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Original Research

Assessment of the efficacy and safety of biological agents in rheumatoid arthritis

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ABSTRACT:
The possibilities of modern therapy for rheumatic diseases (RD) have now significantly expanded, primarily due to the use of genetically engineered biological drugs (GIBP). The aim is to evaluate the short-term efficacy and safety of BAs in patients with various RH. **Material and methods.** The study included all patients with RD who received BAs: rituximab (RTM), infliximab (INF), adalimumab, etanercept, tocilizumab, abatacept in 2009-2012. The efficacy and safety of the treatment was assessed after 6 months. Based on parameters specific to specific diseases (eg, BVAS, DAS28, BASDAI), the effect of BAI was defined as "remission", "improvement" and "no response". **Results:** The study included 107 patients (49 men and 58 women; mean age 41.5 years) with rheumatoid arthritis (n = 34), ANCA-associated vasculitis (n = 34), systemic lupus erythematosus (n = 16), cryoglobulinemic vasculitis (n = 11), ankylosing spondyloarthritis (n = 8), systemic vasculitis with lesions of large arteries (n = 6) and other RH. In all cases, there was a severe course of systemic autoimmune disease refractory to standard immunosuppressive therapy. The most commonly used RTM (n = 66) and IFN (n = 31). The high frequency of prescribing RTM is explained by the fact that all patients with ANCA-associated vasculitis, systemic lupus erythematosus and cryoglobulinemic vasculitis received this drug, which in total accounted for more than half of the patients included in the study. The overwhelming majority of them received GIBP for the first time. Against the background of treatment, remission was achieved in 62 cases (57.9%) and improvement in 42 (39.3%) cases. Mild or moderately expressed in 22 (20.6%) patients, severe adverse reactions in 6 (5.6%) patients. **Conclusion:** Treatment of BAI provides significant improvement in a significant proportion of patients with various RH who have not responded to standard immunosuppressive therapy.
Key words: tocilizumab, rheumatoid arthritis, functional activity, quality of life.

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common and severe chronic inflammatory disease of the joints, the frequency of which in the population ranges from 0.5 to 1.0% [1, 2]. Over the past decade, significant progress has been achieved in the treatment of RA, associated both with the improvement of tactics for the use of basic anti-inflammatory drugs (DMARDs), and with the development of a new class of drugs - the so-called genetically engineered biological drugs (GIBPs) [3-5]. The mechanism of action of GIBP is depletion and disruption of the interaction of cells involved in the development of inflammation, or inhibition of the activity of proinflammatory cytokines [6]. Until recently, inhibitors of the proinflammatory cytokine tumor necrosis factor α (TNF α) were the main BAs for the treatment of RA. However, the experience of long-term use of these drugs in real clinical practice (primarily materials from national registries) indicates that 1/3 of patients are refractory to therapy, less than 1/3 manage to achieve remission, and some patients develop side

effects leading to to interrupt treatment [7]. This served as a stimulus for the development of new approaches to the treatment of RA associated with the suppression of the activity of other inflammatory mediators [4].

In recent years, researchers' attention has been drawn to interleukin (IL) 6, a pleiotropic cytokine that is synthesized by many cells (T- and B-lymphocytes, fibroblasts, endothelial cells, monocytes, etc.) involved in the development of inflammation, and exhibits a wide range of pro-inflammatory biological effects. [8-10]. Recall that IL 6 transmits intracellular signals in two ways: binding to the membrane (m) IL 6 receptor (P) and trans-signaling (trans-signaling) [11]. In this case, the intracellular part of mIL 6R is not involved in signal transmission. This requires another protein, gp130 (IL 6R β-chain, CD 130), which is present in cells that do not express mIL 6R. Along with mIL 6R, there is a soluble (p) form of IL 6R, which forms a complex with IL 6, which has the ability to bind to gp130 and induce the transmission of an activation signal (trans signaling). While the classical effects of IL 6 are limited to the effect on cells expressing mIL 6R (hepatocytes, monocytes, macrophages, and some subpopulations of lymphocytes), trans-signaling allows IL 6 to activate cells lacking mIL 6R but expressing gp130, including synovial cells ... This underlies a wide range of pathological effects of IL 6 (fever, increased concentration of acute phase proteins, anemia, autoantibody synthesis, pannus formation and destruction of joints, activation of Th17 cells, etc.) in RA [10–12] (Fig. 1). Obviously, their correction requires suppression of IL 6 receptor signaling, and not only the activity of IL 6 itself or mediators (for example, TNF α) that induce its synthesis.

