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REVIEW ARTICLE

Efficacy and Safety of Anti-Tumor Necrosis Factor-A Biosimilars in Rheumatological Practice and Their Registration, Patenting

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Abstract

The aim of the work is to analyze and systematize data regarding the efficacy and safety of anti-tumor necrosis factor-α biosimilars**,** as well as their registration and patenting. Studies were conducted using databases on the Internet: Ukrainian patent office, the European patent office, the US patent office, the Food and drug administration, European Medicines Agency, State enterprise "The State Expert Center" of Ukraine. The breakthrough in the treatment of rheumatoid arthritis is the discovery and administration of anti-TNF-α agents, such as infliximab, adalimumab, etanercept, certolizumab pegol, golimumab. Numerous randomized clinical trials and meta-analysis data indicate high efficacy and acceptable safety of anti-TNF-α biosimilars for the treatment of rheumatoid arthritis. The development and registration of anti-TNF-α biosimilars reduces the costs of health care and patients for biological therapy, increases patient access to treatment with the latest drugs, and contributes to the further development of biotechnology. Thus, effective anti-tumor necrosis factor-α biosimilars may be more accessible to the general population with rheumatoid arthritis. Despite certain hazards and risks associated with possible violations in the implementation of biological products in real practice, the industry of highly effective biosimilars brings progress both for the development of science and for practical healthcare.

Keywords: *Infliximab, Adalimumab, Etanercept, Certolizumab pegol, Golimumab, Biosimilar, Efficacy, Patent.*

Introduction

Rheumatoid arthritis is one of the most common and severe chronic inflammatory diseases that, in the absence of effective therapy, quickly leads to disability and shortens the life expectancy of patients. The prevalence of rheumatoid arthritis is 0.5-1% (up to 5% in the elderly) and economic losses for society are comparable to coronary heart disease, from 5 to 50 people per 100,000 population fall ill every year [1, 2].

The problem of this disease is also relevant in Ukraine.The appearance of anti-tumor necrosis factor-α (TNF-α) agents in the late 1990s.Meant the breakthrough in the treatment of rheumatoid arthritis, since they not only controlled inflammation, but also prevented or slowed down the development of irreversible joint erosion.

It has been shown that TNF-α is one of the important cytokines in the pathogenesis of rheumatoid arthritis, and its blocking is an effective method of antirheumatic therapy. The central role of TNF-α in the development of events in rheumatoid arthritis was the basis for the creation of drugs-anti-TNF-α agents.

This led to a change in the strategic goal of rheumatoid arthritis therapy-achieving remission, and not just symptomatic improvement and slowing the progression of joint destruction. Presently there are 5 main anti-TNF-α agents: infliximab, adalimumab, etanercept, certolizumab-pegol, golimumab [3]. Infliximab is a chimeric monoclonal antibody based on mouse and human components.

Adalimumab, golimumab are recombinant monoclonal antibodies, the peptide sequence of which is identical to human lgG1. Etanercept does not belong to the class of monoclonal antibodies and has a slightly different mechanism of action. It is an artificial dimeric hybrid protein molecule ("fusion protein"), including the TNF receptor, which is linked to the human Fc-fragment of human IgG1.

Certolizumab pegol is a polyethylene glycolated Fab' fragment of humanized anti-tumor necrosis factor alpha monoclonal antibody. Analysis of the results of numerous clinical studies indicates the high efficacy of anti-TNF-α agents in the treatment of adult patients with rheumatoid arthritis and children with juvenile rheumatoid arthritis. However, it should be emphasized that the introduction of anti-TNF-α agents into clinical practice not only increased the effectiveness of therapy and improved the prognosis of patients suffering from the most severe forms of rheumatoid arthritis, but also led to a dramatic increase in the cost of treatment.

Introduction to biosimilars in medical practice can significantly reduce costs and increase the availability of treatment with anti-TNF-α agents, but there are concerns about their clinical use due to the difficulty of copying biological antibodies [4, 5]. In addition, a huge interest in the development of biosimilars- anti- TNF-α agents is associated with the expiration of patents for many original drugs and the possibility of biosimilar developing [6, 7]. The aim of the work is to analyze and systematize data regarding the efficacy and safety of anti-tumor necrosis factor-α biosimilars, as well as their registration and patenting.

Materials and Methods

Studies were conducted using databases on the Internet: Ukrainian patent office, the European patent office, the US patent office, the Food and drug administration, European Medicines Agency (EMEA), State enterprise "The State Expert Center" of the Ministry of Health of Ukraine. It has used retrospective, logical, systematic and analytical methods.

