УДК 615. 007. 21:612. 43/45. 018. 2+577:154. 365

BIOTECHNOLOGICAL DRUGS: SCIENTIFIC, REGULATORY AND EDUCATIONAL ASPECTS

Zaychenko A., Professor, Doctor of Medical Sciences
anna.zajjchenko@gmail.com
Gorchakova N., Professor, Doctor of Medical Sciences
gorchakovan@ukr.net
Shumeiko O., Associate Professor, PhD of Medical Sciences,
ashu@i.ua
Klymenko O., Associate Professor, PhD of Medical Sciences,
klymenkoolena75@gmail.com
Khodakivska O., Associate Professor, PhD of Pharmaceutical Sciences,
olga.hodakovskai@gmail.com
Bogomolets National Medical University, Kyiv, Ukraine
MironenkoV., Associate Professor, PhD of Medical Sciences,
tmb@kpi.ua
National Technical University of Ukraine
"Igor Sikorsky Kiev Polytechnic Institute", Kiev, Ukraine

Abstract - Our century is characterized by the introduction of innovative technologies that are used in all spheres of life, including in pedagogy, which helps to familiarize students with modern medical and pharmaceutical technologies.
These drugs are obtained by using biological objects by means of special technological processes of cell engineering, hybrid technologies, engineering enzymology, engineering immunology, and others. Biotechnological preparations include certain antibiotics, hormonal and vitamin preparations, blood preparations, cytokines, immunomodulators, enzymes, lipids, polysaccharides, monoclonal antibodies, and others. Biotechnological preparations differ from chemical synthesis drugs not only in their production technology, but also in their significant molecular weight, complexity of the spatial structure of the protein, a certain ratio of isoforms, instability of molecules, and other properties. At the same time, they have a significant cost due to the complexity of the technological process: it is impossible to create analogues of biotechnological drugs by chemical synthesis. If desired to reproduce biotechnological products, biosimilars are obtained which must be subjected to complete preclinical (in vitro and in vivo) studies, taking into account the definition of pharmacokinetics and clinical trials. In Ukraine the exchange of biosimilars is regulated by the pharmacovigilance system.
To improve the quality of teaching the pharmacology to students of medical and pharmaceutical faculties, it is necessary to modernize educational technologies. For this purpose, biotechnological preparations are included in the pharmacology program for students of medical and pharmaceutical faculties.

Keywords -biotechnological preparations, biosimilars, monoclonal antibodies, professional training.

I. INTRODUCTION

The 21st century is characterized by the implementation of innovative technologies that are used in all spheres of the life, including pedagogy, biology, medicine, clinic [1]. The development of medical science, encourages lecturers to familiarize students during lectures and workshops with new achievements of pharmacology, pharmacy, biology, which helps to develop a new type of motivational sphere. To improve the quality of pharmacology teaching for students of medical and pharmaceutical faculties it is necessary to upgrade innovative pedagogical technologies adjusted in accordance with international standards. This will contribute to the development of creativity of future doctors and pharmacists, professional competence, the creation of a new position of a personality [2]. The personal component of professional competence acquisition is closely related to the development of new professional knowledge of theoretical subjects that will improve the implementation of new drugs in the clinical environment. One of the modern drugs whose representatives were included in

the program of pharmacology for students of both medical and pharmaceutical faculties are biotechnological drugs which help to treat rheumatoid arthritis, multiple sclerosis and other serious diseases more successfully [3].

II. THE AIM

The aim of the work is to form a system of teaching modern knowledge about the pharmacology of biotechnological preparations.

III. MATERIAL AND METHODS

Methods analysis of modern literature data on the issues under the consideration, the determination of practical aspects of teaching the features of biotechnological preparations in pharmaceutical universities and relevant faculties of medical universities.

IV. RESULTS AND DISCUSSION

Biotechnology as a science was born in the 70s of the twentieth century, when the transfer of genetic material from one organism to another was carried out. Modern biotechnology is a scientific discipline that studies the possibility of using living organisms, their systems or life products to solve technological tasks and the possibility of creating living organisms with the necessary properties by genetic engineering [4], and at the same time the methodology of biologically active substances production including drugs.

