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Safety aspects and access to biological treatment in Poland

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Abstract

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

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

Key words: biologics, adverse side-effects, access

Biotechnology

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

Biological drugs

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

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

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

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

Monoclonal antibodies

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

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

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

Cytokines

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

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

Fusion proteins

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

Biological drugs in the world

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

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

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

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

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

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

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

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

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

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

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

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

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

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

-Trastuzumab (Herceptin, Roche) – an antibody,

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

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

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

Biological drugs in Poland

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

-cancer therapy with trastuzumab,

-chronic myeloid leukaemia with imatinib

-intestinal stroma tumour with imatinib or sunitinib,

-multiple sclerosis with interferon beta,

-viral hepatitis B or A with interferon alpha,

-renal carcinoma with sunitinib,

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

The safety aspects of biological therapy

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

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

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

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

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

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

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

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

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

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

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

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