Current issues of therapy with 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.

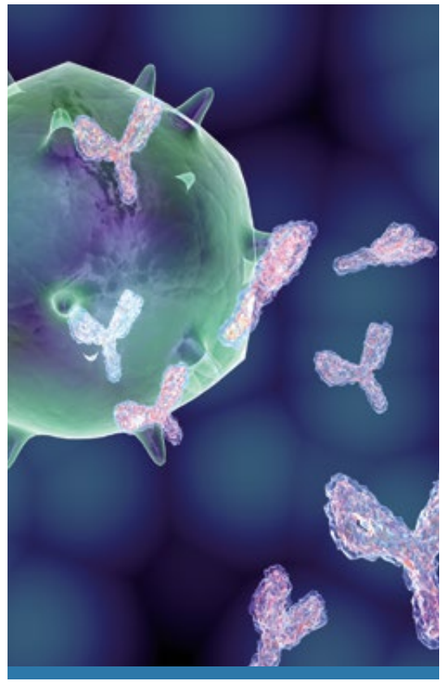
Differences across European Member States in national healthcare systems, structures and processes impact biosimilar uptake. Such differences may be any or all of the following:

- 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)

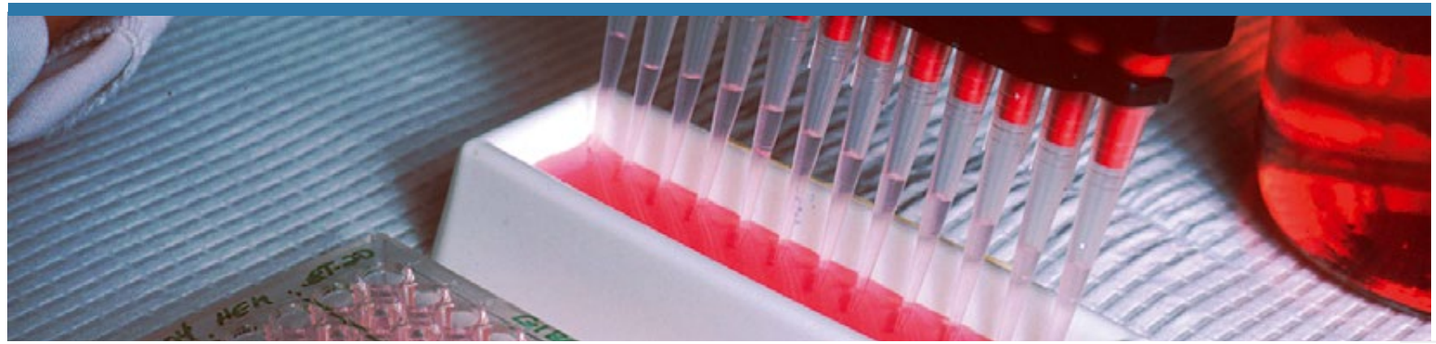
Erbitux is a chimeric monoclonal antibody rather confusingly distributed by BMS and Eli Lilly in the United States and by Merck KGaG in Europe. It is a EGFR inhibitor used for treatment of metastatic colon cancer, metastatic non-small cell lung cancer and head and neck cancer. In the US, having generated 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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