Tumor necrosis factor (TNF) inhibitors are the most widely used. Their effectiveness has been established in RA, ankylosing spondylitis (AS), Crohn's disease and other diseases. An important target is B-lymphocytes, which play an important role in the pathogenesis of systemic lupus erythematosus (SLE), systemic vasculitis, and RA. Monoclonal antibodies (mAbs) to B-lymphocyte CD20 receptors (rituximab - RTM) have been registered for the treatment of RA and vasculitis associated with antineutrophilic cytoplasmic antibodies (ANCA) in the USA and Europe. In addition, belimumab, which interacts with BLyS, has become the only new drug in the past 50 years to be approved for use in SLE. For the treatment of RA, tocilizumab (TCZ; mAb to interleukin 6 receptors - IL6) and abatacept (ABC), which blocks the interaction of CD80 / CD86 on the surface of antigen-presenting cells and CD28 on naive T cells, are also used today. Currently, many drugs are at various stages of study. There is no doubt that the list of GIBPs will expand in the coming years. The aim of this prospective, uncontrolled study was to investigate the short-term efficacy and safety of BAs in patients with different RH.

MATERIALS AND METHODS

The study included patients with RD who were admitted to the Clinic of Nephrology, Internal and Occupational Diseases named after V.I. EAT. Tareeva in 2009–2012. and who received GIBP: RTM, infliximab (INF), adalimumab (ADA), etanercept (ETC), TCZ, ABC. The diagnosis was established on the basis of generally accepted criteria and, if necessary, confirmed morphologically. The GIBP was prescribed in accordance with standard treatment regimens.

Control studies after discharge from the hospital were carried out at least once every 3 months. The efficacy and safety of the GIBP was assessed 6 months after the start of treatment. To assess the status of patients, parameters specific to specific diseases were used, for example, BVAS (Birmingham Vasculitis Activity Index) - for systemic vasculitis, DAS28 - for RA, BASDAI - for AS. When evaluating the effectiveness of treatment, "remission", "improvement" and "no response" were distinguished. Remission was understood as the absence of signs of systemic disease activity with a decrease in the HA dose, and improvement was understood as a decrease in the number of affected organs or systems and / or a decrease in the severity of the lesion. For example, for RA, remission was determined according to the recommendations of the American College of Rheumatology / European Antirheumatic League (ACR / EULAR), and improvement was recorded with a 20% response according to the ACR criteria. For systemic vasculitis, remission was understood as BVAS = 0 with a decrease in the HA dose, and improvement was defined as a decrease in BVAS by at least 50% compared to the baseline value.

When assessing safety, adverse reactions (ADs) were considered severe, which were the cause of death, directly threatened life, led to the need for hospitalization or an increase in its duration.

RESULTS

The study included 107 patients (49 men and 58 women). The median age was 41.5 years (range 18 to 81 years). The main indications for the appointment of BAI were RA (n = 34), ANCA-associated vasculitis (n = 27): granulomatosis with polyangiitis (Wegener; n = 24), microscopic polyangiitis (n = 2) and eosinophilic granulomatosis and polyangiitis (Cherdzha-Strauss; n = 1), SLE (n = 16) and cryoglobulinemic vasculitis (n = 11).

The duration of the disease at the time of GIBP administration ranged from 4 months to 44 years. All patients had insufficient efficacy or poor tolerance to standard immunosuppressive therapy. RTM (n = 66) and IFN (n = 31) were most often used among GIBPs.

The high frequency of RTM treatment was determined by the fact that this drug was prescribed to all patients with ANCA-associated vasculitis, SLE, and cryoglobulinemic vasculitis, which in total accounted for more than half of the patients included

in this study. The overwhelming majority of patients received a BA for the first time.