Results and Discussion

Biosimilars of Infliximab

One of the first "biological agents" used in rheumatological practice was infliximab, which is a chimeric IgG1 monoclonal antibody consisting of 75% of human protein and 25% of mouse. The mouse fragment binds TNF, while the human fragment provides effector functions. Studies have shown that infliximab suppresses the pathological effects of TNF by specifically binding and neutralizing both free and transmembrane TNF, as well as lysis of TNF-producing cells by fixing complement or due to antibody-dependent cytotoxicity.

For more than 20 years, at the highest level of evidence-based medicine, its effectiveness has been confirmed in the treatment of more than 1 million rheumatoid arthritis patients with different prescription and activity of the process [8].

CT-P13 (Remsima™; Inflectra™) is the first infliximab biosimilar that has been approved for use by regulatory authorities in many countries around the world. Successful registration of CT-P13 is based on two clinical trials in which CT-P13 was compared with infliximab (Remicade, Janssen Biotech, Inc.), as part of phase I (Planetas) in 250 patients with ankylosing spondylitis [9] and phase III (Planetra), which included 606 patients with active rheumatoid arthritis, who had insufficient effect of methotrexate monotherapy [10, 11].

Obtained by comparing the efficacy and safety of biosimilar infliximab and "reference" infliximab (Remicade) during clinical trials, as well as large-scale post-registration studies, show similar efficacy and safety of therapy and confirm the possibility of "switching" from the original drug on his bioanalogue in clinical practice [12, 13, 14, 15]. This has confirmed by Meta-analyzes. Meta-analysis of 7 randomized controlled trials involving 2606 patients has carried outd to assess the relative efficacy and safety of biosimilar-infliximab and originator-infliximab in combination with methotrexate compared to placebo plus methotrexate in active rheumatoid arthritis.

It has establishe that biosimilar and originator- infliximab, in combination with methotrexate, represent effective interventions for active rheumatoid arthritis, with a low risk of serious adverse events. No significant difference between biosimilar and

originator-infliximab was found in terms of efficacy and safety [16].

Baji P et al. has carried out meta-analysis to compare the efficacy and safety of infliximab-biosimilar and other available biologicals for the treatment of rheumatoid arthritis (RA), namely abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab. Thirty-six RCTs were included in the meta-analysis. All the biological agents proved to be superior to placebo.

For ACR20 response, certolizumab pegol showed the highest odds ratio compared to placebo, followed by abatacept, tocilizumab and infliximab-biosimilar. For ACR50 response, certolizumab pegol showed the highest odds ratio compared to placebo, followed by tocilizumab, and infliximab-biosimilar. Regarding the occurrence of serious adverse events, the results show no statistically significant difference between infliximab-biosimilar and placebo.

No significant difference regarding efficacy and safety was found between infliximab-biosimilar and the other biological treatments. Authors found no significant difference between infliximab-biosimilar and other biological agents in terms of clinical efficacy and safety [17].

Biosimilars of Adalimumab

A new drug from the group of biological agents, adalimumab, which is a preparation of human monoclonal antibodies to TNF, was later developed. Adalimumab is an IgG1 recombinant human monoclonal antibody. There is a great positive experience in the world of using adalimumab for treating inflammatory rheumatic diseases, including the results of numerous randomized clinical trials, while the effectiveness and safety of treatment with this drug is at least as good as established for other TNF inhibitors [18, 19, 20, 21, 22].

Bae and et al. has carried out meta-analysis of 8 randomized controlled trials to assess the relative efficacy and safety of biosimilar adalimumab and originator adalimumab plus methotrexate compared to those of placebo plus methotrexate in patients with active rheumatoid arthritis who showed an inadequate response to methotrexate.

The ACR20 response rate was significantly higher in the biosimilar + methotrexate and adalimumab + methotrexate groups than in the methotrexate group, with no difference in the ACR20 response rate between the biosimilar + methotrexate and adalimumab + methotrexate groups. Biosimilar+ methotrexate had the highest probability of being the best treatment in terms of the ACR20 response rate, followed by adalimumab + methotrexate and methotrexate. The ACR50 and ACR70 response rates showed a distribution pattern similar to that of the ACR20 response rate.

Safety based on the number of serious adverse events did not differ significantly among the three interventions in the follow-up period of 12 to 24 weeks. Biosimilar and originator adalimumab, in combination with methotrexate, represent an effective intervention for active rheumatoid arthritis despite treatment with methotrexate. No significant difference was found between biosimilar and originator adalimumab in terms of efficacy and safety.

