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Access to biological treatment in Poland and in the world – the role of Health Technology Assessment

Biológiai terápiákhoz való hozzáférés Lengyelországban és a világon – az egészségügyi technológiaértékelés szerepe

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A „biológiai terápiák" megnevezés rendszerint a gyógyszerek olyan csoportjának a megnevezése, amelyek előállítása rekombináns DNS technológiát is magába foglaló biológiai eljárások segítségével történik. Ezek a gyógyszerek három kategóriába sorolhatók – szignál fehérjék (pl. eritropoetin), monoklonális antitestek és ún. fúziós fehérjék. Klinikai vizsgálatok bizonyítják, hogy a biológiai terápiák számos betegségben a legkülönfélébb területeken jelentenek új, hatékony kezelési alternatívát, úgymint reumatológia, onkológia, bőrgyógyászat, tüdőgyógyászat stb. Mindazonáltal a betegek hozzáférése ezekhez a gyógyszerekhez az egyes európai országokban igen különböző, függően a gyógyszerek mellékhatásprofiljától, a helyi jogszabályi környezettől és farmakoökonómiai tulajdonságaitól. Jelen cikkben a biológiai terápiákhoz való hozzáférés néhány kiválasztott problematikáját tárgyaljuk meg mind lengyel, mind európai perspektívából.

The term „biological drugs" (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.

BIOTECHNOLOGY

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

At present, biotechnology finds applications in various fields of medicine but also in food production, crime investigation techniques or waste management technologies [2].

BIOLOGICAL DRUGS

Biological drugs belong to biopharmaceutical products, formed in biotechnological processes, most often in colonies of live cells and not by chemical synthesis [2]. The significant differences between a chemically obtained drug and a biological drug result from the fact that a biological drug has got a bigger molecular weight and is digested in the gastric tract, the latter feature enabling its parenteral administration. The complexity of technological processes, associated with the production of biological drugs, is observable during the process of obtaining the, so-called, follow-on or biosimilar biologics, which, however, are always the products which merely imitate innovative biological drugs, unlike generic drugs, which are the exact copies of original medicinal products.

Biological drugs include, among others, vaccines, blood and blood-derived preparations, antitoxins, growth hor-

mones, 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. Biological drugs have thus been finding applications in many branches of medicine, including the treatment of anaemia, fibrocystic disease of the pancreas, growth deficits, haemophilia, leukaemia, hepatitis, genital papillae, transplant rejections, certain types of neoplasms, asthma and diseases from autoimmunity.

MONOCLONAL ANTIBODIES

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. An example of such a cellular ligand is CTLA4-Ig – abacept – which blocks CD28-CD80/86 reaction.

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.

An attempt to put the terminology of monoclonal antibodies in order has led to the definition of a classification, which allows to distinguish among antibody types by the suffixes of their names. Accordingly, the „ximab" suffix denotes a chimeric antibody, „zumab" unveils a humanised antibody, „mumab" – human antibody and the „cept" suffix has been reserved for the receptors of soluble cytokines.

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). In biological therapy, the safety aspect in administration of biological drugs is of key importance for the treated patient [4]. 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. Following Pichler, adverse effects in the course of treatment with monoclonal antibodies result from excessively secreted cytokines (alpha type) during treatment, hypersensitivity reactions (beta type), cytokine balance disturbances (gamma type), cross reactions (delta type) and nonimmunological reactions (epsilon type) [4]. Clinically, the alpha type is manifested by influenza-like symptoms, including muscular and arthral pains and elevated body temperature. 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.

BIOLOGICAL DRUGS IN THE WORLD

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, an antibody directed against against TNF-alpha, recommended in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylytis;
- Anakinra, IL-1 neutralising cytokine, recommended in the treatment of rheumatoid arthritis;
- Bevacizumab, an antibody, directed against the vascular endothelial growth factor (VEGF-A), recommended in the therapy of colorectal carcinoma;
- Cetuximab – an antibody, directed against the epidermal growth factor receptor (EGFR), recommended in the therapy of metastatic colorectal carcinoma;
- Etanerecept, 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;
- Infliximab, an antibody, directed against TNF-alpha, recommended in the therapy of rheumatoid arthritis, Crohn's disease and psoriatic arthritis;
- Omalizumab, an antibody, directed against Immunoglobulin E, used to improve asthma control in patients with severe, chronic, allergic asthma;
- Palivizumab, 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, an antibody, directed against the vascular endothelial growth factor (VEGF-A), recommended in the therapy of age-related exudative maculopathy [5];
- Ritiximab, 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 – 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 [6]. 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.