Biotechnological preparations include medicines obtained using the biological objects (microorganisms, human cells and tissues, plants, animals, insect and mammal cells, hybrid cells, yeast, genetically engineered strains of microorganisms, DNA, RNA) with the help of special technological processes of cell engineering, hybrid technologies, engineering enzymology, engineering immunology, etc.). Thanks to the use of biotechnological preparations, positive results were obtained in the treatment of such serious diseases as bronchial asthma, hepatitis C, diabetes mellitus, rheumatoid arthritis, cancer, anemia, hemophilia and others [5].

Among biotechnological preparations are antibiotics, vitamins, hormone - like substances, their synthetic substitutes, insulin, growth hormones, enzymes, fibrinoleptics, lipids, polysaccharides, monoclonal antibodies, organic acids, amino acids, allergens, antigens, preparations from human blood and plasma, as well as vaccines, cytokines, immunomodulators, alpha - beta-gamma interferons, immunosuppressants, immune sera, immunoglobulins, interferons, interleukins and others.

Biotechnological preparations differ from chemical synthesis preparations in a significant molecular weight and complexity of the spatial structure of the protein. They are characterized by the presence of the quaternary structure, a certain ratio of isoforms and high heterogeneity. Biotechnological preparations differ from chemical ones by more complex structure in combination of protein with high heterogeneity and glycosylation degree. At the same time the structural instability of the molecule of biotechnological agents and impurities was noted.

The living organisms are used for the production of biotechnological agents and, therefore, the active substances are very dependent on the primary state of these living organisms. Biotechnological preparations are considered to be the medicine of the future as they are more effective and safe and allow to carry out targeted therapy for severe diseases, whose success of treatment becomes possible today thanks to biotechnological preparations. However, a significant disadvantage of biotechnological preparations is their high cost [5], which is associated with complex algorithms of their production. First, to solve the problem of wider introduction of biotechnological preparations it was proposed to synthesize their analogues as it happens with the majority of generic preparations. Meanwhile by the usual synthesis of such a drug it was impossible to create such a biotechnological product. Therefore, with the help of modern technologies, wishing to recreate a biotechnological product a biosimilar is obtained [6].

Biosimilar is a version of a registered biotechnological drug but it is not an accurate reflection of the biotechnological products with which they were compared in the study. They proved the similarity on the basis of a comprehensive comparison of the similarity of physical and chemical characteristics of efficiency and safety [7]. To solve the issue of the effectiveness and safety of biotechnological drugs, individual approaches were used in relation to clinical studies, clinical trials, production, quality control of drugs, prescribed in the treatment process and pharmacological evaluation of treatment results [7, 8].

It is paid attention to the fact that biosimilars obtained during the production may differ in a pharmacokinetic profile and immunogenicity. The last may appear as generalized reactions in the form of the hypersensitivity reaction which is more common. However, there is also neutralization of endogenous protein in case of loss of interferon efficiency or neutralization of endogenous protein in case of the erythrocyte aplasia [3].

Biosimilars are sometimes characterized by heterogeneity of isoforms. In connection with the above study of the biosimilars effectiveness there are more stages of comparison with generic drugs, including comparative physico-chemical, biological parameters, comparative to clinical studies in vitro and in vivo, together with pharmacokinetic tests, as well as comparative studies of effectiveness in the clinic. The effect on the immune system is manifested in the form of a pathological reaction of the immune system as the hypersensitivity.

Telling in the lecture of the history of the pharmacology, first it is remembered the empirical period (the use of drugs in the form they are met in the nature), for example, in the form of plant materials. Then students are focused on the etiological period (the second half of the XIX century - the first 30 years of the twentieth century) which was associated with the research of the outstanding French scientist and physician Louis Pasteur. It was he who discovered the nature of fermentation, proved the possibility of life in the absence of oxygen, developed the scientific basis of vaccination and vaccine therapy, proposed a method of sterilization (pasteurization, etc.).

The biotechnological period of the development began in 1933 with the publication of the work of A.Claver and L.H.Z.Perkin “Methods of studying of metabolism in fungi” which was the impetus for the development of industrial sealing equipment and mechanization of the processes of creating conditions for the production of antibiotics (1936-1945). Genotechnical period of the biotechnology began in 1953 and gets upgraded to the present time.

