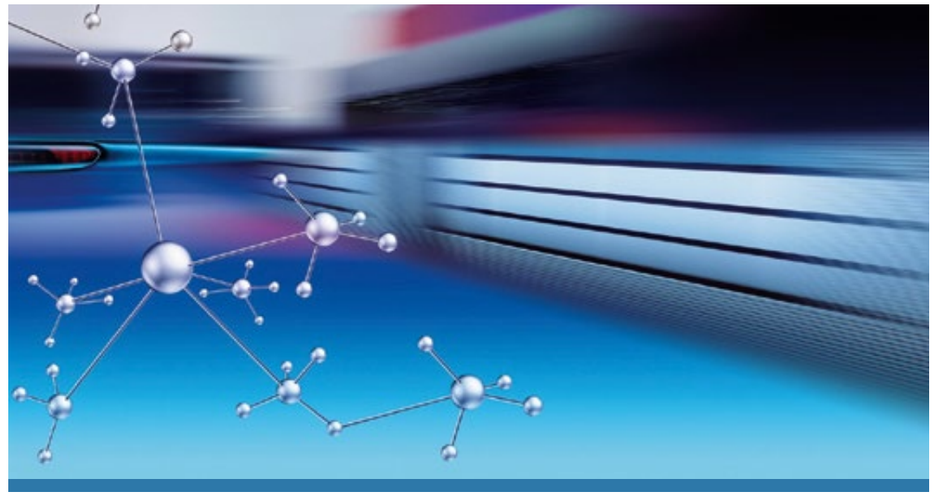
Conclusions: **Due to medicinal product complexity in most of the European Union countries the automatic substitution of a reference biological product by a biosimilar product is not allowed. Local regulations are needed in each of the Member States according to EMA guidance.**

BACKGROUND

Biological medical products, being comprised of proteins, hormones, monoclonal antibodies and gene or cell therapies are produced with advanced technologies. Currently more and more diseases can be treated with targeted therapies. In order to ensure proper safety and efficacy of the final product the manufacturing process of the biologicals is carefully controlled due to its sensitivity and high level of expertise required. The biosimilar products are developed to be as similar as possible to the reference medicinal product in terms of safety and efficacy and in the European Union EMA is the authority responsible for review of the marketing authorisations for the biosimilars. However the final decision on whether to substitute a reference biological medicinal product is the responsibility of the authorities in each of the EU Member States.

Taking into consideration the complexity of the molecules, manufacturing sensitivity, the potential to induce immunologic reactions, it is especially important for clinicians to be involved in the decisions related to the medication choice and possible substitution.

The TPPC task force worked on a review of regulations towards biosimilar drugs reimbursement and definitions in 2011-2012 [1]. As a continuation



of that discussion the automatic substitution regulations are currently in scope of our interest.

METHODOLOGY

In order to prepare the review of the regulations regarding automatic substitution of a reference biological product with a biosimilar product at EMA and in each of the European Union Member States we worked in parallel and; on one hand we performed an internet search and on the other; we contacted directly the Regulatory Bodies in EU Member States. In relation to the internet search there was initially no limitation towards the countries in scope, however due to Poland being an EU member state, the defined scope of countries of interest was specially focused on EU.

Prior to different databases search we have checked for the difference between interchangeability, switching and automatic substitution terms.

Then the databases have been reviewed to identify published regulations concerning reference biologic and biosimilar drugs automatic substitution. The search done by TPPC focused on the following words: "biosimilars", "biological drug", "biological drug substitution", "authomatic substitution", "substitution guidelines" , "substitution regulations" and it was conducted using the Internet.

In parallel, we emailed all European Union Member States' Regulatory Agencies asking for information regarding local regulation towards automatic substitution. The same predefined set of questions was send to the Agencies in order to gather information if the automatic substitution is allowed and if the topic is regulated by legal Acts at country level. In case that such regulation exists we asked for reference documents or website link to access such documents.

FINDINGS

According to European Commission document related to biosimilar products interchangeability is a medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber [2].

Automatic substitution is a practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [2].

The term switching is related to the decision taken by the treating physician to exchange one medicine for another with the same therapeutic intent in patients who are undergoing treatment [2].

WHO has recognized that a number of important issues associated with the use of similar biotherapeutic products (SBPs) need to be defined by the national authorities. They include, but are not limited, to the following: intellectual property issues; interchangeability and substitution of SBP with RBP; and labelling and prescribing information [3].

EMA has only responsibility to review the marketing authorization submission and the decision whether to substitute or not the reference biological product with a biosimilar is on the responsibility of each of the EU Member States competent authorities [4].

Since October 2011, pharmacists in Germany may substitute biotechnologically manufactured products among each other which have been approved with reference to the same reference product and which have been produced by the same manufacturer with the same manufacturing process. The only difference between such substitutable products is their trade name [5]. At the point in time of publication of the European Commission consensus information paper, no country had explicitly authorized the substitution of biological products from different manufacturers, and a number of EU Member States have put legal, regulatory, and political provisions in place that prevent this practice [2].

The Association of British Pharmaceutical Industry (ABPI) working on the biosimilar topic took into consideration EMA guideline on biosimilars from 2006 [6] and the EMA guidance published in 2012 [7] which states that the decision to treat a patient with a reference or a biosimilar medicine is only to be taken following the opinion of a qualified healthcare professional. ABPI recommends that automatic substitution should not apply to any biologic; this includes automatic substitution of a biosimilar for its reference product. Substitution should only ever occur with the knowledge and explicit prior consent of the treating physician [8].

The part of the project based on direct answers from Regulatory Agencies is described in table 1. From 31 countries we contacted we have obtained the answer from 21 countries. Based on the obtained information it is clear that the automatic substitution is not allowed in Austria, Germany, Bulgaria, Czech Republic, Latvia, Luxembourg, Belgium, Denmark, Estonia, Finland, Hungary, Italy, Norway, Portugal, UK, Slovenia, The Netherlands and Switzerland; however most of the countries have no local regulations towards automatic substitution. In Italy the choice is under the decision, control and responsibility of physician. Written criteria for drug substitution are published in Finland and Hungary. In Finland the automatic substitution (generic substitution in pharmacies) of biological products is not allowed. The criteria for substitution of medicines are described in the section 5c of the Medical Act and practically exclude automatic substitution by biosimilars. Based on those criteria a list of substitutable products is prepared 4 times per year. In Finland biosimilar products are not treated as "generic medicinal products", which could be substituted. In Sweden there is no legislation that excludes a biosimilar product from the substitution system, however due to the complexity of the biological products up to now no biosimilar product has been included on the substitution list. In Belgium there is a publicly available report prepared by the Federal Health Care Knowledge Centre (KCE): 'Barriers and opportunities for the uptake of biosimilar medicines in Belgium' and the substitution (the passage of a specialty subject to a prescription to another specialty by the pharmacist, without consulting the doctor) is not all. In France, according to the new legal regulation, since January 2014, substitution is planned to be allowed only in a restrictive way: when initiating a course of treatment, and if the biosimilar belongs to the same grouping as the prescribed product, known as a "similar biologic group" and only when the physician hasn't marked on the prescription that it is a not substitutable product [9]. According to the French law it is clear that patients who have already started treatment on a biological medicine must not have their medicine substituted by a pharmacist [10]. In Czech Republic there is no specific legal regulation towards the automatic substitution problem. However, most of the medical societies in the Czech Republic have official recommendations regarding the suitability of substitution between the reference biological product and biosimilar, not recommending automatic substitution. From Latvia we obtained the information that according to the State Agency of Medicines of the Republic of Latvia there is no automatic substitution of reference biological product by biosimilar product allowed and there are no legal regulations regarding to automatic substitution by biosimilar products in Latvia. In Austria and Germany the automatic substitution is not allowed by law. Mainly due to the differences between the original product and the biosimilar cannot be done at pharmacy and the replacement may only be expressly ordered by a doctor [11].

In Lithuania, automatic substitution of biological product by biosimilar product is allowed only in case, when biosimilar product has the same INN [16]. Despite EMA guidance that the substitution should be regulated at each Member State level still some of the countries don not have local regulations in place. We draw such conclusion based on the internet search we have performed and the answers we have obtained from the regulatory agencies in the EU countries.

SINCE OCTOBER 2011, PHARMACISTS IN GERMANY MAY SUBSTITUTE BIOTECHNOLOGICALLY MANUFACTURED PRODUCTS AMONG EACH OTHER WHICH HAVE BEEN APPROVED WITH REFERENCE TO THE SAME REFERENCE PRODUCT AND WHICH HAVE BEEN PRODUCED BY THE SAME MANUFACTURER WITH THE SAME MANUFACTURING PROCESS.

Table 1. Automatic substitution – practice and regulations in EU

	Is the automatic substitution of reference biological product by biosimilar product allowed in your country?	Are there any legal regulations in your country in relation to automatic substitution by biosimilar products?
AUSTRIA[12]	No	Yes
BELGIUM[13]	No	Yes
BULGARIA	No	No
THE CZECH REPUBLIC	No	Not regulated by Health Authorities, but medical societies have regulations.
DENMARK	No	No
ESTONIA	No	No
FINLAND[14]	No	Yes
FRANCE[9]	Only for new treatment	The 2014 Social Security Financing Law (SSFL), including Article 47 on biosimilar substitution, was signed and published in the Official Journal on 23 and 24 December 2013 respectively.
GERMANY[11]	No	Yes
HUNGARY[15]	No	Yes
ICELAND	Information not clear	-
IRELAND	Information not clear	-
ITALY	No	-
LATVIA	No	No
LITHUANIA [16]	only in case, when biosimilar product has the same INN	Yes
LIECHTENSTEIN	Information not clear	No
LUXEMBOURG	No	No
THE NETHERLANDS[17]	No	No
NORWAY[18]	No	Yes
PORTUGAL	No	Yes
SLOVENIA	No	No
SWEDEN[19]	Theoretically yes, in practice not	Yes
UNITED KINGDOM[20]	No	No
SWITZERLAND[21]	No	No

DISCUSSION

According to our search, Poland has no local regulations towards automatic substitution of reference biological products by biosimilar ones. From most of the countries we obtained an answer to our questions informing that they have no automatic substitution in place, even in case they are not having local regulations. Due to already practical experience with biosimilar products in Australia we also checked the status regarding automatic substitution there. The results were similar to our findings in EU. PBS does not permit automatic substitution of biosimilars with different INN. The pharmacists cannot substitute a glycosylated biosimilar for its comparator drug. Where the drug has the same INN, then the cheapest product can be supplied unless the prescriber stipulates the use of a particular brand [22].

The applicant of the biosimilar marketing authorization must submit a risk-management pharmacovigilance plan and biosimilars are priorities for pharmacovigilance. The approval pathway for a biosimilar is based on the determination of its

similarity to an approved biologic based on fewer patient data than were required for the initial approval of the reference product" and this create a need to collect safety data through effective post-approval safety surveillance systems. Biosimilars are biological medicines too, the molecule active substances of which are highly similar, but are not identical to the reference product [23].

In the US we found that according to the information from September 2013 the legislation regulating substitution was already introduced in several States and it defines that the substitution should occur only when the FDA has designated a biologic product as interchangeable; the physicians when prescribing a medicinal product should be able to prevent substitution and if such occurs then the prescribing physician should be notified of the substitution. The same principle is related to the patient who should be notified of the substitution. The pharmacist and the physician should keep records of the substitution [24].

CONCLUSIONS

Due to the medicinal product complexity in most of the European Union countries the automatic substitution of a reference biological product by a biosimilar product is not allowed. Local regulations are needed in each of the Member States according to EMA guidance.

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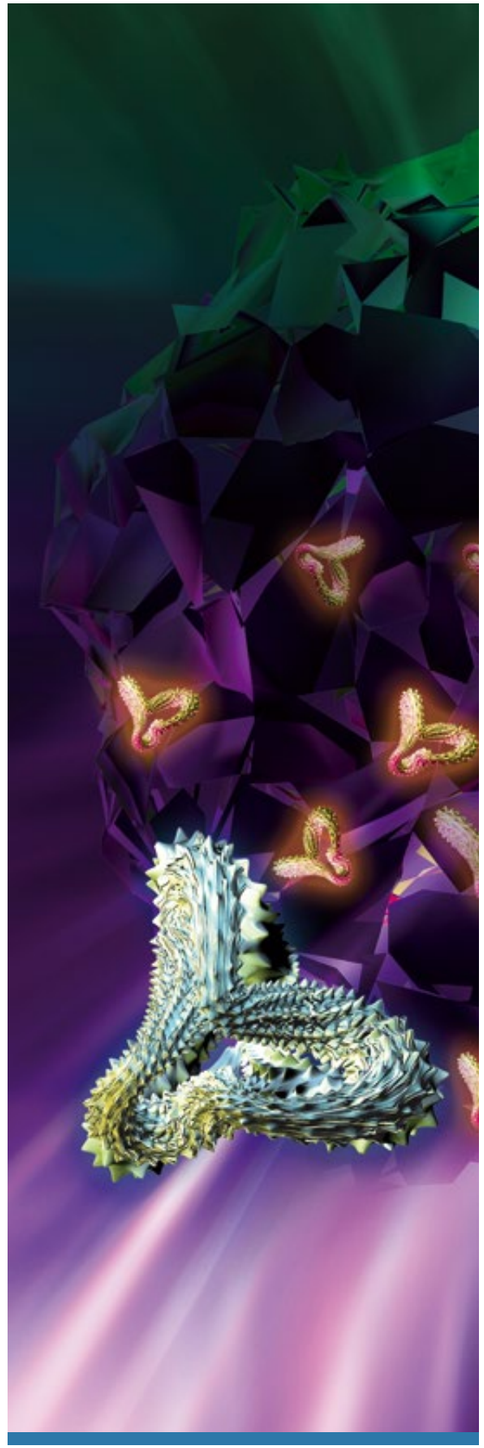

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The Polish Expert Group Position Statement on the safety of biological treatments with monoclonal antibodies and fusion proteins

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ABSTRACT

Objective: **The first biological therapeutics have already reached their patent expiration dates and corresponding biosimilars have been approved by the EMA and FDA. The approval of products similar, but not identical to already known innovative biologics is stirring a lot of debate about safety concerns, as well as the relevance of these differences to clinical practice.**

Methods: **A Group of 13 experts involved in various aspects of biological therapies in Poland was established. Modified Delphi method of voting was performed to achieve consensus regarding the most important aspects of biological treatment in Poland, with particular concern regarding biosimilars.**

Results: **Ten final statements were discussed and voted upon. The statements cover general aspects of biosimilars, including expected cost--benefit ratios, extrapolation of clinical indications, interchange, switching, patient information and the requirement of patient consent. The state of post-marketing pharmacovigilance of biologicals (innovative ones as well as biosimilars) was also discussed.**

Conclusions: **The Expert Group agreed that introduction of biosimilars is an important achievement in biological therapies, with the potential to reduce treatment costs and increase their availability. Experts also agreed that the safety of biological treatments should be monitored more carefully in Poland. There is an unmet need in Poland for the creation of a registry collecting data needed for the assessment of safety and efficacy of both biosimilars and their reference products in accordance with the experience and principles introduced in other European countries.**

INTRODUCTION

For over 15 years, biological drugs have been a vital therapeutic tool used by experts in multiple fields of medicine, such as oncology, haematology, rheumatology, gastroenterology, transplantation, ophthalmology and allergology. There are a (?) number of indications where biological drugs are administered chronically, particularly in the treatment of inflammatory rheumatologic disorders or inflammatory bowel disease. With the progress of medical knowledge, both the regulatory and evidence-based indications for the use of biological drugs have extended. Multicentre clinical studies have shown unequivocal proof of the effectiveness of innovative therapies; however, long-term follow-up and pharmacovigilance are necessary to assess the safety profile of medications, especially with regard to delayed adverse reactions, such as the risk of developing cancer, cardiovascular complications or autoimmune reactions.

Another problem involves the growing costs of biological treatment, particularly with monoclonal antibodies and fusion proteins. This is due to the specificity of the manufacturing technology as well as the need to conduct appropriate clinical studies with the innovative drugs. One way to reduce treatment costs is the marketing of biosimilars. A biosimilar is a biological drug with a mode of action and structure analogous to those of the original biologic, and manufactured after the expiry of the patent of the latter [9]. Both the European Medicines Agency (EMA) and the US Food and Drug Association (FDA) have specified the requirements for biosimilar medicinal products to be approved for treatment. These regulations have sparked controversy and debate among many scientific associations, especially with regard to the extrapolation of indications, drug switching, drug interchangeability, and consequently the safety and monitoring of treatment. It is worth emphasizing that in line with the recommendations of both the EMA and scientific associations, the choice of therapy is at the discretion of the physician. Medical practitioners bear the actual, moral, ethical as well as legal responsibility for their patients' health and for providing them with accurate information on the efficacy and safety of the administered treatment. The ongoing debate and often contradictory opinions whether to support or refute the usefulness of biosimilars in clinical practice place physicians in an uneasy position [1,13,20,23]. In an attempt to clarify these issues, opinions were gathered from independent experts in various fields of medicine to summarise the relevant data that

are currently available and to develop a position statement to act as a guideline for medical practitioners dealing with biological therapy in Poland.