Only in three patients were two HIBPs successively used (INF → RTM, INF → TCZ, ADA → RTM). The reason for changing the drug was the ineffectiveness of the previous therapy. Remission was achieved in 62 (57.9%) and improvement in 42 (39.3%) patients. Only 3 (2.8%) patients did not respond to treatment. The objectives of this study did not include the analysis of long-term outcomes, however, a high relapse rate can be stated after discontinuation of treatment. In 3–12 months after discontinuation of the drug, relapse developed in 18 (58.1%) of 31 patients.

At the same time, the resumption of therapy with GIBP made it possible in most cases to achieve remission again. Tolerability of the GIBP was satisfactory. 22 (20.6%) patients had mild or moderate HP, including vascular reactions upon administration (n = 8), influenza-like syndrome (n = 4), mild or moderate leukopenia (n = 4), mild infections (n = 3), increased aminotransferase activity (n = 2), urticaria (n = 1). These HPs were reversible and did not require discontinuation of therapy. Severe HPs were represented by agranulocytosis in two patients (which developed after the administration of RTM and in one case was complicated by herpes zoster), severe infusion reactions in two (against the background of the administration of INF and RTM) and sepsis also in two (one of them received RTM, the other - INF). The overall incidence of severe HP was 5.6%.

GIBP received 34 patients with RA (14 men and 20 women; mean age 46.3 years): 18 - INF, 7 - RTM, 5 - TCZ, 3 - ADA, 2 - ABC, 1 - ETC. In two patients, two drugs were used (INF → RTM, INF → TCZ). GIBPs were prescribed due to the persistence of high RA activity (according to DAS28) despite therapy with methotrexate (MT) at a dose of 15-25 mg / week and / or other DMARDs (leflunomide, sulfasalazine, aminoquinoline derivatives), usually in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and / or HA in low doses The mean DAS28 at the time of BAA administration was 5.8. All patients received BAA in combination with a previous DMARD (usually MT), the dose of which was subsequently reduced with a decrease in disease activity. Remission was achieved in 16 (47.1%) patients, improvement - in 18 (52.9%) patients. The mean DAS28 after treatment with BAs was 2.9. Tolerability of the treatment was satisfactory, the incidence of serious HPs was 5.9% (in one case, with the first injection of IFN, a severe infusion reaction developed, another patient after treatment with RTM had an episode of systemic infection of unspecified etiology).

DISCUSSION

The results of the study confirmed the high efficacy and acceptable tolerability of BAs in patients with various RD. In general, the condition improved in the vast majority of patients (97%), and remission was achieved in 58% of cases. It should be noted that the appointment of a BA in all cases was preceded by a powerful standard immunosuppressive therapy, which did not lead to an adequate decrease in the activity of the disease.

The results of treatment of BAIs in different RHs were generally comparable, and the remission rate ranged from 47 to 63%. Our assessment of the effectiveness of treatment may be somewhat overestimated, as the study was open and uncontrolled. We did not analyze long-term results, since the follow-up period was relatively short (6 months). With a longer follow-up, in some patients, a worsening of the condition associated with the cancellation of BAI can be expected. For example, 3–12 months after discontinuation of RTM, a relapse of cryoglobulinemic vasculitis developed in 73% of patients. The study design did not involve comparing the effectiveness of different GIBPs. In addition, some of them, such as ABC or ETC, were used in isolated cases. The overwhelming majority of patients started treatment with BAs for the first time, therefore, the study does not allow assessing the effectiveness of replacing one drug with another. Approximately 2/3 of patients received RTM.

The high frequency of its prescription reflects the fact that RTM is considered the drug of choice in the treatment of patients with ANCA-associated vasculitis and cryoglobulinemic vasculitis among the GIBPs, which constituted a significant proportion of patients included in the study. In RA, IFN was most often used as the first GIBP, less often RTM and other drugs. In this case, the choice of the GIBP was often dictated by the availability of the appropriate drug in the pharmacy of the medical institution. Tolerability of the GIBP was acceptable. Although ADRs occurred quite often, they in most cases were mild or moderately pronounced and transient, so therapy could be continued. Serious ADRs were observed in 6 (5.6%) of 107 patients, four of them received RTM and two received INF. Serious ADRs were observed in patients with a severe progressive form of systemic ANCA-associated vasculitis, who received powerful immunosuppressive therapy prior to RTM administration. These factors could contribute to the occurrence of HP associated with the suppression of the protective functions of the organism.