However, follow-up in randomized clinical trialss is short and not all safety outcomes can be assessed in randomized clinical trialss. Thus, additional long-term evaluations are needed [23]. Mengato D et al. Have conducted a meta-analysis of 6 randomized studies of the use of the adalimumab biosimilar for rheumatoid arthritis. These results proves that the equivalence data between biosimilar and originator are robust [24].

Biosimilars of Etanercept

The discovery of soluble receptors for TNF (sTNFR) allowed them to be used to block the biological effects of this cytokine in experimental and clinical conditions. Two main types of sTNFR molecules are known: p75 and p55. Both types of molecules exist in membrane-bound and soluble forms and are natural inhibitors of TNF activity. The cloning of sTNFR genes allowed the creation of recombinant forms of both types of receptors for use in clinical practice. The drug was called etanercept and is registered as indicated by rheumatoid arthritis [25, 26].

The clinical efficacy of etanercept has been proven in numerous studies, including randomized clinical trials. The principal advantage of etanercept over monoclonal

antibodies to TNF-α is the fact that its administration leads to much less frequent opportunistic infections, including tuberculosis [27, 28].

SB4 was developed as a biosimilar to Enbrel (etanercept) and was approved as Benepali, the first biosimilar of etanercept licensed in the European Union (EU). The quality assessment of SB4 was performed in accordance with the ICH comparability guideline and the biosimilar guidelines of the European Medicines Agency and Food and Drug Administration. Extensive structural, physicochemical, and biological testing was performed with state-of-the-art technologies during a side-by-side comparison of the products.

Similarity of critical quality attributes was evaluated on the basis of tolerance intervals established from quality data obtained from more than 60 lots of EU-sourced and US-sourced etanercept. Additional quality assessment was focused on a detailed investigation of immunogenicity-related quality attributes, including hydrophobic variants, high-molecular-weight species, N-glycolylneuraminic acid, and α-1, 3-galactose.

This comprehensive characterization study demonstrated that SB4 is highly similar to the reference product, Enbrel, in structural, physicochemical, and biological quality attributes. In addition, the levels of potential immunogenicity-related quality attributes of SB4 such as hydrophobic variants, high-molecular-weight aggregates, and α-1,3-galactose were less than those of the reference product [29, 30, 31, 32].

GP2015 is the second biosimilar of the reference p75 TNF receptor-Fc fusion protein etanercept. It is approved for use in all indications for which reference etanercept is approved, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis.

GP2015 has similar physiochemical and pharmacodynamic properties to those of reference etanercept, and the pharmacokinetic biosimilarity of the agents has been shown in healthy volunteers. GP2015 demonstrated clinical efficacy equivalent to that of reference etanercept in patients with moderate-to-severe plaque psoriasis; the tolerability, safety and immunogenicity profiles of the two agents were also generally similar. Switching between GP2015 and reference etanercept had no impact on clinical efficacy, tolerability or immunogenicity. The role of reference etanercept in the management of inflammatory autoimmune conditions is well established and GP2015 provides an effective biosimilar alternative for patients requiring etanercept therapy [33, 34, 35].

Golimumab

Golimumab is a fully human monoclonal antibody to TNF-α. The affinity of golimumab for soluble TNF, determined in vitro, exceeds that of infliximab and adalimumab by 2.4 and 7.1 times, respectively [36]. Golimumab binds and neutralizes both soluble and membrane-bound forms of TNF [37, 38]. In 2009, golimumab for subcutaneous administration 1 time per month was approved by the FDA (Food and Drug Administration) and registered in the USA, Europe and Canada for treatment (in combination with methotrexate) rheumatoid arthritis with high activity from moderate to severe forms as well as psoriatic arthritis and ankylosing spondylitis in the active phase.

In January 2011, the European Commission approved the use of golimumab in combination with methotrexate for the treatment of adult patients with severe highly active rheumatoid arthritis, progressive bone and cartilage destruction of the joints (according to x-ray studies) who had not previously received methotrexate therapy. July 1, 2011 golimumab was registered in Japan for the treatment of rheumatoid arthritis, including to prevent the development of joint destruction in patients who could not get an adequate response to standard therapy [39].

In Ukraine, golimumab is also registered. The effectiveness of golimumab in patients with rheumatoid arthritis was assessed in a systematic review [40]. Four randomized controlled trials with 1231 golimumab-treated and 483 placebo-treated patients were included.