METHOD

Definitions

In a broad sense, a biological drug is a product manufactured by living organisms. The presented position statement concerns biological drugs – monoclonal antibodies and fusion proteins derived from cell cultures in vitro using genetic engineering.

A biosimilar drug is similar, but not identical, to a registered reference drug with regard to quality, safety and efficacy (WHO). Biosimilarity status is achieved when procedural requirements specified by the FDA and EMA are met. The proposed pathway suggests a preliminary lack of clinically significant differences between a biosimilar and its reference analogue in terms of safety, purity and potency (FDA) or quality, safety and efficacy (EMA) [10,22]. It is noteworthy that these regulations are innovative in nature and have been developed specifically for biosimilar drugs, which emphasizes their distinctness from generic drugs.

A biosimilar pharmaceutical product ("me-too" biologic, non-innovative biologic) is a medication that targets the same antigen as an innovative drug but whose equivalence with regard to pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity has not been proven in accordance with EMA or FDA standards. "Me-too" biologic medicinal products have been excluded from analysis in the presented position statement.

The following definitions were adopted in the discussion. Interchangeability was defined as the administration of the same active ingredient produced by different manufacturers (where the administration of a biological or biosimilar drug is random) allowing for automatic substitution of one drug for another. Switching was defined as a switch from one administered drug to another (with the same active ingredient but produced by different manufacturers) upon the decision of the physician.

EXPERT GROUP

The position statement was developed in collaboration with national consultants (in rheumatology, haematology, and gastroenterology), heads of coordinating teams for biological treatment (in rheumatology, allergology, and dermatology), experts in different fields of medicine (rheumatology, allergology, gastroenterology, oncology, dermatology, ophthalmology, clinical immunology, and experimental pharmacology) who deal with the issues of biological therapy and had agreed to participate in the Expert Group. A SWOT (strengths/weaknesses/opportunities/threats) analysis was performed for the appointed Expert Group (supplementary materials).

The Expert Group included:

- Prof. Karina Jahnz-Różyk (allergologist, clinical immunologist) – Head,

Members:

- Prof. Anna Filipowicz-Sosnowska (rheumatologist),
- Prof. Jerzy Gil (gastroenterologist),
- Prof. Paweł Grieb (experimental pharmacologist),
- Prof. Wiesław W Jędrzejczak (haematologist),
- Witold Owczarek, MD-PhD (dermatologist),
- Prof. Tadeusz Płusa (allergologist, pulmonologist),
- Prof. Lidia Rutkowska-Sak (paediatrician, rheumatologist),
- Prof. Grażyna Rydzewska (gastroenterologist),
- Prof. Jerzy Szaflik (ophthalmologist),
- Prof. Witold Tłustochowicz (rheumatologist). On 13th May 2014, prof. Tłustochowicz announced his decision to withdraw from the Expert Group,
- Prof. Piotr Wysocki (oncologist),
- Monika Łazicka-Gałecka, MD-PhD (ophthalmologist),
- Ewa Więsik-Szewczyk, MD-PhD (rheumatologist, clinical immunologist).

A BIOSIMILAR DRUG IS SIMILAR, BUT NOT IDENTICAL, TO A REGISTERED REFERENCE DRUG WITH REGARD TO QUALITY, SAFETY AND EFFICACY (WHO). BIOSIMILARITY STATUS IS ACHIEVED WHEN PROCEDURAL REQUIREMENTS SPECIFIED BY THE FDA AND EMA ARE MET.

WORK PHASES

A modified Delphi process was implemented in order to develop the position statement. In the first phase, an open online debate was held concerning selected aspects of biological therapy, taking into account the specificity of Polish regulations (coordinating teams), the issues of safety and biological treatment regimens in different indications, treatment costs, the outlook for the introduction of biosimilar drugs and the extrapolation of indications. Subsequently, 10 issues out of those discussed in a direct debate were selected at an Expert Group meeting. In the next phase, these issues were subject to closed online voting. Each of the issues was evaluated separately and independently by particular experts. Issues were rated from 0 (I completely disagree with the presented opinion) to 10 (I fully support the presented view). Thirteen experts participated in the voting. The mean values and standard deviations (SD) were calculated for the obtained results. The maximum concordance rate is defined by the highest mean and the lowest SD.

RESULTS

Ten issues were identified to describe the current state of knowledge and the experts' attitudes concerning biological therapy, and treatment with innovative and biosimilar medications in the Polish setting. The results are presented in table 1.

DISCUSSION

Biological drugs are increasingly used in various indications and will undoubtedly constitute one of the most dynamically developing therapeutic pathways of contemporary medicine, considering both: innovative therapies, and the possibility of registering biosimilar drugs, i.e. analogues of innovative drugs with expired patents. Long-term administration of biological drugs is not uncommon, which involves significant costs for the patient and/or state budget [9]. Therefore, convincing experts that the introduction of biosimilar drugs yields economic benefits is an important element of the presented position statement (statement 1). It is a way to

Table 1. The Polish Expert Group Position Statement on the safety of biological treatment with monoclonal antibodies and fusion proteins: results of the Delphi method

STATEMENT	DELPHI SCORE (MEAN, SD)
The introduction of biosimilars-monoclonal antibodies/fusion proteins (BS-mAb/FP)-is associated with benefits, mostly due to reduced costs and increased availability of the treatment	9.46±1.45
Although BS-mAb/FP may be applicable in indications and/or patient populations approved for the reference drug despite the lack of formal studies, such extrapolations must be approached with caution	7.69±2.59
The current state of knowledge does not allow for recommendations to interchange reference drugs with their biosimilar analogues	8.08±3.07
The current state of knowledge allows physicians to decide on the switching of a reference drug with its biosimilar analogue	7.54±3.23
Patients should be informed of such switching	9.0±2.16
Patients should consent to such switching	7.54±3.6
Intolerance following treatment with mAb/FP (reference drug) disqualifies the patient from any attempts at treatment with BS-mAb/FP and vice versa	7.61± 2.4
The lack of effect following treatment with mAb (reference drug) disqualifies the patient from any attempts at treatment with BS-mAb/FP and vice versa	8.23±2.17
There is a need for closer monitoring of adverse events caused by mAb/FP and/or BS-mAb/FP treatment than that currently in place	8.23±2.17
There is a need to create a national registry of patients receiving biological treatment	7.61±3.33

generate competition, potentially leading to price reduction of innovative therapies offered by monopolistic manufacturers. This is because any newly introduced biosimilar product would be cheaper than its reference analogue [17] for at least 2 reasons. Firstly, which may be observed at the level of molecular studies/fundamental sciences, there would be no need for a creative but often ineffective search for a target molecule, one out of many with potentially beneficial effects. Instead of this risky path, the manufacturers' task would be only to find their own way of producing the medicinal product with already established therapeutic properties and clinical indications. Secondly, at the clinical study level, there would be limited requirements for conducting these studies to prove bioequivalence and bioeffectiveness comparable with those of the reference drug.

Reduced costs of therapy would eventually lead to the expansion of the patient population receiving treatment. For example, in the Polish setting this could translate into the inclusion of rheumatoid arthritis patients with moderate disease activity, persistent despite treatment with conventional DMARDs (DAS 28 3.2–5.1) into the biological treatment programme, which would be in accordance with global standards. According to the recommendations of international associations, physicians should be aware of the costs of administered treatments. It is the physician who is directly responsible for treating the patient, and the physician's ultimate goal is to provide the patient with an optimum therapeutic strategy, the selection of which—especially in the case of chronic diseases—requires joint decisions and consequently, shared responsibility on the part of the patient. According to EULAR, a biosimilar drug is defined as an equivalent therapeutic option for patients qualified for biological treatment [20].

Experts (mostly medical practitioners) emphasise the fact that any potential reduction of treatment costs must not overshadow the safety of therapy. A debate over this issue has shown insufficiency of the current Polish clinical pharmacovigilance protocols for treatment with reference biologics (statement 9). On the one hand, it seems that the practice of reporting adverse reactions is uncommon despite the existing relevant legal regulations. On the other hand, the scope of questions concerning safety aspects is, in many drug programmes, insufficient. Moreover, too-short patient follow-up periods in the programme lead to difficulties in the detection of potential delayed adverse reactions, where the cause-and-effect relationship between drug administration and the event may not be direct. This includes reactions such as cardiovascular complications, autoimmune disorders or neoplastic growth. One example of this type of correlation among conventional drugs is exposure to cyclophosphamide, which increases the risk of bladder cancer for life. The lack of data concerning the safety of treatment with innovative drugs in Poland makes it difficult to establish a reference point to compare the safety of treatment with biosimilar products. The available knowledge on this topic is derived mainly from data collected from populations in other European countries. The debate over this issue revealed a clear divergence in expert opinions as to the possible solutions to this problem (statement 10). Worldwide practice and literature data suggest that most safety data are collected through registries [8,24]. The registries should meet specific formal requirements with regard to the recruitment of the study and control populations, follow-up duration, and the assessed and reported clinical parameters [6]. The question of whether in the Polish reality these should constitute an element of drug programmes, take the form of observational studies or of a broad national registry remains unanswered.

In statements 2, 3 and 4, the experts addressed controversial issues associated with the introduction of biosimilar drugs: the extrapolation of indications, interchangeability and switching between innovative drugs and their biosimilar equivalents.

The extrapolation of clinical indications consists in the use of a biosimilar drug for the indication for which the reference drug is used, but for which the biosimilar has not been assessed. Both the EMA and FDA are in favour of the extrapolation of indications [14]. The extrapolation

of indications seems possible; however, more experience in this field is required. Extrapolation is more justified in cases where both the underlying pathogenesis of the disease and the mechanism of drug action are identified. Nonetheless, a given drug may display different modes of action in different therapeutic indications, e.g. in oncology and rheumatology; therefore, the FDA and EMA admit the need for conducting separate studies for specific indications [7]. In such cases, the decision on whether or not to extrapolate the indication should be made on a case-by-case basis [15].

It is necessary to include the limitations of extrapolation in clinical practice, e.g. those associated with populations described as particularly sensitive, such as the paediatric population or patients with inflammatory bowel disease [2,5,12].

Another controversial issue is switching from an original biologic drug to a biosimilar and vice versa with the consent of the physician, or interchangeability (automatic substitution) at the pharmacy level. Although this does not seem to be a problem for experimental pharmacologists, medical practitioners, who recommend and are responsible for treatment, consider safety data regarding drug interchangeability to be insufficient for this kind of practice to be encouraged. Both the interchanging and switching of drugs hamper observational studies and pharmacovigilance. It is worth emphasizing that in such cases adverse events should be reported, and these reports should include not only the name of the active ingredient, but also the drug's trade name. The EMA maintains that the assessment process of biosimilars does not include recommendations on interchangeability or switching and leaves these regulations at the discretion of individual countries. The EMA stresses that the issue of switching drugs should be discussed individually between the patient and attending physician 11. Further scientific data are needed to prove that the efficacy and safety of therapy in patients treated permanently with a specific biological drug are the same as those in patients whose treatment was switched from a reference drug to a biosimilar [16,18,19].

There is an ongoing analysis of relevant clinical studies, thus the opinion in this regard may be verified once scientific data proving the safety of such actions have been obtained [3,4]. In clinical practice, any change in treatment is associated with providing the patient with accurate information, which is also a legal requirement for physicians (statement 5). Experts disagree on whether such change in treatment should involve obtaining an informed consent of the patient, expressed in a separate document (statement 6).

Yet another issue is switching therapies in cases where the original innovative drug, or its biosimilar analogue, is not tolerated. It seems that for safety reasons, the treatments should not be switched in cases of drug intolerance; however, exceptions to this rule might be made but require individual and detailed analysis of the risk-benefit ratio (statement 7). In cases of no therapeutic effect, continuation of therapy based on switching drugs with a similar mechanism of action is unjustified (statement 8). This is especially important in the case of targeted therapy for oncological indications. EULAR holds a similar view and emphasizes that biosimilar infliximab may not be considered to be a distinct therapeutic option in patients with inadequate response to innovative infliximab. There was a 97% consensus among European experts in this regard [21].

In summary, it is noteworthy that the strongest consensus was reached when the Expert Group analysed statement 1 (reduction of costs and increased availability of treatment) and statement 10 (pharmacovigilance). The remainder of the assessed aspects revealed discrepancies in expert opinions, sometimes considerable, as evidenced by standard deviations from the mean.

Subjectivity is one disadvantage of the Delphi method; therefore, the results represent the lowest (III) level of scientific evidence according to the principles of evidence-based medicine. On the other hand, this form of evidence may be useful in the case of no hard scientific data, as it allows for the summation of the opinions of competent individuals and helps define problems that require further studies. The position statement presented here concerning innovative biological and biosimilar drugs may not serve for purposes where a higher degree of certainty is needed. The complex and dynamic problem of using innovative and biosimilar biological drugs places a duty on all health care professionals to systematically monitor this process.

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Pharmacoeconomic evaluation of fixed-dose triple combination for antihypertensive therapy in Ukraine

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ABSTRACT

In Ukraine, the efficacy of treatment of arterial hypertension is only 19% in urban areas and 8 % in rural populations. The most important reasons of low efficiency of antihypertensive therapy (AHT) are a wrong choice of tactics of the patient management and low adherence of patients to treatment. The latter decreases with increasing amounts of prescribed drugs. One possible way to increase patients' compliance to treatment and the effectiveness of therapy is to use fixed--dose combinations (FDCs) of antihypertensive drugs (AHDs). The share of FDCs consumption (in terms of DDDs/1000/day) in Ukraine in the total structure of AHDs consumption is 25%, which is significantly less than the proportion of patients (60%), requiring combined AHDs. This is an indirect evidence of low compliance of Ukrainian patients to HD treatment and the need of pharmacoeconomic study of benefits of antihypertensive therapy using FDCs. As a result of pharmacoeconomic cost-effectiveness analysis it has been found that antihypertensive therapy in patients with moderate and severe AH using triple FDC Val+Aml+HCTZ compared with three dual FDC: Val+HCTZ, Val+Aml, Aml+HCTZ provides greater clinical efficacy (the number of patients with the achieved target level of blood pressure). This triple FDC Val+Aml+HCTZ has pharmacoeconomic benefits (greater cost efficiency), compared with only one dual FDC Val+HCTZ. This gives the opportunity to save money, presents additional advantages in efficiency and justifies benefits from its use by hypertensive patients in need of appointing the third AHD CCB amlodipine in addition to the existing dual one using valsartan and hydrochlorothiazide.

THE FEATURE OF NON-DRUG TECHNOLOGIES IN TERMS OF CLINICAL AND ECONOMIC ANALYSIS IS LESS SCRUTINY OF BOTH EFFICIENCY AND SECURITY AND THE COSTS ARE MUCH LESS STUDIED.

INTRODUCTION

Arterial hypertension (AH) is the leading cause of death from cardiac diseases which defines a high social significance of the problem of treatment of this disease [1,2].

In spite of the wide range of antihypertensive drugs (AHDs) in the pharmaceutical market of Ukraine, only a small proportion of patients with hypertension are treated effectively. Effectiveness of the treatment is only 19% in urban areas and 8 % in rural populations [2], in Russia the frequency of achieving the target level of blood pressure (BP) is 21.5% [1]. The most important reasons of low efficiency of antihypertensive therapy (AHT) are a wrong choice of tactics of the patient management and low adherence of patients to treatment. To find adequate therapy in patients at high risk of cardiovascular complications is the most difficult natter. Results of multicenter clinical studies confirm that the achievement of target BP values of less than 130 and 80 mm Hg are observed in 10-12% of patients with diabetes mellitus and no more than 17 % of patients with renal failure [3,4]. Such a low level of the target BP imposes special requirements on the selection of AHDs. Antihypertensive monotherapy is effective not more than in a half of patients with a moderate increase in BP. ALLHAT studies have proved that only 60% of patients with AH of 1-2 degree reach the target BP values with monotherapy [4]. Frequency of use of a combination therapy in patients with hypertension of 2-3 degree is from 45 % to 93% [5, 6]. The most extensive trial HOT showed that to achieve DBP level less than 90 mm Hg the combination therapy was required in 63% of cases, and to achieve DBP less than 80 mm Hg – in 74 % of cases [7].

More pronounced effect of the combined AHT is due to different mechanisms of action of drugs to be combined, which solves the problem of AH multiple factors. The simultaneous use of different classes of drugs can influence the several links of AH pathogenesis – the activation of the renin-angiotensin-aldosterone and sympathoadrenal systems, endothelial dysfunction and renal impairment, myocardial hypertrophy and hypertrophy of the vascular wall [1, 2, 8]. The combination therapy allows ensuring the BP effective control on a background of good endurance without increasing doses of preparations. STRATHE study showed that the use of the combination therapy allows achieving the desired effect from the very beginning of the treatment of hypertensive patients 9.

