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Abstract. The paper provides an overview of modern genetically engineered biological agents (GEBAs) used in the treatment of rheumatoid arthritis (RA) in the Russian Federation. The spectrum of medicinal agents of this group used in the Novgorod region has been analyzed. The analysis of treatment regimens of 68 patients demonstrates high efficiency of combination therapy of GEBAs and disease modifying anti-rheumatic drugs due to a decrease in the activity of the process of more than 78 % of the patients and to achieving remission of 2.9 % of them. It is indicated that GEBAs therapy requires careful screening procedures of patients, exclusion of infectious processes, cancer and severe pathology of internal organs. The reasons for the difficulties in achieving remission against the background of GEBAs therapy of the observed patients, as well as complications arising during the treatment, are given.

1. Introduction

Autoimmune diseases are the second leading cause of chronic diseases. One of these pathologies is rheumatoid arthritis (RA), a disease that primarily affects the joints, and secondarily the internal organs. This disease occurs with comorbid pathology, and its treatment is accompanied by adverse drug reactions [1, 2].

Rheumatoid arthritis is the most common inflammatory arthropathy in the world. According to an estimate, RA occurs among 1% of the world population throughout life [3]. Young able-bodied people are more likely to have RA. The course of the pathological process is characterized by the early development of disability and an unfavorable life prognosis [4].

Earlier, due to the lack of medicinal agents and clear recommendations, RA treatment did not suppress the activity of the process, which contributed to the disablement of patients in the first 5 years from the onset of the disease [5]. Due to the fact that the study and emergence of knowledge about new components of RA pathogenesis offer us a better understanding of the pathogenesis on a new level, genetically engineered biological agents (GEBAs) appeared and the prognosis of patients with RA improved significantly, which made it possible for EULAR to put forward the main treatment postulate – “treat to target” [6, 7, 8].

GEBAs are a group of medicinal agents obtained by modern methods of biotechnology, including agents of monoclonal antibodies [6]. In their production, such methods of genetic engineering as the creation of recombinant DNA with the control of the expression of a certain gene are used [9].

Chimeric monoclonal antibodies of the IgG1 class, obtained by attaching the F(ab)2-fragment of a mouse monoclonal antibody to the Fc-fragment of human immunoglobulin, stand out. They are created

from mouse hybridomas using recombinant DNA technology. Such a compound reacts with a specific cytokine. In order to reduce the specific weight of the "mouse" protein in such a molecule, humanized antibodies have been created, in which the proportion of human immunoglobulin is significantly increased [10]. To eliminate a number of disadvantages inherent in monoclonal antibodies, recombinant DNA technologies have been developed and recombinant antibodies that have a higher antigen target specificity have been obtained.

For medicinal agents based on monoclonal antibodies, all INNs end with "-mab" (monoclonal antibody). If the active molecule of a medicinal agent is a mouse antibody, then the ending is "-omab". INNs for chimeric antibodies are registered with the ending "-ximab", for humanized antibodies – "-zumab", and for completely human antibodies – "-umab" [11].

GEBAs are expensive medicinal agents, therefore, in the overwhelming majority of cases, they are prescribed to patients with the process not stopped by the prescription of disease modifying anti-rheumatic drugs or who have intolerance to them. The high cost of GEBAs inevitably leads to an increase in direct medical costs and, therefore, creates an additional load on the state budget [12]. In Russia, treatment with genetically engineered biological agents to expand their availability is funded from the federal budget and is included in the List of types of high-tech medical care.

The aim of the study was to evaluate the range and prescription regimens of GEBAs used for the treatment of RA in combination with disease modifying anti-rheumatic drugs (DMARDs) in the cases of patients with high activity of the process.

Tasks:

1. To study the general characteristics of monoclonal antibody drugs for the treatment of RA.
2. To investigate the pharmaceutical market for GEBAs in Russia and compare it with the range of medicinal agents used to treat patients in the Novgorod region.
3. To analyze the medical records of RA patients treated with GEBAs.