Of these, 436 were treated with golimumab at 50 mg every 4 weeks (a dosage approved by the US Food and Drug Administration). At

an average of 4-6 months, compared to patients treated with placebo and methotrexate, patients treated with the FDA-approved dosage of golimumab and methotrexate were 2.6 times more likely to reach ACR50 and 0.5 times as likely to have overall withdrawals. Golimumab-treated patients were significantly more likely than those taking placebo to achieve remission, and to have improvement in functional ability on the Health Assessment questionnaire.

The studies were too small and short to be powered sufficiently for safety outcomes, but no substantive statistically significant differences were noted between golimumab and placebo regarding adverse events, serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events, and withdrawals due to inefficacy and deaths.

Certolizumab Pegol

A new variant of neutralization of TNF-α using antibodies was the use of not a whole humanized antibody molecule to this cytokine as a therapeutic agent, but its Fab-fragments linked to polyethylene glycol. Created in this way the drug was called certolizumab pegol.

The role of polyethylene glycol is to slow the elimination of certolizumab pegol from the body. In the United States, certolizumab pegol (Cimzia) was officially approved in 2008 for use in Crohn's disease and in May 2009 for the treatment of moderate and severe rheumatoid arthritis as monotherapy or in combination with traditional basic drugs. The European Medical Agency has licensed the use of certolizumab pegol in combination with methotrexate or as monotherapy if methotrexate is contraindicated or not tolerated [41].

In Ukraine, certolizumab pegol is not registered. There is a moderate to high certainty of evidence from 12 randomised controlled trials (5422 participants) that certolizumab pegol, alone or combined with methotrexate, is beneficial in the treatment of RA for improved ACR50 and health-related quality of life, an increased chance of remission of RA, and reduced joint damage as seen on x-ray. Fewer people stopped taking their treatment, but most of these who did stopped due to serious adverse events. Adverse events were more frequent with active treatment. Authors found a clinically but not statistically significant risk of serious adverse events [42]. Clinical studies of certolizumab pegol, golimumab biosimilars have not been identified, since they are under patent protection.

Comparative Assessment of Anti-TNF-α biosimilars

Of interest is the meta-analysis of a comparative assessment of anti-TNF-α biosimilars. Komaki Y and et al. have systematized 9 studies in 3291 patients with rheumatoid arthritis and ankylosing spondylitis (5 infliximab, 2 adalimumab, and 2 etanercept). Biosimilars of infliximab showed similar rates of clinical response compared to the reference agent in rheumatoid arthritis and ankylosing spondylitis.

Frequency of anti-drug antibody and adverse events were similar except for a slightly, but significantly, higher risk of upper respiratory tract infections with biosimilar. Biosimilar of adalimumab showed no differences among any outcomes compared to the reference agent. Biosimilars of etanercept showed no differences for clinical response and frequency of adverse events, but showed a significantly lower rate of anti-drug antibodies at 24-30 weeks.

In the present study, biosimilars of anti-TNF-α agents had an overall comparable efficacy and safety profile compared to their reference agents in RA and AS supporting their use for these conditions [43]. Despite the appearance of more accessible biosimilars than the original anti-TNF-α agents, the position that the prescription of these drugs too early is unjustified is still unshakable.

It has proved that step-by-step intensification of therapy (step-up): initially methotrexate monotherapy (or combination therapy with methotrexate and standard basic anti-inflammatory drugs), and only with insufficient effectiveness of this therapy is the appointment of anti-TNF-α agents as effective as combination therapy methotrexate and anti-TNF-α agents starting from the debut of the disease [44].

Thus, the use of anti-TNF-α biosimilars can suppress the activity and progression of

rheumatoid arthritis, improve the function and quality of life of patients. Biosimilars have a stable effect and are comparable in effectiveness with reference drugs. The analysis and systematization of the registration and patenting of anti-TNF-α biosimilars in Ukraine, Europe, and the USA has carried out. Obtained data are given in Table I.

Table 1: Data on registration and patenting of anti-TNF-α biosimilars in Ukraine, Europe, USA