One drawback of the AH combination therapy is regime complication and increased cost of treatment, since the patient should administer at least two medicines, the multiplicity prescriptions of which may be different. The use of fixed-dose combinations (FDCs) of AHD allows leveling the problem. Fixed-dose combinations reduce the number of tablets taken and enhance patients' adherence to treatment, which is an important factor of its effectiveness. The advantages of FDCs include ease of prescription and dose titration; reduction in the incidence of adverse events; reduction of the cost of treatment [1,2,8]. All this leads to an increase in patient compliance to treatment and therefore to increase in the number of patients achieving the target BP level as well as to reduction of the incidence of side effects.

Most drugs among FDCs are dual combinations. The most modern approach to AHT improvement is the creation and application of triple FDCs of AHDs. Triple therapy is recommended for the treatment of AH in patients whose BP is not adequately controlled by dual FDC. In this context, current clinical guidelines recommend the combination of ACE inhibitors or BRA, CCB and diuretics [1, 2, 8]. Most recently, in the pharmaceutical market of Ukraine a modern triple FDC was registered: valsartan-amlodipine-hydrochlorothiazide (Val+Aml+HCTZ). This triple FDC is essentially a combination of two of the most used effective dual combinations of AHDs of the last decade: ACE inhibitors or BRAs with diuretics and ACE inhibitors or BRA with CCB. Components of these FDC are the drugs of the first line in the AH treatment [1, 2, 8].

Analysis of the evidence of clinical effectiveness of individual components of the triple FDC Val+Aml+HCTZ confirms that these are drugs with a high level of evidence. It has been found out

that thiazide and thiazide-type diuretics are preferred for the first line of AHT in patients without risk factors, superior to CCB and ACE inhibitors in the prevention of cardiovascular events (CVE) and thus less expensive [10]. High clinical efficacy of amlodipine in preventing the risk of CVE in patients with AH was confirmed in a number of multicenter clinical trials: PREVENT [11], CAMELOT [12], ASCOT-BPLA/CAFÉ [13], ALLHAT [10,14], of valsartan – in clinical trials: VALUE [15], VALIANT [16], Val-HeFT [17,18], JIKEI HEART [19], KYOTO HEART [20].

Thus, to date, there is strong evidence of clinical effectiveness of AHDs hydrochlorothiazide, amlodipine and valsartan in the reduction of the number of CVE. This was the prerequisite for the triple FDC based on them.

Clinical efficacy of the triple FDC Val+Aml+HCTZ has been proven in the randomized double-blind trial [21]. First of all, this FDC is effective and safe for the treatment of patients, uncontrolled BP with two AHDs, as well as for patients who have already received three drugs to control BP. However, to date there is no information about the pharmacoeconomic benefits of this FDC taking into account peculiarities of the Ukrainian pharmaceutical market of AHDs.

The objectiveof this research isthe pharmacoeconomic study of advantages of the new triple FDC valsartan-amlodipine-hydrochlorothiazide compared with three other AHT regimens using dual FDCs: valsartan-hydrochlorothiazide (Val+HCTZ), valsartan-amlodipine (Val+Aml) and amlodipine-hydrochlorothiazide (Aml+ HCTZ) in terms of a Ukrainian payer.

To implement this objective it was necessary to conduct:

- evaluation of AHD consumption with allocation of the share of FDCs of AHDs consumption in the pharmaceutical market of Ukraine using ATC/DDD-methodology;
- analysis of clinical efficacy of the triple FDC valsartan-amlodipine-hydrochlorothiazide according to clinical trial [21];
- determine costs and pharmacoeconomic indicators of the analyzed AHT regimens using FDCs.

MATERIALS AND METHODS

Estimation of AHD consumption with allocation of the share of FDCs consumption in the pharmaceutical market of Ukraine during 2012 was carried out according to the data retrieval system MORION using ATC/DDD-methodology [21]. For pharmacoeconomic evaluation of the triple FDC Val+Aml+HCTZ the cost-effectiveness analysis was used. Cost-effectiveness ratio (CER) for each treatment regimen was calculated according to the formula (1): CER = DC/Ef (1), where DC – direct costs (costs of treatment regimen); Ef - effectiveness of treatment regimen. The costs and consequences of treatment regimens were compared in terms of the additional costs, which a treatment regimen imposes over another treatment, compared with the additional effectiveness (in terms of outcome) it provides. An incremental cost effectiveness ratio (ICER) was computed according to the formula (2): ICER = (DCr) - (DCc)/(Efr) - (Efc) (2), where is DCr - direct costs of reference treatment regimen; DCc - direct costs of compared treatment regimen; Efr - effectiveness of reference treatment regimen; Efc - effectiveness of compared treatment regimen [22].

For calculating the costs, retail prices of trade original drugs, relevant to INN FDC according to data in March 2013, were used. To convert hryvnia to euro, 13.97:1 ratio as at March 18, 2014 was used.

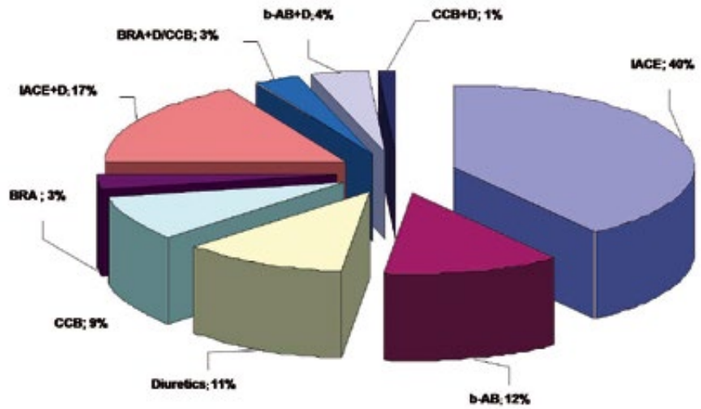
RESULTS

The results of evaluation of AHDs consumption in the pharmaceutical market of Ukraine during 2012 are shown in Fig. 1.

Note: IACE – inhibitors of angiotensin converting enzyme; b-AB - b-adrenoblockers; D – diuretics; CCB – calcium channel blockers, BRA – angiotensin receptors blockers, IACE+D – fixed combination of angiotensin converting enzyme inhibitors with diuretics; BRA+D/CCB - fixed combination of inhibitors of angiotensin receptors blockers with diuretics or calcium channel blockers; b-AB+D - fixed combination of b-adrenoblockers with diuretics; CCB+D- fixed combination of calcium channel blockers with diuretics.

THUS, TO DATE, THERE IS STRONG EVIDENCE OF CLINICAL EFFECTIVENESS OF AHDS HYDROCHLOROTHIAZIDE, AMLODIPINE AND VALSARTAN IN THE REDUCTION OF THE NUMBER OF CVE. THIS WAS THE PREREQUISITE FOR THE TRIPLE FDC BASED ON THEM.

Fig. 1. Structure of AHD consumption in Ukraine during 2012 (data are presented in % of the overall index DDDs/1000/d).



The findings confirm that in the overall structure of consumption the share FDCs of AHDs is 25%. Given the high proportion (over 60%) of Ukrainian consumers (patients with AH) requiring combined AHT [2], such consumption of FDCs AHDs is not high enough to ensure effective AHT in Ukraine. This in turn indirectly indicates low compliance of patients with AH, and the need to confirm the pharmacoeconomic benefits of FDCs AHDs, in particular FDCs of a new generation the cost of packing of which is usually higher than that of monotherapies.

Evaluation of the clinical efficacy and safety of AHT using the triple FDC Val+Aml+HCTZ in patients with moderate or severe stage of hypertension (BP: systolic > 145 mm Hg, diastolic > 100 mm Hg) compared with three other AHT regimens using dual FDC: valsartan-hydrochlorothiazide (Val+HCTZ), valsartan-amlodipine (Val+Aml) and amlodipine-hydrochlorothiazide (Aml+HCTZ) was carried out according to the trial: Triple antihypertensive therapy with amlodipine, valsartan and hydrochlorothiazide: a randomized clinical trial [21].

Analysis of the clinical efficacy of the AHT regimens under study. The clinical trial [21] was carried out during 8 weeks. All the patients were divided with the application of randomization into 4 groups, the patients of which received the AHT appropriate regimen (Table 1). The patient of the first group (1st regimen) received the dual FDC Val+HCTZ at a dose of 160 mg/12.5 mg during the first week, during the next week – the triple FDC Val+Aml+HCTZ at a dose of 160 mg/5mg/12.5 mg, and during the next six months – this FDC at a higher dose of 320 mg/10mg/25 mg. The patient of the second group (2nd regimen) received the dual FDC Val+HCTZ during the first two weeks at a dose of 160 mg/12.5 mg, during the next six month – at a dose of 320 mg/25 mg. The patients of the third group (3rd regimen) received the dual FDC Val+Aml during the first two weeks at a dose of 160 mg/5 mg, during six month – at a dose of 320 mg/10 mg. The patients of the fourth group (4th regimen) received the dual FDC Aml+HCTZ during the first two weeks at a dose of 5 mg/12.5 mg, during the next six weeks – at a dose of 10 mg/25 mg.

As indicators of the clinical efficacy of the AHT regimens under study, reduction of the daily SBP and DBP was used. At the end of the study in each study group the number of patients who achieved the target BP was determined (< 140/90 mm Hg) (Table 1). It has been found that the triple FDC Val+Aml+HCTZ is the most effective compared to other treatment regimens – 70.8 % of patients who achieved the target BP. Using the triple FDC Val+Aml+HCTZ for the treatment of 1000 patients makes it possible to additionally achieve the target BP in 260 patients compared with using the dual FDC Aml+HCTZ, in 225 patients compared with the usage of the dual FDC Val+Aml and 167 patients as compared to using the dual FDC Val+HCTZ.

Analysis of safety of the therapy regimens. In the clinical trial [21] the safety of the therapy regimens under study were determined by the presence of side reactions. In the course of the study, not a single case of death was found. Less than 1 % of patients experienced serious side reactions occurring with the same frequency in each study group. Most often, the patients reported side reactions such as dizziness: 1.0 %, 1.1 %, 0.4 % and 0.2 %, hypotension: 0.7 %, 1.1 %, 0 % and 0 %, peripheral edema: 0.2 %, 0 %, 0.4 % and 0.9 %, respectively to the therapy regimens that were used: Val+Aml+HCTZ, Val+HCTZ, Val+Aml and Aml+HCTZ. Therefore, the analyzed regimens were comparable in the number and severity of side reactions, which allows not taking into account the costs associated with their correction in subsequent calculations.

Thus, AHT in patients with the moderate and severe AH using the triple FDC Val+Aml+HCTZ compared to three dual FDC: Val+HCTZ, Val+Aml,

Table 1. Characteristic of the studied regimens of antihypertensive therapy and clinical efficacy

TREATMENT REGIMENS	1ST WEEK	2ND WEEK	3RD - 9TH WEEK	EF,%
1.	Valsartan + Hydrochlorothiazide, 160 mg / 12.5 mg	Valsartan + Amlodipine + Hydrochlorothiazide, 160 mg / 5mg / 12.5 mg	Valsartan + Amlodipine + Hydrochlorothiazide, 320 mg / 10mg / 25 mg	70.8
2.	Valsartan + Hydrochlorothiazide, 160 mg / 12.5 mg	Valsartan + Hydrochlorothiazide, 320 mg / 25 mg		48.3
3.	Valsartan + Amlodipine, 160 mg / 5 mg	Valsartan + Amlodipine, 320 mg / 10 mg		54.1
4	Amlodipine + Hydrochlorothiazide, 5 mg / 12.5 mg	Amlodipine + Hydrochlorothiazide, 10 mg / 25 mg		44.8

Note: Ef - % of patients with the achieved target BP according to data of clinical trial [21].

Table 2. Costly characteristic of the studied antihypertensive therapy regimens

NO	FDC	PACK SIZE	RETAIL PRICE OF THE PACKAGE, €	COST OF ONE TABLET, €	COST OF TREATMENT IN THE FIRST TWO WEEKS (14 DAYS), €	COST OF TREATMENT IN THE NEXT SIX WEEKS (42 DAYS), €	TOTAL COST, €
1.	Val+HCTZ	tab. 160 mg + 12.5 mg, No14	12.52	0.89	6.23 (first week)	0.89	72.24
	Val+Aml+ HCTZ	tab. 177.5 mg (160/5/12.5 mg), No28	20.35	0.73	5.11 (second week)	60.90	
2.	Val+HCTZ	tab.160 mg + 12.5 mg, No14	12.52	0.89	12.46	74.76	87.22
3.	Val+Aml	tab. 5 mg + 160 mg, No 28	9.67	0.35	4.90	29.40	34.30
4.	Aml+HCTZ	tab. 5 mg + 12.5 mg, No 30	6.47	0.22	3.08	18.48	21.56

Aml+HCTZ ensures the higher clinical efficacy and, meanwhile, is as safe as the treatment using the said dual regimens.

Cost analysis. When calculating the cost of the therapy regimens under study, the cost of treatment was only taken into account, based on the retail price of the packaging of the relevant drugs, the cost of a daily and a course dose.

The obtained results of the calculation of the cost of treatment are shown in Table 2.

In order of descending of the cost of treatment the regimens under study can be arranged in the following sequence: Val+HCTZ (87.22 €) > Val+Aml+HCTZ (72.24 €) > Val+Aml (34.30 €) > Aml+HCTZ (21.56 €). The triple FDC Val+Aml +HCTZ is the cheapest only compared to the dual FDC Val+HCTZ. The usage of the dual FDC Am-

l+HCTZ requires the least cost under Ukrainian reality, which provides the least clinical efficacy - 44.8% of patient with the achieved target BP. This makes it possible to use this AHT regimen as a reference during the pharmacoeconomic analysis.

Comparison of the cost-effectiveness ratio (CER) of the analyzed AHT regimens showed that the lowest cost of the efficiency unit is characteristic of the dual FDC Aml+HCTZ, but this scheme is the least efficient (Table 3).

The use of dual FDC Val+Aml has the advantages of cost-effectiveness compared with the dual FDC Val+HCTZ and the triple FDC Val+Aml +HCTZ, but inferior to these regimes in terms of clinical efficacy. The triple FDC Val+Aml+HCTZ is characterized by high clinical efficiency - the proportion of patients with the achieved target BP equals to 70.8 %. When comparing the two AHT regimens: the dual FDC Val+HCTZ and the triple FDC Val+Aml+HCTZ, the latter is dominant, that is cheaper and more efficient and has greater cost effectiveness (102.03 € per 1 patient with a target BP) compared with the regimen Val+HCTZ (180.58 € per 1 patient with a target BP).

The results of the pharmacoeconomic cost-effectiveness analysis by the results of the clinical study have shown that AHT based on the triple FDC Val+Aml+HCTZ in patients with moderate and severe AH provides greater clinical efficacy compared with the other three treatment regimens using the dual FDCs and has pharmacoeconomic advantages compared with only one dual FDC Val+HCTZ.

DISCUSSION AND CONCLUSIONS

A key factor contributing to poor BP control is nonadherence to prescribed antihypertensive medications. Improving patient adherence to AHT is the key to improving BP goal attainment. For most patients, however, combinations of two or more AHDs are necessary for adequate BP control. Patient adherence to AHT decreases with increasing number of pills in multiple pill regimens, but fixed-dose triple-combination treatments for hypertension provide a tool for addressing patient nonadherence associated with pill burden. For patients whose AHT includes multiple medications, the use of a single-pill, FDC therapy can signicantly improve compliance and thereby help patients achieve BP goals [24].

Numerous single-pill, 2-drug combinations are available in the pharmaceutical market of Ukraine, and single-pill triple-combination Val+Aml+HCTZ recently received Ukrainian national authority approval. The use of single-pill, fixed-dose triple-combination therapy are appropriate in patients with uncontrolled hypertension who are taking 2 separate drugs, a 2-drug combination, or 3 separate drugs [25, 26, 27]. Prescription drug costs sometimes (but not always) are higher for single-pill combination therapies compared with the component drugs [28], yet reduced health care utilization in patients prescribed single-pill combinations.

A KEY FACTOR CONTRIBUTING TO POOR BP CONTROL IS NONADHERENCE TO PRESCRIBED ANTIHYPERTENSIVE MEDICATIONS. IMPROVING PATIENT ADHERENCE TO AHT IS THE KEY TO IMPROVING BP GOAL ATTAINMENT.

The share of consumption (in terms of DDDs/1000/d) of FDC AHD in Ukraine during 2013 year in the total structure of AHDs consumption is 25%. This is more than in Russia (5%) [29] and closer to the volume of consumption in the European countries Germany (15%) and France (19%) [30]. Obviously, Ukrainian doctors follow the principal of current clinical guidelines in the treatment of hypertension.

But the share of FDCs AHDs consumption in Ukraine is significantly lower than the proportion of patients (60%), requiring the combined AHT. This indicates low compliance of Ukrainian patients to AH treatment and the need for pharmacoeconomic study of benefits of antihypertensive therapy using FDCs of AHDs.