Students should pay attention to the fact that in Ukraine a significant element of the biosimilar metabolism regulation is pharmacovigilance and safety monitoring because biosimilars are more often prescribed for the treatment of severe cancer and immunodeficiency conditions [9]. These remedies are more likely to cause adverse effects on the immune system and other organs and systems due to their mechanism of action [3].

Biotechnological preparations are included in the program of the pharmacology for students of medical and pharmaceutical faculties. At practical lessons and lectures on the topic "hormones" it is paid attention to biosimilar analogues of insulin and growth hormone. Insulin obtained by genetic engineering has many biosimilars at the pharmaceutical market such as insulin aspartate, insulin lyspro, Insulin glargine. Now the production of insulin biosimilars continues and the requirements for their quality are growing [10, 11, 12]

When analyzing the pharmacodynamics of vitamin preparations, attention is paid to alpha-tocopherol which is obtained with the help of the biotechnology. At classes and lectures whose topic is the pharmacology of drugs that affect hematopoiesis and hemostasis, we mention blood factor drugs (factors VIII and IX), thrombolytic agents (dabigatran, rivaroxaban, apixabsen), hematopoietic growth factor – erythropoietin and granulocytic macrophage colony stimulating

factor. The latter increase the number of leukocytes during chemotherapy and reduce the risk of secondary infection of the patient [13]. Considering the pharmacology of drugs that affect the immune system, it is also focused on hematopoietic germ factors, which are natural cytokines prescribed together with chemotherapy [14, 15]. In addition to granulocyte-macrophage colony stimulating factor, which supports leukopoiesis, it is necessary to recall erythropoietin which stimulates the formation of red blood cells, and interleukin-II, which contributes to the production of platelets [16]. Cytokines as signal molecules synthesized by leukocytes also include interferons, interleukins, which have immunomodulatory effects and are therefore included in the pharmacotherapy of immunodeficiency states.

At practical lessons during the analysis of antitumor pharmacological agents we pay more attention to the drugs of monoclonal antibodies which can be targeted therapy in the treatment of malignant tumors but they can also, unfortunately, show a negative impact on the immune system. Other biological products, such as vaccines, also have antitumor effect but due to the stimulating effect on the immune system. Vaccines for cancer treatment contain associated with tumor antigens to enhance the activity of the immune system against cancer cells. The antigens associated with the tumor may be protein. They are located on the surface or inside the tumor cell and, therefore, can cause apoptosis or acquire the properties of killers. The BC6 vaccine activates the overall immune response of the body which can be directed both to the activity of bacteria and tumor cells [17].

The largest group of biotechnological drugs is monoclonal antibody preparations [17]. Monoclonal antibodies are antibodies that are produced by immune and other cells cloned from a single β-ligocytosis precursor cell that are specific to a certain antigen. The producers of monoclonal antibodies are hybridomas. They are proteins that bind to a single site of an antigen and are produced by single cells.

The range of the application of monoclonal antibodies is extremely wide. Students of the 3rd course mainly are given examples of monoclonal antibody preparations and indications for their prescription. For example, imizinum is prescribed for the prevention of bleeding; trastuzumab, rituximab – for cancer; adalimumab, infliximab – for autoimmune diseases. For diseases of the respiratory system omalizumab, reslizumab are prescribed; the cardiovascular system - abciximab, hepatitis C – bavituximab. Monoclonal antibodies can be classified according to the technology of their production and protein-chemical structure: mouse, chimeric, humanized, completely human antibodies [19-24].

There is a classification of monoclonal antibodies by modification of the structure, namely divided into immunotoxins, conjugates with radioisotopes, antibodies with double specificity. It is also possible to allocate monoclonal antibodies by surface receptors which are guided action of monoclonal antibodies to CD markers, monoclonal antibodies to receptors IL, monoclonal antibodies to THF-α, monoclonal antibodies to molecules of cellular adhesion. To facilitate the recognition of the monoclonal antibodies it was observed that they all end in "mab", obtained from mice are "omab", chimeric antibodies are "ximab", humanized antibodies are "zumab" fully human are "umab" [21-23].