The main indication for the appointment of GIBP in rheumatology is RA. We used HIBP in RA patients in accordance with the 2010 EULAR recommendations [2], that is, with the ineffectiveness of at least one standard DMARD (most often MT at a dose of 15-25 mg / week) and the presence of unfavorable prognostic factors: 1) the presence of rheumatoid factor (RF) and / or antibodies to cyclic citrullinated peptide, especially in high titers; 2) high disease activity; 3) erosive changes in the joints.

The therapy of BAIs was usually started with INF, which has been used in clinical practice for more than

12 years, which makes it possible to judge both the effectiveness and safety of its long-term use [6]. In some cases, other GIBPs were used, primarily RTM and TCZ. All patients responded to treatment, and remission was achieved in almost half of the cases. In two patients, IFN was replaced with RTM or TCZ due to insufficient efficacy. In both cases, the replacement of the GIBP made it possible to achieve a significant improvement. R. Moots and B. Naisbett-Groet [7] analyzed the materials of studies that examined the results of replacing an insufficiently effective TNF inhibitor with another BA in RA patients. It has been shown that in such cases, the administration of another TNF inhibitor - RTM or ABC - leads to a significant decrease in inflammatory activity.

In accordance with the recommendations of the International Society for the Study of AS (ASAS) / EULAR 2011, in patients with AS, treatment of BAs should be started with high disease activity and insufficient effectiveness of NSAIDs [8]. We considered secondary amyloidosis, which was present in 2 out of 8 patients, as an additional indication for their appointment. In the event of the development of this complication, it is especially important to achieve suppression of inflammatory activity in order to prevent the progression of renal pathology. Administration of TNF inhibitors led to remission in 7 out of 8 patients. The effectiveness of GIBP in SLE is confirmed only by the results of uncontrolled studies [9]. For example, M. Ramos-Casals et al. [10] retrospectively analyzed 188 cases of RTM use in adult SLE patients. 91% of them showed significant improvement in at least one manifestation of the disease. The response rate in 103 patients with lupus nephritis was also 91%. However, the efficacy of RTM has not been confirmed in two large, randomized, double-blind, placebo-controlled trials in patients with extrarenal manifestations of SLE (EXPLORER) or class III / IV lupus nephritis (LUNAR) [11, 12].

At the same time, in two phase III studies (BLISS-52 and BLISS-76), belimumab (a mAb to a factor that stimulates the survival of B cells, BLISS) was significantly more effective than placebo in 1684 SLE patients who received standard therapy [13]. Although the role of RTM in the treatment of patients with newly diagnosed SLE remains controversial, given the negative results of randomized clinical trials, our little experience, as well as global practice, confirm the possibility of its prescription in patients with various forms of SLE (including lupus nephritis) with insufficient efficacy or poor tolerance. standard immunosuppressive therapy [14].

Patients with systemic vasculitis constituted a significant proportion of patients who received BAs in our study. For ANCA-associated vasculitis and cryoglobulinemic vasculitis, we used RTM, and for vasculitis with large-caliber vasculitis, mainly INF. As in the other groups, the reason for the prescription of GIBP was the persistence of high activity of the disease, despite the standard anti-inflammatory therapy. In the overwhelming majority of patients, BAI therapy has achieved a complete or at least partial response. The efficacy of RTM in ANCA-associated vasculitis has previously been established in several randomized, open-label trials. The RITUXVAS study included 44 patients with ANZA-associated renal vasculitis [15] who received 4 infusions of RTM (375 mg / m2 per week) in combination with CP (two high-dose infusions; n = 33) or pulse therapy CP for 3–6 months, followed by its replacement with a maintenance dose of azathioprine. All patients took GC. Within 12 months, remission was achieved in 76 and 82% of patients in two groups ($p = 0.68$). It should be noted that there was a high incidence of significant ADRs in both groups (42 and 36%, respectively; $p = 0.68$).

The efficacy of TNF inhibitors (mainly INF) in patients with vasculitis with lesions of large vessels is confirmed by case reports and small open studies [18]. The Mayo Clinic summarized the experience of using various TNF inhibitors in 20 patients with refractory arteritis Takayasu (17 patients received INF, ADA - 2 and ETC - 1) [19]. The median duration of treatment was 23 (8.7–38.9) months. Remission was achieved in 18 (90%) of 20 patients, including persistent - in 10 (50%). Nevertheless, 6 out of 18 patients who achieved remission developed a relapse of the disease during therapy with TNF inhibitors. Treatment was discontinued due to relapse, persistence of activity, lack of steroid-saving action (in 11), HP (in 4), or for other reasons (in 4).