The FDC of Val+Aml+HCTZ is a valuable addition to the armamentarium of drugs in the treatment of hypertension, because of its high efficacy in reducing BP, its tolerability, and the high compliance of patients with treatment. The results of the pharmacoeconomic cost-effectiveness analysis showed that AHT in patients with moderate and severe AH using the triple FDC Val+Aml+HCTZ compared to three dual FDC: Val+HCTZ, Val+Aml and Aml+HCTZ provides greater clinical efficacy (the number of patients with the achieved target BP). The said triple FDC Val+Aml+HCTZ has pharmacoeconomic advantages only compared to one dual FDC Val+HCTZ which makes it possible to save money and additional benefits of efficiency as well as justifies the advantages of its use by hypertensive patients in need of appointing the third AHD CCB amlodipine in addition to the existing dual therapy with valsartan and diuretic hydrochlorothiazide. ■

Table 3. The results of the cost-effectiveness analysis of antihypertensive therapy using fixed-dose combinations

NO	TREATMENT REGIMEN	TOTAL COST, €	EF	CER, € / 1 OF A PATIENT WITH THE TARGET BP	COST DIFFERENCE, €	EF ADD.	ICER, € / 1 ADD. OF A PATIENT WITH THE TARGET BP
1.	Val+Aml+HCTZ	72.24	70.8	102.03	53.90	26	2.07
2.	Val + HCTZ	87.22	48.3	180.58	132.45	3.5	37.84
3.	Val+Aml	34.30	54.1	63.40	15.27	9.3	1.64
4.	Aml+HCTZ*	21.56	44.8	48.13	-	-	-

Note: 1) Ef – % of patients with the achieved target BP;
2) Ef add. – % of patients with the achieved target BP compared with the reference therapy (Aml+HCTZ);
*3) * - reference treatment regimen.*

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Mammography screening in the OECD and its impact on health and health system related indicators

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ABSTRACT

Background: **Mammography screening, with its primary aim of breast cancer mortality reduction, is well implemented in most OECD member states. Overdiagnosis and overtreatment are often controversially discussed as potential consequences of screening. The objective of this study was to examine whether high mammography screening rates are associated with (a) higher incidence of and (b) lower mortality rates from breast cancer, and (c) higher inpatient mastectomy rates in OECD countries.**

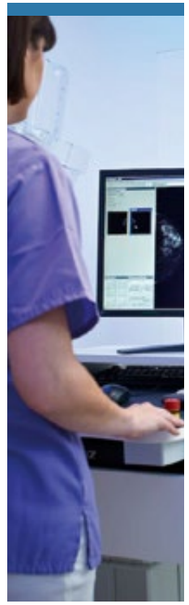
Methods: **For this investigation, an ecological study design was chosen. Data of mammography screening rates, standardized incidence and mortality rates of breast cancer and inpatient mastectomy rates were derived from the database OECD.Stat Extracts for 2008 (or nearest year). Bar charts and scatter plots with associated R^2 were produced.**

Results: **Mammography screening rates showed a broad distribution among OECD states. Specific health indicators were, on average, less favorable in those countries where more women were screened. A high degree of variance explained by screening rates could be found for incidence rates of breast cancer and mastectomy rates (R^2=0.522 and R^2=0.258, respectively). For mortality rates, this was lower, but of medium size (R^2=0.227).**

Conclusion: **Due to the ecological nature of the data, international variations in treatment guidelines and documentation of health indicators, the results must be interpreted with caution. However, the findings are in line with the contemporary literature. In the light of the observed correlation between mammography screening and less favorable health indicators, the role – whether explanatory or confounding – of potential overdiagnosis, overtreatment, and the time point of screening implementation remain controversial.**

INTRODUCTION

AFemale breast cancer is the most prevalent neoplasm worldwide. In 2008, 5.2 million women were suffering from the disease [1], which is also the leading cause of death from cancer among the female population in Europe [2]. However, today it is believed that evidence-based screening tests, like mammography screening for breast cancer in women aged 50-69 years, followed by appropriate treatments, have the potential to prevent a large number of breast cancer deaths and, by that, reduce mortality rates of breast cancer [3]. Therefore, mammography screening programs, with the primary aim of breast cancer mortality reduction, have been implemented in most of the OECD countries during the last decade [4,5], in particular since the European Council recommended the implementation in December 2003 in all Member States [6]. After the adoption of screening, many studies have examined the effect of this diagnostic intervention on mortality rates and possible consequences, such as overdiagnosis and overtreatment, referring to the possibility that such breast cancers are diagnosed and treated which otherwise would have never posed a risk [4,7–10].



Nevertheless, to our best knowledge, the overall perspective of all OECD states concerning the association between mammography screening and health-related indicators has not been well studied in a comprehensive manner. Consequently, the aim of this investigation was to examine whether high mammography screening rates in females, aged 50-69 years, are associated with (a) higher incidence rates of breast cancer, (b) lower mortality rates from breast cancer, and (c) higher inpatient mastectomy rates, as a surrogate for subsequent health care activities, in OECD countries.

MATERIALS AND METHODS

Data sources and definitions

For this investigation, an ecological study design was chosen, as aggregate data concerning mammography screening rates, incidence and mortality rates of breast cancer and mastectomy rates were available from the database OECD. Stat Extracts (http://stats.oecd.org/; February 21st, 2014).

Mammography screening rate was defined as the percentage of females aged 50-69 years being screened. For some OECD countries, this data was based on encounter data of a screening program, and for others, it was based on surveys [5]. Whenever information of both sources were available for a country, the encounter data was used, as it was assumed to be more accurate. Breast cancer was defined as malignant neoplasms of the female breast (ICD-10-CM code: C50). Age-standardized incidence rates (for the World Standard Population for 1960) [11] and age-standardized mortality rates (for the total OECD population for 2010) [12] of malignant neoplasms were included in the analysis per 100,000 females. Mastectomy rates were defined as inpatient mastectomy procedures per 100,000 females (ICD-9-CM code: 85.4) [13].

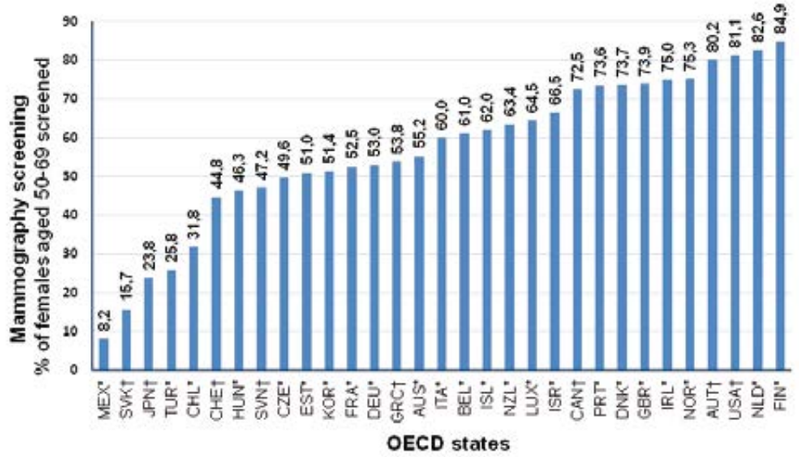
Data from the index year 2008 were included in the analyses. If no data for the index year were available, the method of last observation carried forward was applied (to a maximum of three years back, i.e. 2005).

In this study, all 34 OECD states were included initially. Poland, Spain and Sweden had to be eventually excluded from all analyses, as mammography screening rates – the main variable of interest in this study – were not available for these countries.

Statistical methods

Bar charts and medians with 25th and 75th percentiles as well as minimum and maximum percentages were presented to describe mammography screening rates among OECD states. Scatter plots with the corresponding R^2, as a measure of explained variance, were produced. This was used to estimate the bivariate correlation between mammography screening, which was determined as the independent variable, and various dependent variables (incidence rates, mortality rates and mastectomy rates; included separately). Exponential, linear and logarithmic regression models were tested and fitted, based on which of the three types showed the best explained variance of the two variables examined. For the interpretation of associations, a correlation coefficient, extracted root of R^2 in a bivariate analysis, between 0.1 - <0.3 was assumed to represent a small effect, between 0.3 – <0.5 a medium effect, and ≥ 0.5 a large effect [14]. Analyses were carried out using the Microsoft Excel 2007 spread sheet.

Figure 1.
Mammography screening rates in females aged 50-69 years in OECD states in 2008 (or nearest year)



Bar chart with corresponding percentage of females aged 50-69 screened for each state are provided. * corresponds to encounter data of a mammography screening program and † to survey data. Poland, Spain and Sweden had to be excluded as a mammography screening rates were not available.

RESULTS

Mammography screening rates

Mammography screening rates in 2008 showed a considerably broad distribution among OECD states, from 8.2% in Mexico up to 84.9% in Finland (Figure 1, Supplementary Table 1). The median screening rate was 60.0% with a 25th Percentile of 48.4% and 75th Percentile of 73.7%.

Incidence rates

In countries where a high proportion of the female population aged 50-69 years was screened, age-standardized incidence rates of breast cancer were higher than in OECD states where mammography screenings were less often performed (Figure 2). Overall, an exponential increase of incidence rates was found with a high degree of explained variance of R^2 = 0.522. Compared to countries with similar screening rates, the Slovak Republic was an outlier with a rather high age-standardized incidence rate (53.4 per 100,000 females), while only few women had undergone mammography screening in 2008 (15.7%).

Mortality rates

The age-standardized mortality rates from malignant neoplasms of the female breast were higher in those OECD countries in which a larger share of the female population was being screened with mammography, shown by a logarithmic increase of mortality rates in relation to screening rates (Figure 3). The variance in the proportion of women screened could explain observed mortality rates from breast cancer to a medium degree (R^2=0.227). Korea was an exception in this analysis. It was shown to have the lowest breast cancer mortality of all OECD countries (7.3 per 100,000 females), whereas a relatively high amount of women underwent mammography screening (Screening rate of 51.4%). Across all other countries with high mammography screening rates (>40%), there was only a small variation in mortality rates found. They were all in the range of 20-40 deaths per 100,000 females.

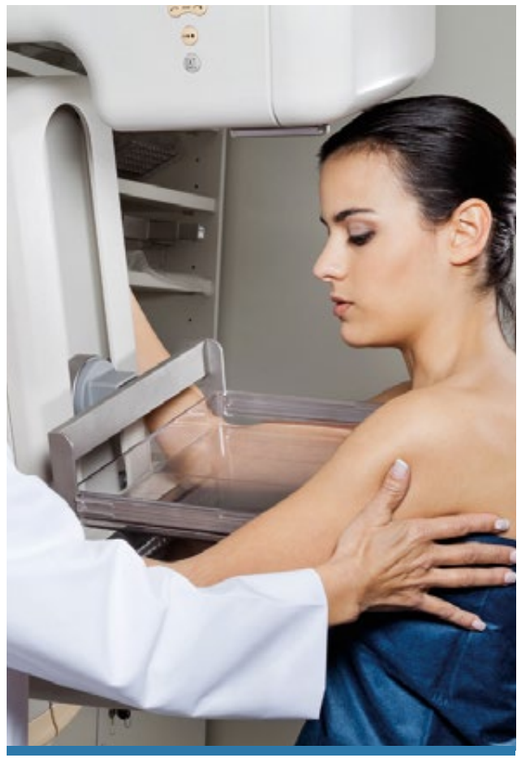
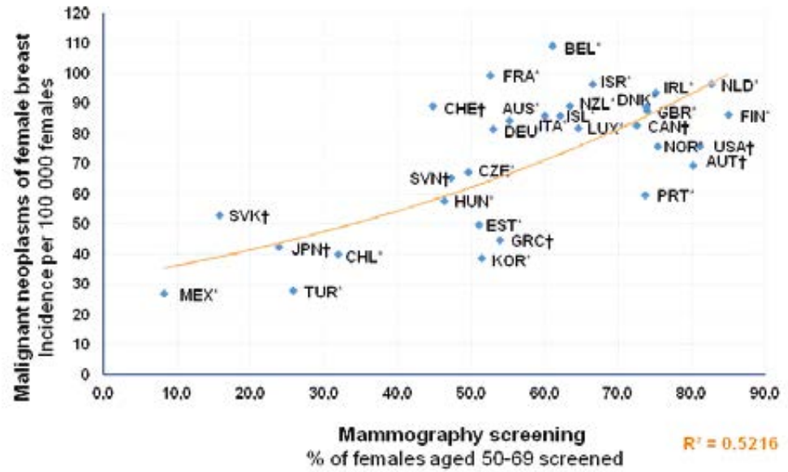
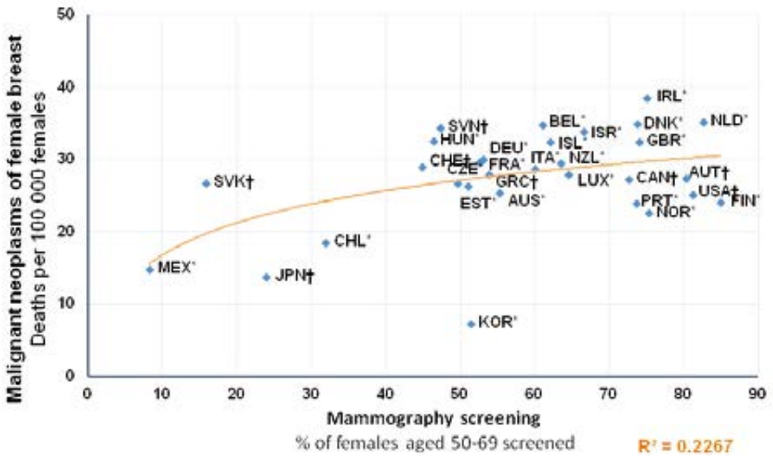


Figure 2.
Age-standardized incidence rates of breast cancer in relation to mammography screening rates in females aged 50-69 years in OECD states in 2008 (or nearest year)



Scatter plot with an exponential regression line and corresponding R^2 are provided. Incidence rates were age-standardized for the World Standard Population for 1960. * corresponds to encounter data of a mammography screening program and † to survey data. Poland, Spain and Sweden had to be excluded as a mammography screening rates were not available.

Figure 3.
Age-standardized mortality rates of breast cancer in relation to mammography screening rates in females aged 50-69 years in OECD states in 2008 (or nearest year)

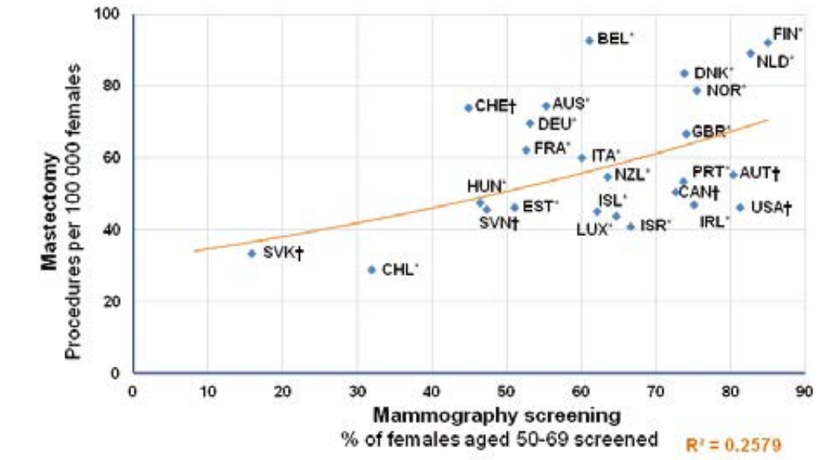


Scatter plot with a logarithmic regression line and corresponding R^2 are provided. Mortality rates were age-standardized for the total OECD population for 2010. * corresponds to encounter data of a mammography screening program and † to survey data. Poland, Spain and Sweden had to be excluded as a mammography screening rates were not available. Mortality data for Turkey was not available and was excluded in this graph.

Mastectomy rates

Inpatient mastectomy rates were higher in OECD countries with higher percentages of women screened, with an exponential relationship between these two variables (Figure 4). The variance in mammography screening rates could explain, to a large degree, the observed mastectomy rates (R^2=0.258). However, 6 of the 31 countries considered had to be excluded due to missing mastectomy rates in the period under study.

Figure 4.
Mastectomy rates of breast cancer in relation to mammography screening rates in females aged 50-69 years in OECD states in 2008 (or nearest year)



Scatter plot with a exponential regression line and corresponding R^2 are provided. * corresponds to encounter data of a mammography screening program and † to survey data. Poland, Spain and Sweden had to be excluded as a mammography screening rates were not available. Mastectomy data for Czech Republic, Greece, Japan, Korea, Mexico and Turkey were not available and were excluded in this graph (19.4% missing values).

Especially in the Netherlands and Finland, but also in Belgium, the mastectomy rates were high compared to OECD states with similar screening rates. Chile and Slovak Republic were outliers with rather low percentages of women screened and subsequently low inpatient mastectomy rates. Besides being outliers, both countries differ according to inpatient mastectomy rates and corresponding mammography screening rates. For Chile, the inpatient mastectomy rate is lower compared to the Slovak Republic (28.8 and 33.6 per 100,000 females, respectively), whereas the corresponding mammography screening rate is more than twice as high as in the Slovak Republic (31.8% and 15.7%, respectively).