Active pharmaceutical ingredients	Original drug	Biosimilars have registered in Ukraine	Biosimilars have registered in USA	Biosimilars have registered in EU
1	2	3	4	5
Etanercept	Enbrel , Pfizer	Artrocept, CJSC Farmak (Ukraine) collaboratively with Shanghai CP Guojian Pharmaceutical Co., Ltd., China	Erelzi, Sandoz	Benepali, Samsung Bioepis; Erelzi, Sandoz
Infliximab	Remicade, Janssen Biotech	Flammegis, Celltrion, Korea / Egis	Remsima, Celltrion; Inflectra, Pfizer Europe Ma Eeig; Ixifi, Pfizer Ireland Pharmaceuticals	Flixabi, Samsung Bioepis; Inflectra, Hospira; Remsima, Celltrion; Zessly, Sandoz
Adalimumab	Humira, Abbvie	–	Hyrimoz, Sandoz; Amjevita, Amgen; Cyltezo, Boehringer Ingelheim	Amgevita, Amgen; Cyltezo, Boehringer Ingelheim; Halimatoz, Sandoz; Hefiya, Sandoz; Hulio, Mylan /Fujifilm Kyowa Kirin Biologics; Hyrimoz, Sandoz; Imraldi, Samsung Bioepis; Solymbic, Amgen
1	2	3	4	5
Certolizumab-pegol	Cimzia, Ucb Pharma Sa	–	– Patent expiration 2024	– Patent expiration 2021
Golimumab	Simponi, Janssen Biotech, Inc.	–	– Patent expiration 2024	– Patent expiration 2024

The Registration and Patenting of Anti-TNF-α biosimilars

Performed analysis on the registration and patenting of anti-TNF-α biosimilars indicates that there are 2 biosimilars in Ukraine (Artrocept and Flammegis), 7 biosimilars in the USA, 14 biosimilars in the European Union. Under the patent protection are another 2 original anti-TNF-α agents-certolizumab pegol, golimumab. The cost of original drugs is quite high, the declared cost of biosimilars is lower both in abroad and in Ukraine, which makes these drugs more accessible for patients with rheumatoid arthritis. It should be noted that the European Commission launched an initiative to waive supplementary protection certificates (SPC), which extend intellectual property rights after the expiration of the first patent for drugs [45].

A positive impulse has ripened both in the Council of Europe and in the European Parliament to abandon the SPC. Both institutions strive to achieve the successful completion of the waiver process within this legislative body and decide on its key points. Under the current system, European manufacturers are forced to outsource the drug production in order to ship them to countries that do not use SPC, or to those regions where the validity of the SPC floats earlier than in Europe, and also to stimulate competition after the expiration date SPC actions in Europe.

According to experts, the European industry engaged in generic and biosimilar production, making this decision will create a significant number of additional jobs, will increase patient access to high-quality drugs and will stimulate economic growth in the EU and make Europe a global center for pharmaceutical production.

The evidence base obtained in the process of numerous randomized clinical studies indicates a high efficacy and acceptable safety of anti-TNF-α biosimilars in rheumatoid arthritis, which dictates the need for early registration and widespread use. In addition, the introduction of biosimilars leads to significant savings, since branded products reduce their prices due to the availability of less expensive biosimilars and competition between the biosimilars themselves.

Thus, effective anti-TNF-α biosimilars may be more accessible to the general population with rheumatoid arthritis.

Conclusions

- In world clinical practice, one of the most common and severe chronic diseases is rheumatoid arthritis, which, in the absence of effective therapy, leads to disability and shortens the life expectancy of patients, economic losses.
- The breakthrough in the treatment of rheumatoid arthritis is the discovery and administration of anti-TNF-α agents, such as as infliximab (a chimeric human and mouse IgG1 monoclonal antibody with high affinity, bind both soluble and transmembrane forms of TNF-α), adalimumab (recombinant human monoclonal antibody IgG1), etanercept (a protein consisting of two TNF receptors (p75 and p55) with the addition of a human IgG1 Fc-fragment), certolizumab pegol (a recombinant, humanized Fab' antibody fragment linked to polyethylene glycol), golimumab (fully human monoclonal antibody to TNF).
- Clinical studies have shown the efficacy and acceptable safety of anti-TNF-α agents. But expensive anti-TNF-α agents have been replaced by biosimilars. Biosimilars have the same efficacy and acceptable safety according clinical trials and meta-analysis data, biosimilars price affordable to broad layers of population, but their clinical research is still ongoing.
- The development and registration of anti-TNF-α biosimilars (Ukraine-2 biosimilars, USA-7 biosimilars, the European Union-14 biosimilars) reduces the costs of health care and patients for biological therapy, increases patient access to treatment with the latest drugs, and contributes to the further development of biotechnology.
- A positive impulse has ripened both in the Council of Europe and in the European Parliament to abandon the supplementary protection certificates, which extend intellectual property rights after the expiration of the first patent for drugs.
- Despite certain hazards and risks associated with possible violations in the implementation of biological products in real practice, the industry of highly effective biosimilars brings progress both for the development of science and for practical healthcare.

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