V. CONCLUSIONS

Thus, modern biotechnological preparations make up a significant part of the world and domestic pharmaceutical market. The use of biotechnological preparations is a revolution in the treatment of such severe chronic diseases as diabetes mellitus, bronchial asthma, rheumatoid arthritis, cancer, anemia, hemophilia.

Competence-based approach to the structure of the pedagogical process for students of medical and pharmaceutical faculties aimed at improving the professional orientation meets the needs of the health care

industry and will contribute to modernization of creative and professional activities of future professionals.

VI. PROSPECTS FOR FURTHER RESEARCH

It is reasonable in the future to expose more specifically the modern mechanisms of action of monoclonal antibody preparations for targeted therapy taking into account the indications for the prescription and the application peculiarities in every particular case.

VII. REFERENCES

[1] Oleksina NO, Volosovets OP, Piatnytskyi YuS. Medychna osvita: vidpovidi na vyklyky suchasnosti. *Medychna osvita*.2018; 2: 36-4. [Ukrainian]

[2] Bulakh IY, Voitenko LP, Antonenko YP. Monitorynh yakosti medychnoi osvity. Mizhnarodnyi dosvid. *Medychna osvita*. 2018; 3: 5-12. [Ukrainian] doi: 10.11603/me.2414-5998.2018.3.9328

[3] Talaieva TV, Doroshuk LV, Kudriavtseva IH. Biotekhnolohichni likarski preparaty ta biosymiliary: shcho neobkhidno znaty klinitsystam pry pryznachenni biosymiliariv. *Ukrainskyi revmatolohichnyi zhurnal*. 2015; 1: 3-7. [Ukrainian]

[4] Shirokova I. Biotehnologii na farmryinke. Remedium. *Zhurnal o rossiyskom ryinke lekarstv i meditsinskoy tehnike*. 2012; 9: 8-25. [Russian]

[5] Nesterchuk MM, Baula OP, Hamazin YuO, Doroshuk LV, Matvyeyeva OV. *Features of biological / biotechnological products and biosimilars:* metod rekomendatsiyi. Kyiv: MOZ Ukrayiny, Derzhavnyy ekspertnyy tsentr; 2013. 38 p.

[6] Sylvester K, Rocchio M, Beik N, Fanikos J. Biosimilars: an emerging category of biologic drugs for emergency medicine practitioners. *Current Emergency and Hospital Medicine Reports*.2013; 1(4): 226-35. doi: 10.1007/s40138-013-0023-5

[7] Calvo B. Zuñiga L. EU's new pharmacovigilance legislation: considerations for biosimilars. *Drug safety*. 2014; 37(1): 9-18. PMID: 24190573. DOI: 10.1007/s40264-013-0121-z

[8] Camacho, LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for US oncologists in clinical practice. *Cancer Medicine*. 2014; 3(4): 889-99. PMID: 24810680. PMCID:PMC4303156. DOI: 10.1002/cam4.258

[9] Moorkens E, Meuwissen N, Huys I, Declerck P, Vulto AG, Simoens S. The market of biopharmaceutical medicines: a snapshot of a diverse industrial landscape. *Frontiers in pharmacology*. 2017; 8: 314. PMID: 28642701. PMCID: PMC5462923. DOI: 10.3389/fphar.2017.00314

[10] Eltsova EA, Ramenskaya GV, Smolyarchuk EA, Bushmanova AV. Biosimilyaryi-preparatyi buduschego. *Farmakokinetika i farmakodinamika*. 2015; 1: 12-5 [Russian]

[11] Bezdetko NV. Biosimilyaryi analogov insulina: chto neobhodimo znat klinitsistu. *Ukrayinskiy medichniy chasopis*. 2016; 1(111): 35-41. [Russian]

[12] Golovach IYu. Pytannia bezpeky biosymiliariv analohiv insuliniv: fakty ta poboiuvannia. *Endokrynologia*. 2017; 22(2): 139-45. [Ukrainian]

[13] Walsh G. Biopharmaceutical benchmarks 2018. *Nat Biotechnol*. 2018; 36: 1136-45. PMID: 30520869. DOI: 10.1038/nbt.4305

[14] Rader RA. FDA biopharmaceutical product approvals and trends in 2012. *BioProcess Int*. 2013; 11.3: 18-27.