DISCUSSION

Discussion of methods

The international comparison of aggregate, macro-level data comes with methodological limitations which have to be kept in mind when interpreting the results.

The concept of ecological fallacy has to be mentioned in this context, as an ecological study design was used [15]. Results are based on aggregate data for 2008 (or nearest year); therefore, no assertions about causality or time trends regarding mammography screening and health or health system related indicators can be made, neither on national nor on individual level. Mammography screening rates were based on program or survey data, which are assumed to be more imprecise because of recall bias [5]. Hence, data acquisition is an additional bias. Furthermore, international variations in treatment guidelines and recommendations as well as definitions and documentation of malignant neoplasms influence incidence and mortality rates. Comparable ICD-10 and ICD-9 codes were used, which is an obvious advantage, but coding habits might vary across countries especially with regard to coding of the underlying causes of death [16]. Beyond that, different age-standardizations were used within the OECD data. Incidence rates were standardized for the World Standard Population of 1960, and mortality rates for the total OECD population of 2010, while inpatient mastectomy rates were not age-standardized at all. Due to these differences, as well as further diversities in medical culture, communication to patients, and selective access (e.g. via money or time prices borne by the patient) to screening tests across OECD countries, the conclusions to be drawn from the various measures of association between the rates studied and mammography screening are rather limited.

IN OUR STUDY, IT WAS FOUND THAT MORTALITY RATES ARE LOGARITHMICALLY INCREASING WITH RESPECT TO SCREENING RATES, WHICH IS IN CONTRAST TO THE HYPOTHESIS THAT, IN OECD STATES WITH HIGHER SCREENING RATES, MORTALITY FROM BREAST CANCER IS LOWER.

The strength of our analysis is the comprehensive comparison across OECD states. For most of the 34 OECD states, data were available, even if not all data for each indicator were available for the index year. The exercise was of exploratory nature, and the results found may be seen as a contribution to hypothesis-generation for bespoke study designs.

Discussion of results

Mammography screening rates vary across OECD states, which corresponds to former study results of variations across European countries [3]. The type of screening program, as in nationwide and/or additional opportunistic screening, or population-based vs. non-population-based, is strongly linked to variations in screening rates [3,17]. Apart from that, while the percentage of females screened is a key indicator of screening coverage (and hence access), the quality of administration and interpretation of mammography screening (screening interval, detection rates depending on technological sensitivity, specificity and specialization of staff) differs significantly between countries [3,5,7]. Mammography screening rates are strongly dependent on the phase of implementation of screening (pre-screening, introduction phase and fully-running program). Therefore, the comparison of screening programs as such across countries is challenging [17].

Overall, the type, quality and phase of implementation have important implications on health and health system related indicators.

Concerning breast cancer incidence, an increase of this rate is often associated with the introduction phase of a novel mammography screening program [4,17]. During the course of a screening program, detection rates are expected to decrease again after a certain run-in phase [17]. Therefore, different phases of implementation in the OECD countries could explain the broad distribution of breast cancer incidence rates. Furthermore, the incidence is also strongly dependent on risk factors of the disease, such as genetic predisposition, increased exposure to hormones, overweight and alcohol consumption, which vary widely across the countries under study [5]. The exponential increase of incidence rates in relation to mammography fits the popular notion of "when more is searched, more is found" or, on a scientific level, the controversially discussed allegation of a potential overdiagnosis of breast cancer as a result of wide screening [4,7,18–20]. It is argued that through screening, many slow-growing tumors with a long non-symptomatic phase are detected which would otherwise not have been found in the remaining life-span of the individuals concerned, and would never have been fatal [9]. A systematic review of randomized controlled trials assumed a rate of overdiagnosis of about 30% [7]. Recently, in a randomized screening trial in Canada, it was found out that 22% of screen-detected invasive breast cancers were over-diagnosed, corresponding to one over-diagnosed case in 424 women screened. However, data collection started in the 1980s, and mammography screening at that time might not be comparable to modern standards [8]. An Independent UK Panel on Breast Cancer Screening also warned that estimates of overdiagnosis are subject to several uncertainties, and only rely on small amounts of data. Although the Panel conceded that overdiagnosis may occur, they found the most reliable estimates of overdiagnosis in women invited to screening

to be 11% of cancers diagnosed during lifetime, and 19% of cancers diagnosed during screening programs [19]. In addition, as the severity of tumors was not assessed in this study, it can only be suspected that overdiagnosis of small invasive breast cancers and in situ lesions contribute to higher incidence rates in OECD states, where more women are screened.

In our study, it was found that mortality rates are logarithmically increasing with respect to screening rates, which is in contrast to the hypothesis that, in OECD states with higher screening rates, mortality from breast cancer is lower. This could be explained by the "sticky diagnosis bias": Due to mammography, the number of women diagnosed with breast cancer increases; subsequently, mortality rates inflate, because the diagnosis might "follow" the individual and influence decisions regarding coding of the underlying cause of death [4]. Additionally, screening might also increase mortality via more performed radiotherapies, which are said to be harmful for women with a low risk of local recurrence, which often applies to tumors found by mammography [7]. Nevertheless, current research suggests a decrease of mortality rates by screening of 15% [7], 26% after 6-11 years of follow-up [10], or even up to 48% [21]. An explanation for these varying results might be, apart from methodological issues, that studies usually compared mortality rates before and after the implementation of a screening program. With aggregated data used in this study, it was only possible to compare the rates in countries during one specific year, which might explain the contrasting findings. Moreover, mortality reduction at population level is expected to occur, at the earliest, several years after implementation of mammography programs, and is also depending on the implementation phase [17]. This might be also the reason for a particularly low mortality rate in Korea. An increase of the mortality rate is expected as a result of an increasing incidence rate in Korea within the last years, maybe due to the adaption of western lifestyles. In turn, an increase of the mortality rate at population level will be seen several years afterwards [22]. Contrasting to these findings, it was concluded in the current literature, based on results of a recent randomized screening trial, that mammography did not achieve to reduce mortality from breast cancer for women aged 40-59, and by that, authors recommended to reassess the rationale for mammography screening [8].

Mastectomy rates seem to be exponentially higher in OECD countries with higher mammography screening rates, which corresponds to the hypothesis that activity will follow diagnosis, although data was incomplete for mastectomy rates of the respective countries. Very much like incidence rates, mastectomy rates depend on the stage of screening implementation; whereby mastectomy rates are expected to be higher during implementation and are likely to decline during fully-running screening programs [17]. This might have influenced the differences in mastectomy rates. Besides, variation in mastectomy rates can be a result of diverse national interventional policies (e.g. treatment guidelines and recommendations of therapy) independently from screening policies [17,23]. Related to this, changes in such guidelines, e.g. from mastectomy as the standard treatment towards breast-conserving therapy, are important to take note of (and correct for), as they may differ across OECD states [17,24]. For example, a lower decrease of mastectomy rates during the mammography screening implementation in Germany might be due to a higher proportion of breast-conserving surgeries as a new health policy [17]. In analogy to overdiagnosis, overtreatment – which means 'aggressive' therapy of tumors which would have never posed a risk [4] – is a further possible reason for higher mastectomy rates in states with higher screening rates. A Cochrane review of randomized trials pointed out that mastectomy rates increased by 20% in women who underwent mammography screening, compared to those who were not screened [7]. For Denmark, which also featured high mastectomy rates in our analysis, 33% overdiagnosis and overtreatment was reported, which is still lower than previously expected [9].

However, in the case of Germany, reliable data on the effectiveness of mammography screening with regard to decrease of breast cancer mortality are not yet available, and are expected to be published in five to seven years [25]. For the

UK, the Independent Panel weighs in significant benefits such as an estimated 20% reduction in overall mortality in women invited to a 20-year screening program, against possible harms of diagnosis and treatment of cancer that would never have caused problems, concluding that the screening program should continue, with the proviso that the pros and cons need to be clearly communicated to women [19].

CONCLUSIONS

Due to ecological design used and international variations in definitions, documentation, and guidelines to name but a few, the interpretation of the findings, i.e. the associations shown, needs to be handled with extreme caution. However, our results are in line with much of the current body of the literature. As potential reasons for less favorable levels of specific health indicators in relation to mammography screening, the roles of overdiagnosis, overtreatment as well as the phase of screening implementation can be discussed controversially. Regarding mastectomy rates, one must conclude that variation among OECD states might be partly be independent of screening coverage and due to national health policies, which are themselves prone to differ across OECD states, and even within the same states over time. Contrary to an intuitive hypothesis, mortality rates seem to be higher in OECD states with higher screening coverage. This could be biased or confounded by several factors, one of which is that mortality is expected to decrease in the general population only several years after implementation of a screening program. Therefore, ongoing research is necessary to assess the harm-benefit balance based on data from modern and nationwide mammography screening programs. ■

OECD states	Mammography screening rate	Incidence rate	Mortality rate	Mastectomy rate
		Malignant neoplasms per 100,000	Malignant neoplasms per 100,000	In-patient procedures per 100,000
AUSTRALIA*	55.2	84.8	25.5	74.6
AUSTRIA†	80.2[2]	69.9	27.4	55.5
BELGIUM*	61.0[2]	109.4	34.8	92.9
CANADA†	72.5	83.2	27.3	50.5
CHILE*	31.8[1]	40.1	18.6	28.8
CZECH REPUBLIC*	49.6	67.7	26.8	-
DENMARK*	73.7	89.1	34.9	83.6
ESTONIA*	51.0	50.2	26.3	46.2
FINLAND*	84.9	86.6	24.1	92.2
FRANCE*	52.5	99.7	29.7	62.4
GERMANY*	53.0	81.8	30.1	69.8
GREECE†	53.8	44.9	27.9	-
HUNGARY*	46.3	57.9	32.6	47.6
ICELAND*	62.0	86.2	32.5	45.2
IRELAND*	75.0	93.9	38.6	47.2
ISRAEL*	66.5	96.8	33.9	40.9
ITALY*	60.0	86.3	28.8	60.3
JAPAN†	23.8[1]	42.7	13.8	-
KOREA*	51.4	38.9	7.3	-
LUXEMBOURG*	64.5	82.3	28.0	44.0
MEXICO*	8.2	27.2	14.9	-
NETHERLANDS*	82.6	96.8	35.2	89.4
NEW ZEALAND*	63.4	89.4	29.5	54.9
NORWAY*	75.3	76.2	22.6	78.8
PORTUGAL†	73.6[3]	60.0	24.0	53.4
SLOVAK REPUBLIC*	15.7	53.4	26.8	33.6
SLOVENIA†	47.2[1]	65.5	34.5	45.8
SWITZERLAND†	44.8[1]	89.4	29.0	74.2
SWITZERLAND†	44.8[1]	89.4	29.0	74.2
TURKEY*	25.8	28.3	-	-
UNITED KINGDOM*	73.9	87.9	32.5	66.9
UNITED STATES†	81.1	76.0	25.2	46.3

Supplementary Table 1.

Mammography screening rates in females and corresponding health and health system-related indicators in OECD states in 2008 (or nearest year)

*Data were available for 2008 or nearest year ([1] 2007; [2] 2006 and [3] 2005). * corresponds to program data and † to survey data. Poland, Spain and Sweden had to be excluded as a mammography screening rates were not available.*

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Verification of healthcare needs by the use of National Health Fund Data - mental and behavioural disorders

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Keywords:
medicines consumption, health services research, mental disorders, health care needs

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ABSTRACT

Background: **The ways of gaining the information on healthcare should be verified as the discrepancies between different sources may lead to serious mistakes. Unfortunately, there are few reports on the methodology on healthcare needs assessment especially when mental and behavioural disorders are considered.**

Methods: **The whole-nation statistical data from the Central Statistical Office (CSO) were compared to the whole-nation information on the reimbursed psychotropic medicines from the National Health Found. The most important mental health problems, and the spatial (regional) distribution of mental disorders in Poland were analysed.**

Results: **In 2011 the total number of outpatients registered in psychiatric facilities was 1 404 148 (CSO), and NHF reimbursed psychotropic drugs for 7 870 481 people. The "neurotic disorders" and "affective disorders" were the most frequent mental problems according to CSO but NHF recognized "alcohol dependence syndrome" and "other neurotic disorders" as the most frequent mental health problems in Poland. The mental health needs in general population according to NHF data were 5,61 times higher than the needs for psychiatric care in outpatient facilities according to CSO. In some regions those differences were higher: up to 8 – 13 times.**

Conclusion: **The comparison of data from CSO and NHF revealed the important spatial differences in healthcare inequalities, scale of double-registration of patients and overconsumption of medicines together with underestimation of healthcare needs. Also other information e.g. on patients' non-compliance in alcohol dependence syndrome can be obtained in this way.**

INTRODUCTION

Healthcare needs assessment is the crucial point in preparation and evaluation of almost each kind of healthcare strategies, policies, and planning. However, the methodology of gaining the information on health and healthcare should be verified as the discrepancies between different sources may lead to serious misunderstandings resulting in serious mistakes. Unfortunately, there are few reports on the methodology on healthcare needs assessment especially when mental and behavioural disorders are considered [1]. The most important data indispensable for correct analyses are usually taken from epidemiological investigations and statistical reports [2,3]. However, the role of epidemiology is sometimes overestimated as there are important limitations of epidemiological based needs assessments [4]. It is also generally accepted that the healthcare needs should be assessed by the staff and the patients as well. On the other hand, the problem arises that staff and patients moderately agree about met needs, but agree less often on unmet needs [5]. That is especially true in a case of mental disease and psychiatric problem, so special tools had been developed for assessment of such needs, e.g. Camberwell Assessment of Needs instrument [6], Client Sociodemographic and Service Receipt Inventory (CSSRI-EU) or even EQ-5 D [7]. Also the general practitioners are sometimes involved in assessment of healthcare needs of population [8,9]. Unfortunately, there are no fully objective, diagnoses-based methods for precise assessing health care needs.

> IN POLAND, AMONG THE MOST FREQUENTLY PRESCRIBED DRUGS ARE THE ONES FOR THE TREATMENT OF CARDIOVASCULAR RELATED DISEASES, INCLUDING ANTIHYPERTENSIVE DRUGS

Moreover, the accuracy and timelines of information strongly depend on the different sources of information. The most complete data can be found in the medical records, irrespectively from their forms (paper or electronic ones), but retrieving the information from such dispersed and disseminated sources is very difficult or even impossible. The registers of patients suffering from e.g. psychiatric disorders are another type of sources. The completeness of registers strongly depends on the type of institution (healthcare centres, hospitals, outpatients clinics etc.), and usually covers only the patients from such an institution. The epidemiological data come from different reports and studies, but their accuracy and timeliness may be vague.

It can be assumed that only patients who actually are in need, will take the medicines, and if the medicines are not taken – patients will not recognized the therapy as a need. The patients' "non-compliance" means that doctor had prescribed the medicines but the patient has not bought them in the apothecary and consequently – has not taken those medicines. The scale of non-compliance in pharmacotherapy may range from 15% to even 70% of registered patients suffering from different diseases. So it seems reasonable to verify whether the medicines consumption may be used as a measure for quantification of healthcare needs, at least in selected kinds of diseases [10]. Mental health is an appropriate example for such analysis. It can be assumed that the outpatients who are suffering from mental and behavioural disorders (F00-F99 according to ICD-10) are referred to psychiatric facilities, but there are also the outpatients who use medicines prescribed by general practitioners and specialists other than psychiatrists. The number of all people who use tranquilizers, and other psychotropic medications seems to be a dark figure, and a big one.

The attempt was made to compare the data on mental health diseases from the Central Statistical Office (CSO): Statistical Yearbooks, and Statistical Bulletins, with the National Health Found (NHF) information. If the numbers of patients in both data systems were similar, or even identical - such information would be the reliable measure for health needs assessment. If they were not - information on healthcare needs could be provided also from medicines consumption data.

The aim of the study was to compare the data from different sources to determine whether the actual health needs may be verified by the use of data from National Health Fund.

MATERIAL AND METHODS

The statistical data on the healthcare system and selected diseases are collected according to the State Statistical Program in Poland, by the use of approx. 40 different statistical forms issued and updated every year by the Ministry of Health. The results are presented every year in CSO Statistical Yearbook and in Statistical Bulletins published by the Centre for Information in Healthcare [11,12]. The medicines consumption is registered by the apothecaries and pharmaceutical wholesalers. Those are the sources for analyses performed by different institutions e.g. IMS. The majority of prescribed medicines is reimbursed by the NHF, which has the complete information of all reimbursed prescriptions in Poland (but not of non-reimbursed ones, neither OTC). Moreover, NHF may identify each patient, his/her diagnoses, and each prescription for re-

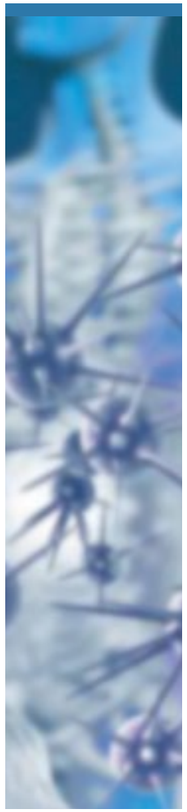
imbursed medicines. The official data published by the CSO were compared with the data on psychotropic drugs consumption obtained from the NHF databases. The newest CSO data have come from the year 2011, so the same year has been chosen for NHF information, in spite of that the newest data could be received from NHF as well. Only the numbers of patients registered by the statistical services and/or by the NHF were taken into account. The patients hospitalized because of mental disorders were not taken into consideration in this study.