In a French multicenter study [20], the efficacy and safety of IFN was studied in 15 patients with Takayasu arteritis refractory to GC, MT and / or azathioprine. After 3, 6 and 12 months, response to treatment (including reduction of the GC dose or their cancellation) was observed in 87, 77 and 73% of patients, respectively. C. Comarmond et al. [21], based on their own observations (n = 5) and literature data, summarized the experience of using TNF inhibitors (INF and ETC) in 84 patients with Takayasu's arteritis. In 30 (37%) patient's remission of vasculitis was achieved, in 45 (53.5%) - improvement. In 27 (32%) patients, the dose of the TNF inhibitor had to be increased due to the persistence of vasculitis activity, and in 15 (18%) patients it was replaced by another drug of the same group. In 92% of patients, it was possible to reduce the dose or to cancel the GC. During follow-up (median 10 months), treatment with a TNF inhibitor was discontinued due to ADR in 17 (20%) patients. Thus, in general, the experience of using TNF inhibitors in the refractory course of Takayasu's arteritis can be considered positive, although the need for additional randomized controlled trials is obvious. Our study also showed high efficiency of RTM in cryoglobulinemic vasculitis. In some patients, after achieving remission of HCV-associated vasculitis,

antiviral therapy with pegylated interferon α and ribavirin was carried out.

The effectiveness of RTM in patients with cryoglobulinemic vasculitis is also confirmed by the results of randomized controlled trials. For example, S. de Vita et al. [22] in a long-term prospective randomized study compared the efficacy of RTM (two infusions of 1 g and a second course in case of relapse) and standard therapy (one of the following regimens: GC; azathioprine or CP; plasmapheresis) in 59 patients with cryoglobulinemic vasculitis with ulcerative - necrotic skin lesions, glomerulonephritis or refractory peripheral neuropathy. In patients with HCV-associated vasculitis, previous antiviral therapy was ineffective or there was no indication for its prescription. The observation period was 24 months. The proportion of patients who continued the prescribed therapy for 12 months in the RTM group was significantly higher than in the comparison group (64.3 and 3.5%, respectively; $p < 0.0001$). Differences in this indicator were also significant after 3, 6 and 24 months. The vasculitis activity index (BVAS) decreased only with the treatment of RTM. The drug was generally well tolerated. In an American randomized study [23], the efficacy of RTM (375 mg / m2 per week for 4 weeks) and standard immunosuppressive therapy were compared in 24 patients with HCV-associated cryoglobulinemic vasculitis, in whom antiviral therapy did not lead to remission of the disease. After 6 months, remission was achieved in 10 (83%) of 12 patients in the RTM group and only in 1 (8%) patient in the control group ($p < 0.001$), and therefore the study was terminated. The median duration of remission in the RTM group was 7 months. RTM had no undesirable effect on viremia or hepatic aminotransferase activity.

CONCLUSION

Our study confirms the high efficacy and acceptable tolerability of various BAs in RA, SLE, and systemic vasculitis. In general, the condition improved in the vast majority of patients (97%), who were refractory to standard immunosuppressive therapy, and remission was achieved in 58% of cases. Based on the data obtained, the efficacy of BAs in RD should not be overestimated, since the duration of follow-up was relatively short (6 months), and over time, the achieved response is lost in some patients. When treating BAI, it is necessary to take into account the risk of developing serious ADR, the frequency of which was higher in patients with severe ANZA-associated vasculitis. Nevertheless, in general, the introduction of GIBP into clinical practice has significantly expanded the possibilities of effective treatment of not only RA and AS, but also other severe RH, primarily systemic vasculitis. It should be emphasized that in systemic vasculitis and SLE, as in RA, BAI is currently recommended to be prescribed only if standard immunosuppressive therapy is ineffective or intolerant, although the results of RTM studies in patients with granulomatosis with polyangiitis (Wegener's) indicate that this drug can serve as an alternative to standard means and at the first stage of treatment.

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