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 [7]. 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) [8]. 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 [7].

SUMMARY

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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BIOGRAPHY

Prof. Karina Jahnz-Rozyk, specialist in fields of allergology and clinical immunology, graduated from Medical Academy, Warsaw, Poland in 1983. From 1984 till now she works in Military Institute of Medicine as Head of Department of Allergology and Clinical Immunology. She achieved university degrees and scientific tittles by binding polish laws – in 1989 Doctoral degree with a thesis: „The influence of inhalative steroids for ventilator parameters in patients with asthma" and in 1997 – Habilitation (postdoctoral) degree with a thesis: „Some cytokines in bonchoalveolar lavage fluid from patients with atopic asthma and chronic bronchitis. Since 2002, she became Professor in Allergology and Pneumonology. She is member of Polish Society of Allergology, European Academy of Allergollogy and Clinical Immunology, European Respiratory Society. Since 2003 she has been member of Polish Society of Pharmacoeconomics (ISPOR Poland Chapter), in 2009-2012 president of the Society. Author and coauthor of 330 publications, she lead 22 clinical trials (II&III phases) in the areas of respiratory and allergic diseases.

(Folytatás a 18. oldalról)

egy ugyanennyi idős lány 5,1 évvel rövidebb életre számíthat, mint az európai átlag. S amennyiben a jelenlegi népegészségügyi helyzet nem változik, életük 21, illetve 25 százalékát nem egészségesen élik le.
A helytelen táplálkozással is összefüggésben lévő szív-, és érrendszeri, valamint daganatos megbetegedések népbetegségnek számítanak, gyermekeink (és a felnőtt lakosság) jelentős hányada túlsúlyos, vagy elhízott. Nemzetközi és hazai kutatások is azt jelzik, hogy a túlzott cukor és só bevitel komoly egészségügyi kockázatot jelent. A magas vérnyomás, az agyvérzés, a szívkoszorúér-betegségek veszélye megfelelő táplálkozással és rendszeres testmozgással jelentősen csökkenthető lenne.
A magyar lakosság sófogyasztása minden életkorban jelentősen meghaladja az ajánlott mennyiséget. A felnőttek napi ajánlott 5 gramm helyett 14-18, míg a gyermekek 3 gramm helyett 3,5 – 13,1 gramm között fogyasztanak sót. Sok esetben a szénhidrátok (így pl. az édességek) teszik ki az étkezések jelentős részét, miközben naponta és testsúly-kilogrammonként mintegy 5 gramm szénhidrátra van szükségünk.
A magas koffein-bevitel felborítja a normál életritmust, mesterséges felpörgést, ezt követően azonban fokozott fáradtságot okoz. Az érzékeny korcsoportokban (pl. gyermekek, serdülők, fiatal felnőttek) a nagy mennyiségű koffein fogyasztása előidézheti a koffein túladagolás tüneteit: erős hányingert és hányást, mellkasi fájdalmat, szapora pulzust, verejtékezést, nyugtalanságot, álmatlanságot, esetenként pánikrohamot. Koffein-tartalmú ital fogyasztásához nem szokott személyek, vagy 18 év alatti gyermekek esetében a túladagolás súlyosabb következményekhez, így akár halálhoz is vezethet.
A legnagyobb veszélyben a gyerekek vannak, hiszen ők általában a magas kalóriatartalmú ételeket, italokat szeretik, amelyek rendszerint sok hozzáadott sót, cukrot, emellett elenyésző mennyiségű vitamint és ásványi anyagot tartalmaznak.
Nemzetközi tapasztalatok szerint a különféle termékekre kirótt adók befolyásolják a termékek fogyasztását, ily módon az egészségkockázatot. Éppen ezért a Nemzeti Erőforrás Minisztérium Egészségügyért Felelős Államtitkársága támogatja a népegészségügyi termékadó bevezetését. Az Államtitkárság intézkedéseivel ahhoz szeretne hozzájárulni, hogy táplálkozási szokásaink kedvező irányú változásának eredményeként legalább annyi ideig éljünk, mint a nyugat-európai uniós polgárok.