The lists of 10 most frequent mental disorders / diseases was constructed on the basis of CSO and NHF data. Additional information was retrieved about diseases and conditions which are usually recognized as the most important mental health problems in Poland. The spatial (geographic) distribution of patients registered by CSO and patient who use psychotropic medicines reimbursed by NHF was analysed using the following data:

Table 1. The number of patients with 10 most often diagnosed groups of diseases (according to the Central Statistical Office) and diseases (according to National Health Found)

CENTRAL STATISTICAL OFFICE DATA		NATIONAL HEALTH FUND DATA	
DIAGNOSIS	NUMBER OF PATIENTS	DIAGNOSIS	NUMBER OF PATIENTS
1. Neurotic disorders	347 263	1. Alcohol dependence syndrome	129 247
2. Affective disorders	269 408	2. Other neurotic disorders	115 561
3. Symptomatic mental disorders	199 663	3. Schizophrenia	103 372
4. Mental disorders due to use of alcohol	170 011	4. Vascular dementia	101 390
5. Dependence syndrome	144 814	5. Recurrent depressive disorder	99 786
6. Schizophrenia	143 511	6. Depressive episode	93 857
7. Specific developmental disorders	72 644	7. Reaction to severe stress, and adjustment disorders	92 598
8. Mental retardation	59 578	8. Other anxiety disorders	90 624
9. Other psychotic disorders (non-schizophrenia)	44 180	9. Other mental disorders due to brain damage and dysfunction and to physical disease	85 438
10. Adult personality and behaviour disorders	34 194	10. Specific developmental disorders of speech and language	59 438
TOTAL NUMBER	1 485 266	TOTAL NUMBER	971 311

Source: CSO Yearbook, CSO Bulletin, NHF database (2012)



1. Absolute numbers of outpatients in each voievodship suffering from mental and behavioural disorders - according to CSO (registered in mental health outpatients facilities).
2. Absolute numbers of outpatients in each voievodship who used the reimbursed medicines for mental and behavioural disorders - according to NHF (reimbursed prescriptions).
3. Prevalence of mental and behavioural disorders in each voievodship according to CSO and to NHF.

RESULTS

According to the Central Statistical Office data the number of patients registered in outpatient psychiatric clinics in 2011 reached 1 404 148 persons. At the same time the National Health Fund reimbursed psychotropic drugs for 7 870 481 people. So the difference was 6 466 333 – the patients which required appropriate medicines and probably suffered from some kind of mental problems, but were not treated by psychiatrists. According to CSO the percentage of Polish population treated and registered in psychiatric outpatient clinic was 3.64%. However, NHF reimbursed therapy with psychotropic drugs for 20.42% of the whole population of Poland.

The structure of patients' populations was analysed according to the 10 most often diagnoses, basing on data from CSO and NHF (Tab. 1).

It should be mentioned here that the number of patients registered and treated because of 10 most frequent conditions (1 485 266) was higher than total number of patients registered by CSO (1 404 148). That indicates that the remarkable number of psychiatric patients (approx. 80 000) were double registered (in different facilities). The number of patients with 10 most popular psychiatric diagnoses equals 1 485 266 according to CSO but only 971 311 according to NHF, as CSO presented its data aggregated into 19 groups of diseases in contrast to NHF – presenting all diagnoses F00-F99. NHF information seems to be much more accurate than CSO data. It should be noted that depression (F32-F33) was not even mentioned in CSO reports. According to NHF data different types of depression are medicated by the reimbursed medicines in 249 697 patients in Poland.

F 10.2 (dependence syndrome) is the only exception to the rule that NHF numbers are higher than CSO ones. The difference equals minus 15567 persons who presumably do NOT consume the prescribed medicines (Tab. 2).

The spatial distribution of patients in all Polish voievodships according to CSO (persons registered in out-patient clinics for patients with mental disorders, addicted to alcohol and drug in 2011) and to NHF (persons who used reimbursed medicines in 2011 - diseases codes F00-F99) is presented in Tab. 3.

Table 2. The difference between CSO and NHF data referring to selected mental disorders (absolute numbers of patients in Poland)

CENTRAL STATISTICAL OFFICE DATA	CSO DATA	NHF DATA	DIFFERENCE CSO-NHF
Difference CSO-NHF	170 011	208 471	38 460
F10.2 Dependence syndrome	144 814	129 247	-15 567
F40-F48 Neurotic, stress-related and somatoform disorders	347 263	347 263	121 735
F 20 Schizophrenia	143 511	148 360	4 849

CSO – Central Statistical Office, NHF – National Health Fund Source: CSO Yearbook, CSO Bulletin, NHF database (2012)

It can be seen that the number of patients according to NHF and CSO in the voievodships are remarkably different. Also the indicators (prevalence per 100 000 inhabitants) are not in accordance one with another as the CSO and NHF data are compared in voievodships. According to CSO data the highest prevalence of mental and behaviour-

Table 3. Regional differences in absolute numbers of patients and prevalence indicators

VOIEVODSHIP	ABSOLUTE NUMBERS				PREVALENCE			
	POPULATION	CSO DATA	NHF DATA	DIFFERENCEBETWEEN NHF AND CSO DATA	CSO DATA	NHF DATA	DIFFERENCE BETWEENNHF AND CSO DATA	RATIO OF NHF/CSO DATA
Dolnośląskie (Lower Silesian)	2 916 577	100 002	518 005	418 003	3429	17 761	14 332	5,18
Kujawsko-pomorskie (Kuyavian-Pomeranian)	2 098 370	93 443	524 228	430 785	4453	24 983	20 530	5,61
Lubelskie (Lublin)	2 171 857	84 182	529 102	444 920	3876	24 362	20 486	6,29
Lubuskie (Lubusz)	1 023 158	45 278	202 137	156 859	4425	19 756	15 331	4,46
Łódzkie (Łódź)	2 533 681	123 324	546 179	422 855	4867	21 557	16 689	4,43
Małopolskie (Lesser Poland)	3 346 796	141 592	570 171	428 579	4231	17 036	12 806	4,03
Mazowieckie (Masovian)	5 285 604	200 282	1 075 282	875 000	3789	20 344	16 554	5,37
Opolskie (Opolskie)	1 013 950	31 410	155 113	123 703	3098	15 298	12 200	4,94

al disorders was found in Łódź voievodship (4867 per 100 000) and the least – in Warmian-Masurian (1918 per 100 000). The latter was in the province with the highest prevalence according to NHF (24992 per 100 000 inhabitants). The least prevalence NHF noted in Opolskie 15297 per 100 000). Also the differences between NHF and CSO data were the highest in Warmian-Masurian, the lowest in Opolskie voievodship. In all provinces (voievodships) the statistical data from NHF were several times higher than reported by CSO, this ratio for Poland was 5.61. The highest value of this indicator (13.03) was noted in Warmian-Masurian voievodship, the lowest one - (4.03) in Lesser Poland.

However, no regularity was found between e.g. population, economic condition of a province, number of psychiatric facilities, psychiatrists, and any of CSO or NHF indicators.

DISCUSSION

The whole-nation surveys on mental health are rather difficult, time-consuming, and expensive methods for assessing health needs. So it is important to find out and use every method which may simplify such an evaluation with appropriate accuracy and timeliness. According to Polish law the National Health Fund has collected data on all reimbursed prescriptions since 2004. That is an unique possibility to evaluate the normative health needs basing on use of medicines of every individual patient irrespectively from the place where the prescription has been given. Statistical offices collect the information from institutions (e.g. healthcare facilities) by the use of statistical forms. It is also regulated by law which information may be collected, by whom and when. The individual data are confidential, but the aggregated information may be published.

"Health needs assessment is a systematic review of the health issues facing a population leading to agreed priorities and resource allocation that will improve health and reduce inequalities" [13]. Usually the epidemiological and statistical data are used for those purposes. Medicines consumption is rather rarely used as a tool for health needs assessment, in spite of that the prescribed medicines are usually bought and used by the patients which are really in need. The quality of data is essential for evaluation and verification of normative health needs (understood as the number of healthcare services required for a given population suffering from a given condition).

MOREOVER, THE IMPORTANT DIFFERENCES IN DIAGNOSES WERE FOUND. ACCORDING TO CSO THE NEUROTIC DISORDERS, AFFECTIVE DISORDERS AND SYMPTOMATIC MENTAL DISORDERS WERE THE MOST OFTEN MENTAL PROBLEMS IN POLAND IN 2011.

The timeliness of data cannot be overestimated when the healthcare needs are considered. The preparation of statistical yearbooks is usually time-consuming and the "Statistical Yearbook of the Republic of Poland 2011" contains the data from year 2010 as the newest ones. In the case of "Health and Healthcare in 2011" published in 2012 the data also come from the previous year. In that respect NHF data are available much sooner than CSO information. NHF data are collected online and the results are available every month. However, the analysis of NHF information require specialists who are aware of different factors influencing healthcare needs.

In contrast to somatic disorders (e.g. pneumonia, hypertension, diabetes) mental diseases and behavioural disorders are rather difficult to diagnose and hard to be monitored [1]. On the other hand, the majority of psychotropic drugs are prescribed by GPs. The percentage of people with mental disorders has been estimated by the use of questionnaires, as high as 36% in a general population [14]. Polish CSO stated that approx. 3.64% of Polish population are treated in psychiatric outpatients facilities. The NHF data indicated that over 20% used psychotropic medicines. The difference was 16.78% and it can be the indicator of underestimation of healthcare needs and/or of overconsumption of medicines. According to Jackson et al. [15] the use of psychotropic medicines was a need in approx. 30% of patients in primary healthcare. So it can be stated that the mental and behavioural disorders in Poland are rather underdiagnosed or underreported in statistical forms.

The most striking feature of presented results are the discrepancies between almost all data obtained from CSO and NHF. For example, the number of patients treated in facilities (according to CSO) may differ from the actual number of people with mental health problems, as one person may be treated in several institutions because of several mental problems at the same year. That is the probable the cause of difference between number of patients registered and treated because of 10 most frequent conditions (1 485 266 patients) and total number of patients registered by CSO (1 404 148 patients). Comparison of data from CSO and NHF revealed the significant differences between both sources. First of all, the number of patients with mental problems in Poland registered by CSO is 5,61 times lower than the number of patients whose prescriptions has been reimbursed. Such underestimation has ranged since 4 to over 13 times depending on the voievodship. It can be used as a measure of health inequalities.

Moreover, the important differences in diagnoses were found. According to CSO the neurotic disorders, affective disorders and symptomatic mental disorders were the most often mental problems in Poland in 2011. On the other hand, NHF recognized alcohol dependence syndrome, other neurotic disorders and schizophrenia as the most often mental health problems at the same year. The differences in the absolute numbers were prominent in the case of F10 (mental and behavioural disorders due to psychoactive substance use - mainly alcohol) – 38 460 patients more in NHF as compared with CSO. However in F10.2 (dependence syndrome) more patients were registered by CSO than by NHF. It means that 15 567 patients with dependence syndrome did not fill the prescriptions. That was the quantitative measure and the scale of non-compliance of patients with dependence syndrome. There was not such difference in the case of schizophrenia. The majority of patients were treated by psychiatric facilities, but only 5000 patients (3.38%) did not filled prescriptions given by doctors. That was not the case in neurotic, stress related and somatoform disorders – almost every third prescription was given by doctors other than psychiatrists. However Henrikssen and Parnas [16] found that noncompliance rates in patients with schizophrenia range from 50%–75% after 1–2 years of treatment, impeding treatment and increasing the risk of relapse, readmission, and suicide 3 - to 4-fold.

CSO data and NHF data present quite different pictures of health needs of patients with mental and behavioural disorders in Poland. It is important, because the statistical data are the bases for preparation of strategic and regional health policies. It seems that the mental health needs assumed in such programs are underestimated.

The corrects use of psychotropic medicines by the general populations may be a valuable tool to predict the health outcomes e.g. in case of suicide rates [17]. That is and emerging problem as the estimation of QALY losses showed that mood disorders ranked second behind pain-related chronic medical conditions [18]. Psychotropic drugs were prescribed by 64% of GP in sleep, anxiety and depressive disorders [19]. Also the use of antidepressants among 65+ year-olds increases with age and proximity to death to very high levels [20].The analysis of spatial distribution of NHF and CSO data on mental and behavioural disorders revealed important health inequalities in different voievodships. Similar phenomena might be seen in other countries [21] but these variations should be further investigated.

CONCLUSION

The comparison of data from CSO and NHF revealed the important spatial differences in healthcare inequalities, scale of double-registration of patients and overconsumption of medicines together with underestimation of healthcare needs. Also other information e.g. on patients' non-compliance in alcohol dependence syndrome can be obtained in this way.

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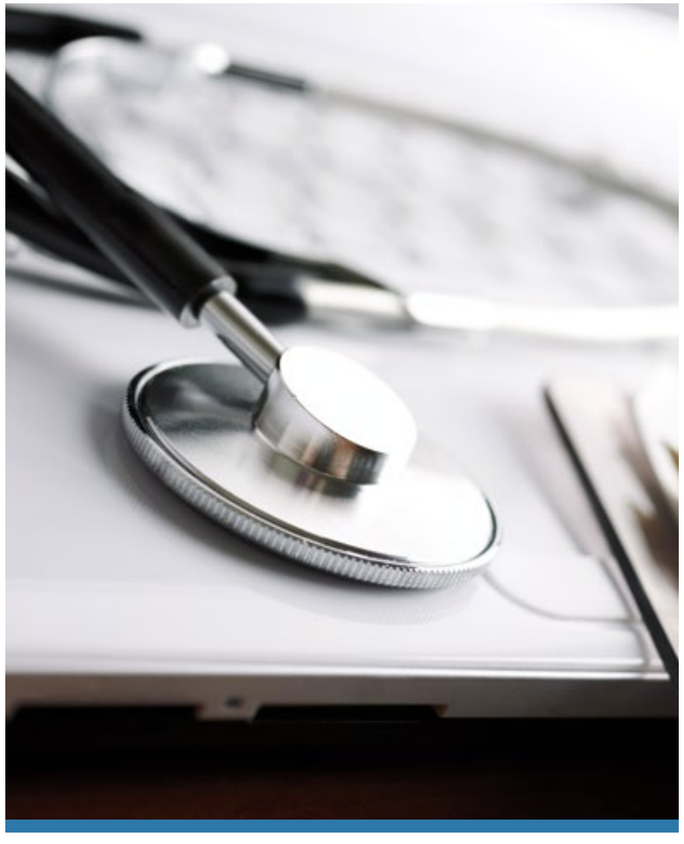
Conflicts of interests: None declared

Keypoints

Central Statistical Office data and National Health Fund data present quite different pictures of health needs of patients with mental and behavioural disorders in Poland as the statistical data refer to the outpatients from psychiatric facilities but NHF – to general population.

Comparison of both sources may be a method for assessing actual mental health needs, to study health inequalities, and non-compliance as well. Strategic and regional health programs should take into account both types of sources.

The correct use of data on psychotropic medicines consumption by the general populations may be a valuable tool to evaluate and predict the health outcomes, QALY and patients' non-compliance. ■



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„Pay-back" mechanism in the Polish reimbursement system - analysis and appraisal

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Keywords:
pay-back, reimbursement act, risk sharing

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ABSTRACT

The text of this review has been based on a diploma thesis, prepared by Mr Borys Podgorny under the supervision of Dr Iwona Skrzekowska-Baran, as part of the XXII Edition of the Advanced Management Training in Pharmacoeconomics, HTA, Pharma Marketing and Law of the Warsaw University Of Technology Business School. The presented review has employed a detailed analysis of appropriate provisions of the Reimbursement Act, while benefiting from the practical experience of the authors, regarding the implementation of the Act and the practical application of its principles.

The results of the conducted analysis indicate a number of significant drawbacks in the current version of the pay-back mechanism, which either prevent any correct calculation of the amounts to be paid back or which may become a breeding ground for disputes and conflicts with marketing authorisation holders, as regards the administrative and legal aspects of the process. In consequence, should the pay-back mechanism remain an integral part of the Polish reimbursement system, it will need urgent legislative amendments to ensure its effective management and, first of all, to streamline the calculation of reimbursable amounts, based on available and verifiable data. Above all, however, it seems still reasonable and appropriate to ask about the sensibleness of and reasons for further existence of such a solution in the Polish legal system, where other legal mechanisms successfully execute the systemic goals in terms of reducing the payer's expenses.