[15] Ramana K, Xavier J, Sharma R. Recent trends in pharmaceutical biotechnology. *Pharm Biotechnol Curr Res*. 2017; 1: 1-10.

[16] Declerck P, Simoens S. A European perspective on the market accessibility of biosimilars. *Biosimilars*. 2012; 2: 33-40. doi: 10.2147/BS.S33524

[17] Reichert JM. Trends in US approvals: new biopharmaceuticals and vaccines. *Trends in biotechnology*. 2006; 24.7: 293-8. PMID: 16759723. DOI: 10.1016/j.tibtech.2006.05.003

[18] Gorchakova NA, Savchenko NV, Shumeyko EV, Shumeyko NV. *Preparatyi monoklonalnyih antitel v meditsinskoy praktike: spektr primeneniya. Farmakologiya i farmakoterapiya: itogi i perspektivyi:* monografiya. Novosibirsk: Izd-vo Sibak; 2014. p. 13-20. [Russian]

[19] Gorchakova N., Heimuller E., Galkin A. Current safety data of the complex herbal medicine with sedative and cardioprotective actions. Innov Biosyst Bioeng. 2018, vol. 2, no. 3, 163–174. doi: 10.20535/ibb.2018.2.3.143029.

[20] Galkin OY, Komar AG, Pys'menna MO. Specificity of manifacturing process validation for diagnostic serological devices. Biotechnologia Acta. 2018;11(1):25-38. doi: 10.15407/biotech11.01.025.

[21] Нєчаєва Я.О., Грабчук С.М., Горшунов Ю.В., Мотроненко В.В., Галкін О.Ю. Рекомбінантні білки терапевтичного призначення: особливості отримання, вивчення безпечності та ефективності // Вісник Запорізького національного університету. Біологічні науки. – 2017. – №2. – С. 85-93.

[22] Galkin O.Yu., Lutsenko T.M., Gorshunov Yu.V., Motronenko V.V. Development of the method for microbiological purity testing of recombinant human interleukin-7-based product // Ukr. Biochem. J. – 2017. – Vol. 89, 3. – P. 52-59. doi: 10.15407/ubj89.03.052

[23] Natochii T, Motronenko V. Comparative Characteristics of Biotechnological Approaches to Obtaining Recombinant Human Cytokines in Bacterial Expressing Systems. Innov Biosyst Bioeng, 2019, vol. 3, no. 3, 128–145. doi: 10.20535/ibb.2019.3.3.170150

[24] Bondarenko L, Gorchakova N, Galkin A. Efficacy Profile of the Homeopathic Combination for Influenza and Acute Respiratory Viral Diseases Treatment and Prevention. Innov Biosyst Bioeng. 2018;2(4): 252-61. DOI: 10.20535/ibb.2018.2.4.148441

УДК 615. 007. 21:612. 43/45. 018. 2+577:154. 365

БИОТЕХНОЛОГИЧЕСКИЕ ЛЕКАРСТВЕННЫЕ ПРЕПАРАТЫ: НАУЧНО-РЕГУЛЯТОРНЫЕ И УЧЕБНО-МЕТОДИЧЕСКИЕ АСПЕКТЫ

Зайченко А.В., *проф., д.мед.н.,*
anna.zajjchenko@gmail.com
Горчакова Н.А. *проф., д.мед.н.,*
gorchakovan@ukr.net
Шумейко Е.В*., доц., к.мед.н.,*
ashu@i.ua
Клименко Е.В., *доц., к.мед.н.,,*
klymenkoolena75@gmail.com
Ходаковская О.В., *доц., к.фарм.н.,*
olga.hodakovskai@gmail.com
Национальный медицинский университет
имени А.А. Богомольца, Киев, Украина
Мироненко В.И., *доц., к.мед.н.,*
tmb@kpi.ua
Национальный технический университет Украины
«Киевский политихнический институт
имени Игора Сикорского», Киев, Украина