2. Materials and methods

Data on the GEBAs registered in the Russian Federation were obtained from the analysis of the State Register of Medicines.

In addition, 68 patients with a reliable diagnosis of RA based on the 2010 ACR/EULAR criteria or the 1987 ACR criteria, a high degree of activity (III degree DAS 28 =6.5±1.01%), who have been undergoing planned treatment in one of the medical institutions in Veliky Novgorod in the period 2019–2020, have been examined. The age of the patients was from 33 to 82 years (59.75±29.3). Among the patients, females predominated, and their proportion was 84%. The duration of the disease since the diagnosis of RA varied widely from 1 to 41 years, the average duration of the disease was 11.46±2.94 years. 89.9% were seropositive in the RF, immunoglobulins G, which recognize proteins that contain the atypical amino acid citrulline (anti-CCP), were found in 94.2%; in 55%, changes in the osteoarticular system corresponded to stages III–IV according to the X-ray classification; 97.2% had the II–III functional activity class.

Comorbid conditions were observed in the cases of all patients. In the structure of comorbid pathology, cardiovascular pathology took the first place and was 98.5%, diseases of the gastrointestinal tract were in second place and were 69.6%, the share of endocrine pathology was 36.2%. The fourth and fifth places in the structure were occupied by such concomitant diseases as osteoporosis which was 34.8% and anemia of chronic diseases – 15.9%.

Before the beginning of the introduction of GEBAs, the patients underwent a generally accepted complex of diagnostic studies: general and biochemical blood tests included the determination of ESR, C-reactive protein (CRP), rheumatoid factor (RF), anti-CCP. X-rays of the hands, feet and pelvic bones were made. To exclude such contraindications to the treatment by GEBAs as oncological diseases and tuberculosis, the patients were prescribed a chest x-ray, diaskintest, and then they were consulted by a phthisiatrician.

The decision on the need for biological therapy was made taking into account the high disease activity – DAS28=6.5, positive anti-CCP values, the absence of contraindications and the effect of treatment with DMARDs [13].

The therapy effectiveness was assessed on the second day after the introduction of GEBAs and was constantly monitored in the subsequent period. In addition to the above biochemical blood parameters, the values of the DAS28 index and the indicators of the visual analogue scale (VAS) were determined.

According to the prescribed GEBAs, 4 groups of patients were formed: group 1 – 9 patients (13.2%) who received TNF-α inhibitors (infliximab), group 2 – 7 patients (10.3%) who received an IL-6 inhibitor; group 3 – 35 patients (51.5%) who were prescribed rituximab; in group 4, which included 17 patients (25%), therapy was carried out with abatacept.

3. Results

On the Russian pharmaceutical market, 16 GIBPs are registered for the treatment of autoimmune diseases. Among them:

1. Anti-tumor necrosis factor agents (TNF-α): infliximab (INN): infliximab (trade name (TN); JSC BIOCAD), remicade (TN; LLC MSD Pharmaceuticals, Russia) flammegis (TN; Celltrion Healthcare Co., Ltd., Korea); adalimumab (INN): khumira (TN; LLC AbbVie, Russia), dalibra (TN; JSC BIOCAD, Russia); golimumab (INN): simponi (TN; LLC MSD Pharmaceuticals, Russia); certolizumab pegol (INN): simziya (TN; UCB Pharma S.A., Belgium); etanercept (INN): erelzi (TN; Sandoz d. d., Slovenia), enbrel (TN; Pfizer Inc., USA).

In this group of medicinal agents, agents based on hybrid molecules and monoclonal antibodies (MAbs) are distinguished.

The latter include chimeric monoclonal antibodies (infliximab (INN)), recombinant monoclonal antibodies containing only human peptide sequences (adalimumab (INN)), a human monoclonal antibody to TNF-a (golimumab (INN)), as well as certolizumab pegol (INN) — a PEGylated Fab' fragment of humanized MAbs.hese agents inhibit TNF-α in the circulation and at the cellular level [14, 15].