BACKGROUND

In spite of more than two years since the implementation of the new reimbursement system in Poland, some of its elements and mechanisms still raise serious controversies and arouse conflicting feelings.A reflection of this situation may be found in the works on amendment of the reimbursement provisions, which have, for some time, been underway at the ministerial level.

A controversial area, often avoided in discussions on the reimbursement system, is the mechanism of the, so-called, pay-back, i.e., a statutory, common obligation, assuming the payback of a reimbursed amount in total or in part if the actual reimbursement expenses exceed the fixed annual budget.

The high complexity of this regulation raises reasonable disputes, regarding a number of substantive issues, such as the range of products, taken into account in the calculation of the amounts to be returned or the conditions to be met to trigger the mechanism for appropriate actions.

In this context, as well as in the absence of any broader examination of the pay-back mechanism in available literature, it seems highly advisable to analyse the assumptions of this solution. This review is an attempt of a systematic and complex approach towards payback-related issues. A starting point of this analysis, as well as its scope, are determined by the existing legislative framework, since nowadays, any implementation of solutions, which would sharply diverge form the (relatively new) regulations, laid down in the actual Reimbursement Act, can hardly be expected.

ANALYSIS

The principle of solution

The 'pay-back' term started to enter wider circulation in 2010, being first used by the persons, involved in the reimbursement issues in Poland, simultaneously with the publication of the reimbursement act project, drafted in its first version and has, since then, at once become one of the symbols associated with the new legislation. Unfortunately, more in the context of risks and uncertainties, carried by the new regulations for the pharmaceutical market.

This term has been introduced not so much in the Act itself but more in its explanatory memorandum. While giving reasons for the implementation of the mechanism, it has been indicated that „the problem of considerable and unforeseeable increase in the expenses for reimbursement, incurred in the course of the financial year, was long ago recognised in other countries of the European Union. "Particular countries have, during the last ten years, been introducing various solutions to prevent and tackle the problem, which – in the majority of cases – are based on the payback of any excessively reimbursed amounts by marketing authorisation holders after the end of financial year. In this context, it has been considered necessary to implement a mechanism in Poland which would allow „sharing the risk of the National Health Fund, associated with the inclusion of subsequent products in the reimbursement scheme, with the industry" [1], referring to the solutions used in France, Portugal, Italy, Belgium and Hungary.

Taking into consideration the final legislative provisions, this pay-back solution "tailored to the Polish reality", has been based on the following two fundamental assumptions:

1) A statutory definition of the total budget for reimbursement – at a rigid level for the years 2012-2014 – or in statutorily defined intervals, starting from the year 2015,

2) A statutory, obligatory mechanism of financial participation by the entities (reimbursement applicants) which have been awarded with positive reimbursement decisions. This participation shall be equivalent to the amount, paid by the public payer above the original plan of reimbursement expenditure (calculated according to mechanisms provided for in the law).

Pre-conditions for pay-back system implementation

The Reimbursement Act defines one, basic condition which, when fulfilled, triggers a whole series of obligatory steps, tests and calculations, used to calculate the amount to be returned for a given reimbursed products (commonly referred to as "pay-back"). This condition is the overrun of the total reimbursement budget, „in the course of the National Health Fund's financial plan implementation" in part assigned to funding of medicinal products, foodstuffs intended for particular nutritional uses and medical products dispensed at pharmacies against prescriptions.

The possibility to verify the fulfilment of the above-mentioned condition should obviously be determined by the existence of a clearly defined reference point, with which the expenses, incurred during a given year, will be compared (the Plan vs. the Execution). The Plan should then be a fixed figure, rigidly defined (e.g., in results of the voted and approved financial plan of the National Health Fund) and evaluated in time, as needed.

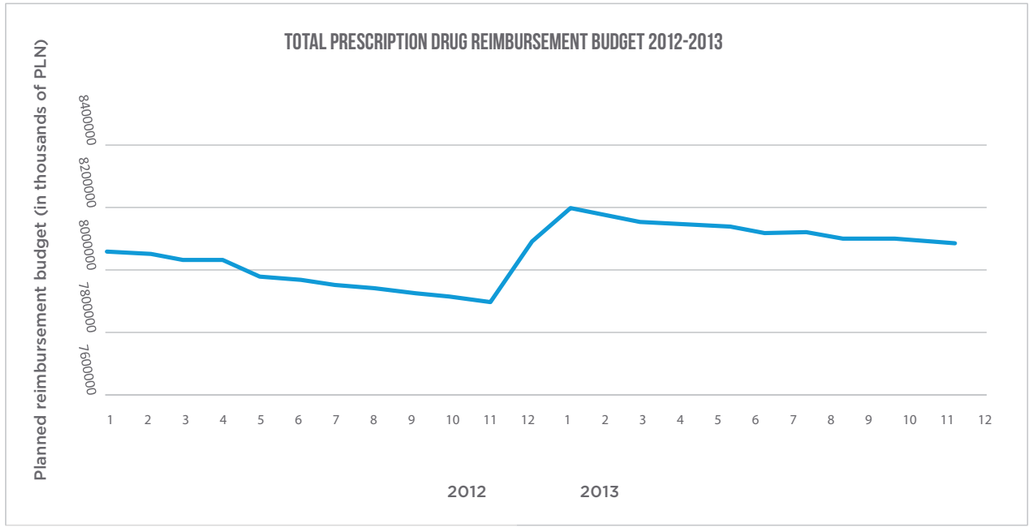
Interpretation difficulties begin already with this condition. Here not only does the legislator use a rather unclear and imprecise term of budget overrun „in the course of implementation of the National Health Fund's plan", but, furthermore, it emerges that the term of total budget for reimbursement in its part of funding the products, dispensed at pharmacy against prescription, has not been clearly defined, either. It is so, as – even if the Reimbursement Act indicates provisions, determining the level of the total budget for reimbursement [2], the implementing rules do not rigidly determine a division of the planned expenses in line with particular budget components, what means that no accurate, partial plans are made for the reimbursement of particular sectors, such as the products available at pharmacy, the products available from drug programmes or from the catalogue of chemotherapy agents. In consequence, pursuant to periodical communications, published by the Economic-Financial Department of the National Health Fund, the height of the planned total budget for the reimbursement of prescribed products is characterised by a rather high volatility, what is well illustrated by the table below.

THE 'PAY-BACK' TERM STARTED TO ENTER WIDER CIRCULATION IN 2010, BEING FIRST USED BY THE PERSONS, INVOLVED IN THE REIMBURSEMENT ISSUES IN POLAND, SIMULTANEOUSLY WITH THE PUBLICATION OF THE REIMBURSEMENT ACT PROJECT, DRAFTED IN ITS FIRST VERSION AND HAS, SINCE THEN, AT ONCE BECOME ONE OF THE SYMBOLS ASSOCIATED WITH THE NEW LEGISLATION

The presented illustration indicates that, with no clear reference point in the actual legislative system, it is difficult (or even impossible) to assess from the point of view of the the reimburse-

Table 1. Payback graph

		PLANNED PRESCRIPTION DRUG REIMBURSEMENT BUDGET IN 2013	EXECUTION	EXECUTION IN ASCENDING ORDER	TOTAL BUDGET
2012	1	8 090 926,00	422 160,45	422 160,45	
	2	8 084 926,00	531 771,18	953 931,63	
	3	8 062 002,00	610 377,57	1 564 309,20	
	4	8 061 995,00	582 700,45	2 147 009,65	
	5	8 003 755,00	576 383,54	2 723 393,19	**10 445 819,00**
	6	7 995 895,00	647 856,48	3 371 249,67	**10 445 819,00**
	7	7 974 787,00	518 610,89	3 889 860,56	**10 445 819,00**
	8	7 965 608,00	553 812,13	4 443 672,69	
	9	7 946 745,00	551 801,10	4 995 473,79	
	10	7 936 385,00	645 959,25	5 641 433,04	
	11	7 918 885,00	598 713,28	6 240 146,32	
	12	8 121 004,00	607 601,39	6 847 747,71	
2013	1	8 243 247,00	599 556,77	599 556,77	
	2	8 211 247,00	582 273,79	1 181 830,56	
	3	8 191 097,00	603 147,69	1 784 978,25	
	4	8 187 597,00	607 477,33	2 392 455,58	
	5	8 182 147,00	569 549,21	2 962 004,79	
	6	8 159 247,00	582 959,76	3 544 964,55	
	7	8 159 247,00	591 496,59	4 136 461,14	
	8	8 142 942,00	555 952,26	4 692 413,40	
	9	8 137 242,00	582 470,32	5 274 883,72	**10 901 083,00**
	10	8 134 742,00	666 854,53	5 941 738,25	
	11	8 123 142,00	598 104,81	6 539 843,06	
		-324 362,00			



ment applicant, i.e., the potential back payer, if the preliminary condition for the calculation of the exceeded amount is met during a given year. The system is also susceptible to errors or frauds, since – with the lack of annual measurements and of the budget amount – determined in advance – a risk cannot be excluded that, in result of provisional "shifts" among particular budget components or the Provincial Departments of the National Health Fund, the plan for a given month is exceeded (e.g., in result of a temporary budget underestimation), while in the annual approach, a surplus of means may be accounted by the National Health Fund. In terms of the regulation in its actual version, even in such a situation, it should be mandatory to precisely calculate both the exceeded amount and the pay-back amount in particular limit groups [3]. On the contrary, the actual system demonstrates high far-reaching volatility and unpredictability in effect of inaccuracy in the legislative solutions, what may in future be a source of disputes and conflicts, regarding correct calculations of pay-back amounts and their height.

The mechanism of calculation of exceeded amounts in particular limit groups

Assuming that – regardless of the above-mentioned controversies – the preliminary condition for pay-back determination is regarded as met for a given reference period, another legislative mechanism will be activated on the pathway, leading to pay-back amount calculation. Namely, the amount of exceeded reimbursement will be calculated for a given limit group. The proportion of reimbursement applicant's share in the exceeded reimbursement in a given limit group will be determined in further sequence.

At this moment, the legislator has decided to abandon the analysis of exceeded amounts at the level of the entire reimbursement budget (total or in its part, dedicated to the reimbursement of prescribed medicinal products) and proceed with further analyses of exceeded amounts in particular limit groups. Such a solution leads to a peculiar observation – the exceeded amounts and the pay-back amounts at limit group level are calculated without any reference to the exceeded amounts at the whole budget level. In other words, in an extreme situation, the exceeding by 1 PLN of the entire reimbursement budget in its part for medicinal products, available at pharmacies, will trigger the whole mechanism of calculating the exceeded amounts for the involved limit groups, i.e., in general, those for which the reimbursement expensed have increased vs. the plan.

At the same time, a situation may not be excluded (while being fully in line with the system assumption) in which the summed up exceeded amounts per individual reimbursement applicant will exceed the total exceeded amount in the whole budget. It should also be added that limit groups are defined in conformity with Art. 15 of the Reimbursement Act, also for the products in the following categories of reimbursement availability: "used in drug programme: and "used for chemotherapy", what suggests that the amounts of exceeding the reimbursement plan in limit groups are also calculated for these products and, consequently, the pay-back amounts as well.

The amount of exceeding the reimbursement plan in a limit group is calculated as the difference between the spent reimbursement amount for a given limit group during a financial year and the planned reimbursement amount in this group. While the first element of the equation does not raise any major controversies, as the reimbursement data in particular limit groups are publicly available, the mechanism of determining the planned reimbursement amounts in particular limit groups requires a broader analysis, as the National Health Fund has not, so far, committed any reimbursement expenditure budgets with breakdown by particular limit groups. Such a requirement does not emerge from the effective legal regulations, either, it is therefore safe to assume that the provisions of the Reimbursement Act do not constitute any new obligation, carried out on an ongoing basis by the National Health Fund and will only be followed when it is necessary to calculate the pay-back amounts. Only then will the reimbursement plans be assigned to particular limit groups.

Following the Reimbursement Act, the planned reimbursement amount is calculated as the

product of the planned reimbursement amount in a given group for the previous year and the total reimbursement budget growth coefficient [4]. Thereby, an artificial and, as it were, automatic mechanism of planned reimbursement calculation in every limit group has been introduced, disregarding not only health and therapeutic trends (e.g., an increased consumption of certain categories of products, justified by epidemiological and/or demographic factors) but also changes in the shape of particular groups. One of the limit groups with foodstuffs for the special nutritional uses may be a good example of dynamic changes which are observed in the limit groups:

NAME	LIMIT GROUP 01.05.2013	LIMIT GROUP 01.05.2014
Neocate Advance	217.7	217.9
Neocate LCP	217.7	217.7
Nutramigen AA	217.7	217.6

Source: The Announcement of the Minister of Health of April 24, 2013 and of April 23, 2014 on the list of reimbursed medicinal products, foodstuffs for special nutritional uses and medical products.

Obviously, any planning of reimbursement amount for 217.7 group, based on the data from May 2013, does not make any sense, as the group was, by decision of the Minister of Health, divided in 2014 into three separate groups. As of today, the regulations do not, unfortunately, provide any answer to the question how to determine the plan for particular limit groups in a situation as the one above (as well as in a reverse situation, i.e., when limit groups are combined), while simplifications of any kind whatsoever, such as building plans per groups on the basis of data from particular products, do not have necessary foundations in the valid legislature.

In each case, the solution, as approved in the Act and concerning the principles of planning reimbursement amounts for particular groups, assumes that some plan already existed for each group in the previous year and this plan will only have to be adjusted by the growth coefficient for the whole reimbursement budget. As it has been indicated, such plans are not built in real time by the National Health Fund, thus the legislator has had to introduce another simplification in order to determine the reference point for the calculation of planned amounts in the limit groups. This simplification is introduced by Art. 73 of the Act which provides that, in order to calculate, for the first time, the exceeded amount, the reimbursement amount for a group, implemented (spent) during the year 2011, will be understood as planned amount of reimbursement for 2011.

Thus assuming purely hypothetically that the exceeded amount will for the first time be calculated for the year 2014, the planned reimbursement level in the limit groups for 2014 will be based on the amount of the real reimbursement in the group in 2011. This solution is for obvious reasons defective and impossible to be implemented, not least for the fact that, in 2011, the term of „limit groups" did not exist in the then effective regulations [5], created by criteria which would have been close to the present ones. Even if one was to admit that the groups of products, being subject to common limits in the year 2011, could be approached as corresponding to the present limit groups, the shape of the groups has undergone (and is still undergoing) such major changes that any attempt of extrapolation of the planned reimbursement amounts for the year 2014 on the basis of data for the year 2011 is doomed to failure, at least for the series of new products, which have been added to the lists since 2012 (including the products with other EAN codes and new product generations) or for the evolution and the shape of the limit groups alone.

Summing up, it seems that the actual principles of planning/calculating reimbursement amounts in the limit groups effectively preclude the calculation of exceeded amounts in particular groups, what may become a serious obstacle to apply the pay-back mechanism in practice. A revision and amendment of these regulations is urgently needed, such that would unequivocally deter-

mine the point of reference (the plan), to which the reimbursement spending during a given reference period, could effectively be compared. It also seems that the concept, which assumes the calculation of exceeded amounts on limit group levels, may be difficult in practice, mainly for the continuous evolution in the shape of the groups, being in a way part of the logic of the Act alone [6].

The mechanism of pay-back amount calculation for individual product

Passing on to the method, by which the reimbursement applicant's share in the total exceeded amount is going to be determined in a single limit group, one should, first of all, indicate that only these applicants participate in the pay-back procedure, for which the dynamics of reimbursement level during a given financial year is either equal or greater from 1 vs. the previous year. Additionally, for the products which were not reimbursed in the previous year, the coefficient of reimbursement level dynamics in a given limit group equals 1. In this way, the products, newly introduced to the group, will always participate in the pay-back process, even if they are characterised by a low market share, while the products with significant, but falling reimbursement amounts, will not be covered by the pay-back system. The products, for which individual risk sharing instruments have been defined, are also excluded from the pay-back system.

Regarding these applicants, which participate in sharing of the exceeded amount in a limit group, the actual participation in the exceeded amount will depend on:

- the share of the reimbursed amount for a given product in the total reimbursement amount in a limit group during financial year (where the calculation of the total reimbursement amount takes into account also the reimbursement value of the products which are excluded from the pay-back, e.g., due to reimbursement drop),
- the proportion of the selling price of a given product to the lowest official selling price of a given product, being the basis for the limit in that limit group in a given financial year (consequently, the more expensive is a product vs. the lowest official price in financial year, the proportionally higher is the pay-back share).

Assuming that the exceeded amount and the share in it have been calculated for a given product, the calculation of correct pay-back amount follows by multiplication of the above-mentioned values by 0.5 coefficient and by "G", an additional adjusting factor.