Реферат - Наш век характеризуется внедрением инновационных технологий, используемых во всех сферах жизни, в том числе в педагогике, способствующих ознакомлению студентов с современными медицинскими и фармацевтическими технологиями. Данные препараты получают путем использования биологических объектов с помощью специальных технологических процессов - клеточной инженерии, гибридных технологий, инженерной энзимологии, инженерной иммунологии и других. К биотехнологическим препаратам относятся определенные антибиотики, гормональные и витаминные препараты, препараты крови, цитокины, иммуномодуляторы, ферменты, липиды, полисахариды, моноклональные антитела и другие. Биотехнологические препараты отличаются от лекарственных средств химического синтеза не только технологией получения, но также молекулярной массой, сложностью пространственного строения белка, определенным соотношением изоформ, нестабильностью молекул и другими свойствами. Вместе с тем, они имеют значительную стоимость, что связано со сложностью технологического процесса – невозможно путем химического синтеза создать аналоги биотехнологических препаратов. При желании воссоздать биотехнологические продукты получают биосимиляры, которые необходимо подвергать полным доклиническим (in vitro и in vivo) исследованиям с учетом определения фармакокинетики. В Украине обмен биосимиляров регулирует система фармаконадзора. Для улучшения качества преподавания фармакологии студентам медицинских и фармацевтических факультетов необходима модернизация педагогических технологий. С этой целью в программу по фармакологии включены биотехнологические препараты.

Ключевые слова - биотехнологичные препараты, биосимиляры, моноклональные антитела, профессиональное обучение**.**

УДК 615. 007. 21:612. 43/45. 018. 2+577:154. 365

БІОТЕХНОЛОГІЧНІ ЛІКАРСЬКІ ПРЕПАРАТИ: НАУКОВО-РЕГУЛЯТОРНІ ТА НАВЧАЛЬНО-МЕТОДИЧНІ АСПЕКТИ

Зайченко Г.В., проф., д.мед.н.,
anna.zajjchenko@gmail.com
Горчакова Н.О. проф., д.мед.н.,
gorchakovan@ukr.net
Шумейко О.В., доц., к.мед.н.,
ashu@i.ua
Клименко О.В., доц., к.мед.н.,,
klymenkoolena75@gmail.com
Ходаківська О.В., доц., к.мед.н.,
olga.hodakovskai@gmail.com
Національний медичний університет
імені О.О. Богомольця, Київ, Україна
Мироненко В.І., доц., к.мед.н.,
tmb@kpi.ua
Національний технічний університет України
"Київський політехнічний інститут
імені Ігоря Сікорського",Київ, Україна

Реферат - Наше століття характеризується впровадженням інноваційних технологій, які використовують у всіх сферах життя, в тому числі в педагогіці, що сприяє ознайомленню студентів з сучасними медичними та фармацевтичними технологіями. Дані препарати отримують шляхом використання біологічних об'єктів за допомогою спеціальних технологічних процесів - клітинної інженерії, гібридних технологій, інженерної ензимології, інженерної імунології та інших. До біотехнологічним препаратів належать певні антибіотики, гормональні та вітамінні препарати, препарати крові, цитокіни, імуномодулятори, ферменти, ліпіди, полісахариди, моноклональні антитіла та інші. Біотехнологічні препарати відзначаються від лікарських засобів хімічного синтезу не тільки технологією отримання, але також значною молекулярною масою, складністю просторової будови білка, певним співвідношенням изоформ, нестабільністю молекул і іншими властивостями. Разом з тим, вони мають значну вартість, що пов'язано зі складністю технологічного процесу - неможливо шляхом хімічного синтезу створити аналоги біотехнологічних препаратів. При бажанні відтворити біотехнологічні продукти отримують біосиміляри, які необхідно піддавати повним доклінічних (in vitro та in vivo) дослідженням з урахуванням визначення фармакокінетики і клінічних випробувань. В Україні обмін біосиміляров регулює система фармаконагляду. Для поліпшення якості викладання фармакології студентам медичних та фармацевтичних факультетів необхідна модернізація педагогічних технологій. З цією метою в програму по фармакології студентам медичних та фармацевтичних факультетів включені біотехнологічні препарати.

Ключові слова - біотехнологічні препарати, біосиміляри, моноклональні антитіла, професійне навчання