2. If this group of medicinal agents is ineffective, antibodies against interleukin-6 (IL-6) are used [16]. 1 interleukin inhibitor, tocilizumab, is registered on the Russian pharmaceutical market by INN: actemra (TN; F. Hoffmann-La Roche Ltd., Switzerland); sarilumab (INN): kevzara (TN; Sanofi-aventis Group JSC, France).

3. Anti-B-cell agent is presented in the RF by rituximab (INN): rituximab (TN; Nanolek LLC, Russia), mabthera (TN; F. Hoffmann-La Roche Ltd., Switzerland), redditux (TN; Dr. Reddy's Laboratories Ltd., India), acellbia (TN; JSC BIOCAD, Russia). Rituximab is a chimeric monoclonal antibody against B cell antigen.

4. The group of medicinal agents that inhibit the activation of T cells includes abatacept (INN): orencia (TN; Bristol-Myers Squibb Company, USA) – a recombinant soluble protein consisting of the extracellular domain of antigen-4 cytotoxic T-lymphocytes combined with a modified Fc-fragment of human immunoglobulin GI. It is produced by genetic engineering on isolated mammalian cell culture.

In the Novgorod region, a limited number of medicinal agents identified by brand names were used.

The results of therapy and the range of GEBAs are shown in the table 1.

Early initiation of RA therapy, taking into account the severity of the process, competent choice of disease modifying anti-rheumatic drugs, selection of optimal doses, replacement of DMARDs with GEBAs in the absence of the effect of the therapy, assessment of the presence of comorbid conditions are aimed at reducing the activity of the process and achieving remission in the patient.

It was observed that a decrease in RA activity was registered in 78.3% of treated patients. In dynamics after 4 months, the ESR indices of these patients tended to decrease from 43.7±16.3 mm/h to 32.9±22.1 mm/h, the CRP indices – from 23.6±13.4 mg/l to 10.5±5.2 mg/l, the VAS scale values – from 45.3±8.05 to 34.3±7.1 mm.

Table 1. Results of treatment with biological agents of patients with rheumatoid arthritis.

Indicators	dosing information	combination therapy with DMARDs	presence of effect according to DAS28	no effect
Group 1 (anti-tumor necrosis factor agents TNF-α (n= 9 patients))				
INN Infliximab (TN remicade, TN flammegis)	200-300 mg IV every 8 weeks. The duration of the course is 2-10 years.	- up to 30 mg of MT per week - 3 patients - MT and SSZ - 2 patients, - 20 mg of LF per day - 1 patient	degree 2 of the activity was reached in the cases of 4 people after 3 years	in the case of 2 patients due to interruptions in the administration because of the absence of MA
INN Adalimumab (TN khumira, TN dalibra) 1 patient	dose 40 mg subcutaneously continuously after 4 weeks Treatment period is 5 years	30 mg of MT per week	degree 1 of the activity was reached in the case of 1 patient after 3 years	
INN Golimumab (TN simponi) 1 patient	50 mg subcutaneously injection every 8 weeks for 4 years	2000 mg of SSZ per day	degree 2 was reached	
Certolizumab pegol (simziya) received by 1 patient	200 mg subcutaneously every 4 weeks for 2 years	15 mg of MT per week and 2000 mg of SSZ per day	degree 1 of the activity was reached	
Group 2 (IL-6 inhibitors (n=7 patients))				
Tocilizumab (actemra)	400-600 mg IV once every 4 weeks Course of administration is 1-8 years	up to 30 mg of MT per week or 20 mg of LF per day	- in the case of 1 patient, the activity decreased to degree 1after 4 years - in the cases of 5 patients, the activity decreased to degree 2 after 1.5-2 years	in the case of 1 patient, 83 years old, with a change of 3 GEBAs, with comorbid pathology
Group 3 (Anti-B-cell agents (n=35 patients))				
INN Rituximab (TN mabthera, TN acellbia)	1 injection of 500 mg IV: subsequently IV every 10 days, then once every six months for from 0.5 to 9 years	- up to 30 mg of - MT per week and 20 mg of LF per day - 2000 mg of SSZ per day. - 400 mg of HC per day	- in the case of 1 patient, remission after 2 years - in the case of 1 patient, decrease in activity to degree 1 after 7 years. - in the cases of 28 patients, decrease in activity up to degree 2 after the first two injections	degree 3 of the activity remained in the cases of 5 patients who received GEBAs for 5-7 months
Group 4 (agents for activated T cells (n=17 patients))				
INN Abatacept (TN orencia)	750 mg IV once every 4 weeks Treatment period is from 1 month to 7 years	- up to 20 mg of MT per week and 20 mg of LF per day - 2000 mg of SSZ per day. - 400 mg of HC per day.	- in the cases of 3 patients, decrease in the RA activity to degree 1 after 3.5 years - in the cases of 9 patients, decrease in the activity to degree 2 after 1 year	in the cases of 5 patients with a treatment period of about six months