It is worth emphasising that, in the initial version of the Act, the whole amount of the exceeded reimbursement was to be paid-back by the applicants. Only at the level of works on the Act at the Senate, it was decided to divide the pay-back amount, introducing „the coefficient of risk sharing between the public payer for health care services and the applicant, the medicinal product of which has been awarded by positive reimbursement decision" [7]. This coefficient has, on one hand, assumed the form of pay-back amount adjustment by 0,5 for the payer, while being, on the other hand, completed by an additional formula, marked in the calculation formula by letter „G" [8]. Unfortunately, the explanatory memorandum to the Act does not specify in detail the reasons, justifying the acceptance of particular calculation solutions, including the „risk sharing solutions". Neither are there any detailed calculations or prognoses of budget revenues pursuant to pay-back payments, what may be surprising in case when an instrument of purely financial character is implemented.

DISCUSSION AND CONCLUSIONS

One of the declared (however not always in public) goals of the Reimbursement Act was a limitation of the reimbursement spending and protection of the State budget against an uncontrolled increase of the reimbursement expenditure in the future. In order to achieve the purpose, a number of mechanisms have been incorporated into the Act to impose a number of constraining requirements on the public payer, such the „reference pricing", price negotiations or obligatory price reductions in case when reimbursement applies to the first equivalent of the original reimbursed product or when market exclusivity period expires.

After the two-year effective period of the Reimbursement Act, it should be stated that the above-mentioned, "economic" goal of the Act has been achieved very effectively. It appears from the data of the Ministry of Health that the reimbursement expenditure decreased in the year 2012 alone by PLN 1.96 billion vs. the year 2011 [9].

In the opinion of the Act authors, the pay-back mechanism was to have been another spending reducing solution, playing, at least, the role of a safety-valve in case if reimbursement demonstrated, for any reason, jumping trends. Even if the concept is not entirely unjustified, it has to be admitted that, for today, this particular tool reveals a number of defects. These defects are of such importance that they may either preclude correct calculations of pay-back amounts at all or they may become a source of disputes and conflicts with marketing authorisation holders on administrative-legal grounds. The costs of such legal proceedings (especially when the loser in the game was either the Minister of Health or the National Health Fund) may really overshadow any possible revenues from the pay-back mechanisms [10].

If, however, the pay-back tool was to remain an integral part of the Polish reimbursement system, urgent legislative changes are needed, which would enable an effective management of the mechanism and, first of all, which would ensure correct and precise calculations of pay-back amounts, based on available and verifiable data. Some changes were partially proposed in the project for the Act amendment of December 18, 2013 [11], however, at their actual stage, they require further processing and final finish. In this situation, the following improvement proposals should receive due consideration:

- a clear, transparent definition of the time point against which the preliminary condition for pay-back calculation could be verified;
- a clear definition of the validity scope for the pay-back mechanism - is the pay-back amount calculated for all limit groups (including the products in drug programmes and in the catalogue of chemotherapies) or for the prescribed products, reimbursed at pharmacies only;
- an implementation of transparent methodology to design a reimbursement plan for limit groups.

Following the Communication of the Economic-Financial Department of the National Health Fund, issued for the period of January-March 2014, the budget for the reimbursement of prescribed products, available at pharmacy, was implemented in 22.69%. In analogous time periods of the years 2012 and 2013, the coefficient was 19.40% and 21.79%, respectively [12]. Thus, even if a clear growing trend in the reimbursement expenditure is observed, still imposing of the obligation to calculate (and pay) the pay-back for the year 2014 is still little probable for the considerable drop in reimbursement during the years 2012-2013 vs. the „reference" year of 2011. Thus, as much time has been left, it would be appropriate to reconsider and implement the required legislative changes to eliminate the actual defects in the structure of the pay-back mechanism. But, first of all, it therefore still seems reasonable to ask about the general sense and reason of the existence of such a solution in the Polish legislative system, if the other legislative mechanisms successfully fulfil the systemic goals of reducing the public payer's expenditure. ■

REFERENCES:

1. Citations from the explanatory memorandum to the Act on the reimbursement of medicinal products, foodstuffs intended for special uses and medical products, forwarded for social consultations in a letter of September 9, 2010
2. See. Art. 3 and Art. 74 of the Reimbursement Act
3. Art. 4 section 8 of the Act, providing that the exceeded amount and the pay-back amount are calculated by the Fund within 30 days from the approval of the financial statement for the previous year, may be regarded as a kind of an „interpretation gate", supporting the verification of the preliminary condition for calculation of exceeded amounts on annual basis. This provision may, however, be interpreted as referring exclusively to the time-point of technical calculation and not to the time-point, constituting the occurrence of the pay-back mechanism
4. Constituting the ratio of the total budget for reimbursement during financial year, decreased by the reserve, mentioned in Art. 3 section 3 of the Act, and of the total budget for reimbursement in the previous year
5. The limit grounds were in that time published in the regulation of the Minister of Health, issued on the basis of Art. 38 section 6 of the Act on providing Healthcare services financed from public funds. The price limits were introduced for the drugs with the same international name or with different international names but revealing the same therapeutic effect
6. For example, the Minister of Health may in certain situations routinely issue decisions, changing limit group definition
7. Resolution of the Senate of May 2, 2011 r., Print No. 4152
8. This coefficient is a ratio (i) of the amount, by which the total budget for the reimbursement of prescribed products is exceeded and (ii) of the sum of exceeded amount in particular limit groups. It may then be assumed that this coefficient is to compensate possible disparities between the total amount of exceeded reimbursement at the total budget level and the summed amount of exceeded reimbursement at the level of the limit groups
9. Source: presentation of the Minister of Health of December 18, 2013 „Summary of the Reimbursement Act". Availabel from: http://www.mz.gov.pl/dla-mediow/konferencje-i-briefing/konferencja-prasowa-ministra-zdrowia-bartosza-arlukowicza-podsumowanie-ustawy-refundacyjnej"
10. It is, among others, indicated in the records from the margin-price dispute, where the main axis of controversy was the legal appropriateness of imposing penalties for some pharmaceutical companies for their alleged exceeding of official prices and margins
11. A draft of September 18, 2013 on amending the Act on the reimbursement of medicinal products, foodstuffs intended for special uses and medical products, as well as of some other acts. Available from: http://www2.mz.gov.pl/wwwfiles/ma_struktura/docs/ustawarefundacja_20130919.pdf"DEF Communications of May 8, 2012, May 7, 2013 and May 6, 2014 - Information on reimbursement amounts, together with the percentage of total reimbursement budget implementation

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Medical Information Center (CIM)

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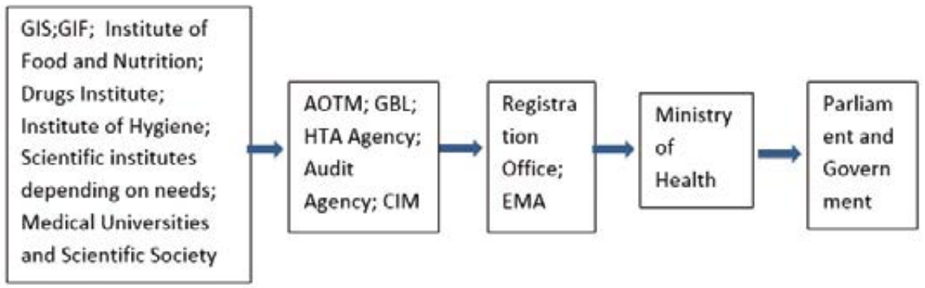
ABSTRACT

Medical Information Center (CIM)

MEDICAL INFORMATION CENTER (CIM)

Many institutions deal, or should deal with the collection, processing and purposeful use of the available scientific information in the world, which targeted, will become an instrument in the activities of the government. These institutions are acting separately, often using information from unverifiable sources, creating imperfect opinions, potentially used by the bureaucratic apparatus. Amplification of that imperfection in the form of an administrative decision is resulting as quality of established law and consequently efficiency of the state, and the quality of its image in the world.

The proposal to create the Medical Information Centre can provide a solution that entering similar, already existing European and national structures, with similar, usually narrowly specialized databases of information or opinion-forming units become the most serious, independent of the influence of lobbying factors tool for the state in the making and amendment of systems and procedures valid in the Polish health care.



The above diagram of the organizational and functional Medical Information Center assumes the use of the potentials of four units:

1. GBL - its scientific background in the form of on-line Thesaurus, Polish Medical Bibliography, international databases,
2. AOTM - in accordance with its statutory purpose, in my opinion should not be used only for the purposes of public payer, but for the assessment of all procedures required evaluation of the proper functioning of the health care system in Poland,
3. Medical Audit Agency - control the efficiency of the system,
4. HTA - the state agency, which guarantees the quality of medical records evaluation serving as the starting material for the registration work and authorization of drugs, medical supplies and medical devices for URPL.

The sources of current information on all aspects of the Polish market of drugs, from registration procedures, to control of the market and the internal control procedures, are:

1. Chief Sanitary Inspectorate (GIS) - should fulfill functions in accordance with statutory appointment. Thus, I want to clearly emphasize that this is not the authority of the State entitled to use the procedures for registration and admission to trading drugs without a prescription and dietary supplements. This feature fulfill URPL appointed by relevant law, therefore any existing GIS competence on drugs and dietary supplements should be immediately transferred to the URPL - proper authority of law, after a proper assessment of the merits and qualifications in the Medical Information Center. GIS should analyze and control the national and international market as specified in the Act.
2. Main Pharmaceutical Inspectorate (GIF) - similarly as GIS in addition to control of drugs and medical products manufacture should after the amendment or writing a new Pharmaceutical Law play the role of the pharmaceutical police, controlling obeying of the law in companies operating in the Polish pharmaceutical market in cooperation with the police, border guards, the Polish army, fiscal institutions and, if necessary and justified with special services. The security interests of the state on the internal market with the principles of the protection of the Polish companies interests (including state protectionism in selected directions of development of the Polish market of drugs from production, import, export to pharmacy retail). The basis for the effective working of the GIF as in the case of GIS is transfer of decision-making in the hands of the government which is the guarantor of efficiency.
3. Chief Veterinary Inspectorate - I have not included the role of the Inspectorate in the sources for the CIM, but I think that in terms of drug production and marketing under the supervision of the Ministry of Agriculture with supervision limited to issue permits for veterinary wholesalers by GIF and supervision of production, requires law changes, specially that many "human" drugs are used on a daily basis in veterinary medicine. In my opinion, the market in this area is beyond the control of the State. The quality of animal and crop production as a raw food has the impact on level of public health and spendings on the remedy.
4. Medical Universities in Poland and cooperating with them (through them) research centers and institutions of other countries, as well as it does today in the GBL, (which is the general distributor of WHO scientific information on Poland) international organizations.

SIMILARLY, INSTITUTES AND RESEARCH SOCIETIES. THE PURPOSE OF SUCH SOLUTIONS IS THE GOVERNMENT ACCESS TO THE LATEST OF POLISH AND WORLD SCIENTIFIC ACHIEVEMENTS PROFESSIONALLY PREPARED AND THEREBY PROVIDING A SOURCE TO DEVELOP THE MOST OPTIMAL SYSTEM SOLUTIONS FOR THE POLISH HEALTH SERVICE.

Similarly, Institutes and Research Societies. The purpose of such solutions is the government access to the latest of Polish and world scientific achievements professionally prepared and thereby providing a source to develop the most optimal system solutions for the Polish health service. World adopted system solutions, after checking their social function and actions quality of already implemented examples, are proven

method of adaptation of the best methods to deal with simultaneous elimination of lower quality solutions.

Obtained information from all signaled above sources, provide the basis for improving the functioning of the registration and admission system of trading dietary supplements and medical products on the Polish market in a way that ensures the safety of their use.

Improvement of quality and transparency in this economy area generates by itself significant savings in the system and the accuracy of management so saved up resources in the most optimal way in terms of function and application of Union and national law. For example the action of the Economic Commission at the Ministry of Health or the previous, however, strongly narrowed actions of AOTM in assessing drug technologies.

Another positive factor affecting the quality of the system and in favor of the CIM acceptance as a system solution is a substantive justification for the revision or creation of a new medical law, by identifying the most secure in the assessment of international researches, solutions that should be implemented into national law.

Additional positives resulting from the implementation of the systemically uniform, existing today as separate entities organization - the authorities of the state are:

1. the quality of medical information,
2. reliability of the information,
3. the acquisition speed of decision-making authorities,
4. independence from the lobbying influence for the opinion creation,
5. cooperation with other government units as component of the stabilizing role of the state in the organization and management of the health care system,
6. with rational and controlled risk management, CIM establishment does not carry additional state expenditures beyond the already existing for separate units included in the CIM,
7. cooperation with CIM analogues in the EU and in the world in the direction of optimizing the Polish health care system as part of integrated systems in Europe, and in some aspects (eg. vaccines and vaccination) in the world.

The above system changes previously existing, not always effective and efficient, circulation medical information system in Poland, perhaps in some circles it is going to be seen as too revolutionary, but I think that insertion of it, as the solution adopted in many EU countries (eg Italy, Spain, the Netherlands, Norway) can be an innovative step in the quality of substantive administrative decision in Polish drug market, and the strengthening of state control in the most socially vulnerable area such as the public health. I am aware of the need to discuss the details of this proposal, but it seems that such a discussion soon can lead to a radical improvement in the health sector by providing substantive answers to the most difficult questions and issues that should be resolved as soon as possible. I hereby declare my participation in substantive discussions on the proposed project and collaboration at every stage of its implementation. ■

Polish Pharmacoeconomic Society activities review 1/2014

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ABSTRACT

Polish Pharmacoeconomic Society activities review 1/2014

Among other activities the Polish Pharmacoeconomic Society supports editing the Journal of Health Policy and Outcomes Research (JHPOR). This year, in Warsaw, on 15 March 2014, JHPOR organized 1st Scientific Conference dedicated to "Safety aspects of treatment with monoclonal antibodies and fusion proteins – the Present and the Future".

Prominent lecturers, experts with experience in the use of biological treatment, provided interesting and interdisciplinary input into the scientific program. The conference emphasized the practical aspects of issues related with biological treatment, in particular regards with to safety aspects of administering medicinal products.

Prof. Karina Jahnz-Różyk opened the conference with a lecture on current issues related to monoclonal antibodies' and fusion proteins' treatment.

Prof. Grieb presented the registration process of biological products and approached the idea of biosimilarity and the registration procedures and requirements in relation to biosimilars in Europe.

Clinical experts from different disease areas presented and discussed their experience with biological products use and the impact on safety of the treatment. Prof. Tłustochowicz focused his lecture on the autoimmunological diseases resulting from treatment with biological products. Prof. Filipowicz – Sosnowska, as a member of the Coordinating Team established by National Health Fund for rheumatologic diseases treatment with biological products, shared her experience in biological products use in the rheumatology area and presented the number of patients treated with biologicals. In relation to rheumatology Prof. Rutkowska – Sak presented the experience with biological treatment in pediatric population.

Prof. Płusa presented his opinion and experience with anti - IgE treatment in the allergic diseases and Prof. Owczarek approached the subject of biological therapies safety in skin diseases treatment.

Prof. Wysocki presented his positive experience with regards to solid tumors monoclonal antibodies treatment. Dr Łazicka-Gałecka presented the experience from ophthalmology and Prof. Rydzewska assessed the safety and risks of biological and biosimilar treatment in case of gastrology.

The use of biosimilar products was discussed also by Prof. Jędrzejczak based on the case of hematology. Very interesting presentation including discussion on differences in observed adverse events reported due to original biological product and biosimilar product.

During the meeting there was also a special scientific debate with the participation of lecturers and guest speakers from Ministry of Health, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Main Medical Library and AHTAPOL dedicated to the discussion on the future of treatment with monoclonal antibodies and fusion proteins. The debate was an important step in the preparation of the final Polish Expert Group Position Statement on the safety of biological treatments with monoclonal antibodies and fusion proteins.

Regarding to the Polish Pharmacoeconomic Society sections activities they continue working on projects initiated last year.

The Health Related Quality of Life Section (HRQoL) finalizes activities related to Quality of Life dictionary. Currently, after receiving reviewers' comments final modifications are made and the team is looking for potential options to publish the dictionary.

As continuation of previous year tradition an educational session dedicated to quality of life topic called "Wiosenne Spotkanie Edukacyjne Sekcji Jakości Życia Polskiego Towarzystwa Farmakoekonomicznego"(Spring educational meeting of the Quality of Life Section of Polish Pharmacoeconomic Society) was organized. It was held in Warsaw at the Medical University on 14th May 2014. During the meeting prof. Marcin Czech presented the use of conjoint analysis and other methods for measuring preferences in health care; mgr Karol Domański talked about the willingness to pay for health improvement and the use of the method of conditional selection and the EQ-5D questionnaire. The clinical significance of quality of life end points in clinical trials was discussed by prof. Maciej Niewada; dr Dominik Golicki presented the theoretical basis and practical implications for using indirect costs and quality of life in pharmacoeconomical analyses. Dr Monika Szkultecka-Dębek and mgr Marta Bem focused the audience attention on vignettes and their use in quality of life assessment.

The Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) continue working on adverse events costs based on therapeutic programs examples. Additionally the discussion initiated in 2013 related to biosimilar products and worked on a paper reviewing the approach to automatic substitution across Europe continued. ■