MT- methotrexate; SSZ – sulfasalazine; LF – leflunomide; GH – hydroxychloroquine

In the course of treatment, complete remission has been achieved (DAS 28 = 1.9±0.4) in the cases of two patients (2.9%) who have been receiving remicade and actemra for more than two years.

4. Discussion

The best results have been obtained in groups 2 and 3, in the cases of patients who have been prescribed rituximab (INN) and tocilizumab (INN). In these groups, a positive effect has been achieved in 85% of patients. On the background of treatment with abatacept (INN) and infliximab (INN), patients noted a significant reduction in pain syndrome, which was assessed on the VAS scale, which corresponded to the literature data [14].

Adverse reactions to the introduction of GEBAs have been registered in patients who have been receiving infliximab. One patient (1.4%) had dermatitis with improvement after adjusting the infliximab dose from 300 mg to 200 mg. In the cases of 2 patients (2.9%), leukopenia was noted, in connection with which the medicinal agent was replaced with abatacept. Our results are supported by data from other researchers who have shown that the withdrawal probability due to adverse events is high for infliximab [17].

Resistance to the received GEBAs therapy has been detected in the cases of 3 patients (4.4%), despite the fulfillment of all treatment standards and protocols. Our data do not contradict the results of other researchers who have noted resistance to RA therapy, which is probably associated with the complexity and versatility of the pathological process in the case of RA [18], comorbid conditions [19], low compliance [20].

The limited range of genetically engineered biological agents identified by brand names is probably related to the drug purchase policy of the Novgorod region.

The problems of reducing the degree of activity of the inflammatory process or its complete resolution against the background of the use of biological agents were probably associated with the severity of the process, delayed treatment, and the presence of several concomitant diseases. Due to interruptions in the financing of purchases of GEBAs, there were also interruptions in their supply, which led to a violation of the treatment regimen due to the lack of a medicinal agent. In such a situation, another negative factor was the low compliance of the patients.

5. Conclusion

1. The use of genetically engineered biological agents in the cases of patients with RA leads to a decrease in the activity of the inflammatory process in patients with a severe course of the disease.

2. The effectiveness of the therapy is influenced by many factors, including the presence of concomitant diseases, therapy regularity associated with the availability of expensive biological agents, as well as the patient's compliance with the treatment.

3. In the Novgorod region, an insufficient assortment of GEBAs is being purchased, which is probably due to the limited possibilities of the budget.

4. Adverse reactions to GEBAs administration have been reported in the cases of patients who were prescribed infliximab. Further development of genetic engineering and the creation of new medicinal agents, reduction in the cost of existing biological agents, early diagnosis and treatment initiation, continuous monitoring of the patient's condition during the treatment are courses of action that will improve treatment results and minimize unwanted reactions to GEBAs.

Research in this direction, as well as the accumulation and analysis of data, continue.

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