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АКТУАЛЬНОСТЬ И ПЕРСПЕКТИВЫ БИОЛОГИЧЕСКОЙ ТЕРАПИИ БОЛЬНЫХ СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКОЙ

For citation: Z.B. Babamuradova, R.V. Gorenkov RELEVANCE AND PROSPECTS OF BIOLOGIC THERAPY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. Journal of cardiorespiratory research. 2023, vol 1.1, issue 32, pp. 170-173.

АННОТАЦИЯ

Наша исследовательская группа изучала наличие и количество фактора некроза опухоли в крови до и после лечения моноклональными антителами. Отбор проб для анализа проводился в INNOVA, частной медицинской исследовательской клинике в Самарканде, Узбекистан. В ходе лечения наша исследовательская группа наблюдала клиническое и лабораторное улучшение после применения моноклональных антител, в отличие от других препаратов, таких как стероидные гормоны или цитостатики.
Ключевые слова: моноклональные антитела, системная красная волчанка, ревматология, цитостатики, инновационное лечение.

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RELEVANCE AND PROSPECTS OF BIOLOGIC THERAPY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

ANNOTATION

Our research group studied the presence and amount of tumour necrosis factor in the blood, before and after treatment with monoclonal antibodies. In the course of treatment, our research team observed clinical and laboratory improvement after application of monoclonal antibodies, unlike other drugs such as steroid hormones or cytostatics
Key words: monoclonal antibodies, systemic lupus, rheumatology, cytostatics, innovational treatment

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TIZIMLI QIZIL YUGURUK BO'LGAN BEMORLARDA BIOLOGIK TERAPİYA O'TKAZISHINING MUHIMLIGI VA ISHLAB CHIQISHLARI

ANNOTATSIYA

Bizning tadqiqot guruhimiz monoklonal antitanachalar bilan davolashdan oldin va keyin qonda o'sma nekrozi omilining mavjudligi va miqdorini o'rgandi. Tahlil uchun namuna olish Samarqand shahridagi INNOVA xususiy tibbiy tadqiqot klinikasida o'tkazildi. Tadqiqotimiz doirasida Samarqand shahar tibbiyot birlashmasi kardio-revmatologiya bo'limida va Samarqand tibbiyot universitetining 1-klinikasida №1 terapiya bo'limida tizimli qizil yuguruk kasalligiga qarshi biologik preparatlar bilan bemorlar davolandi. Davolash jarayonida bizning tadqiqot guruhimiz steroid gormonlar yoki sitostatiklar kabi boshqa dorilardan farqli o'laroq, monoklonal antitanachalarni qo'llashdan keyin klinik va laboratoriya yaxshilanishini kuzatdi.

Kalit so'zlar: monoklonal antitanachalar, tizimli qizil yuguruk, revmatologiya, sitostatiklar, innovatsion davolash

Systemic lupus erythematosus (SLE) is a complex systemic disease characterized by a variety of clinical presentation and course, including renal, mucocutaneous, neurological, musculoskeletal, vascular, hematological, cardiovascular and respiratory manifestations. This disease often presents with general symptoms, which include fever, weight loss, anorexia, splenomegaly, lymphadenopathy, fatigue, malaise, and weakness. Of all the symptoms, the most common and leading to disability appears to be fatigue, which is often difficult to treat. Due to the complex nature of SLE, special knowledge and careful assessment of specific manifestations is required, since each of them may require specific research or treatment [1, 2, 3].

According to various estimates, from 70 to 90% of patients are women, whose onset of the disease occurs in childbearing age. The prevalence of SLE ranges from 20 to 70 cases per 100 thousand women and varies depending on race and ethnicity - the highest rates were recorded among Hispanics, African Americans, Africans, including those living in the Caribbean, and Asians [4]. The annual incidence of SLE is on average 5 per 100 thousand of the population. According to the Centers for Disease Control and Prevention (CDC), incidence rates in the continental United States range from 1.8 to 7.6 per 100,000 per year. According to various sources, the prevalence of SLE is 52 cases per 100 thousand populations. According to the National Arthritis Data Working Group (2008), approximately 250,000 Americans have some SLE. [4, 5, 6].

The male gender, belonging to unprotected social groups, low income, lack of education and living in rural areas have a negative impact on survival [7]. The main causes of death in SLE are the development of nephritis, cardiovascular complications (atherosclerosis) and infections [8]. Despite significant advances in traditional therapy, many of the problems associated with the management of these patients require immediate solutions. Thus, 50–80% of SLE patients show signs of disease activity and / or frequent exacerbations [9], about 30% have to stop working, in 10–30%, the presence of class IV lupus nephritis increases the risk of developing end-stage renal failure with subsequent transfer to hemodialysis [10]. Among the unresolved problems is the development of irreversible organ damage in the first 5–6 years after the onset of SLE, which is due to both its course and side effects of therapy, primarily the long-term use of high and medium doses of GC and CT [11]. Another problem with SLE is the high cost of treatment and patient monitoring. So, according to K.A. Slawsky et al. [12], in 2011 the direct annual costs of treating a patient with SLE in the United States were estimated at 13,735–20,926 dollars. Diagnostics. The diagnosis of SLE should be based on the presence of clinical manifestations of the disease and laboratory findings. To confirm the diagnosis, at least 4 of the 11 criteria of ACR, 1997 are required (sensitivity - 85%, specificity - 95%).

Therapy goals:

• decreased disease activity;

• prevention of recurrence of the appearance of activity; • reducing the daily dose of prednisone / other HA;

• reducing the risk of developing irreversible organ damage;

• improving the quality of life.

Materials and methods. Our research group studied the presence and amount of tumour necrosis factor in the blood, before and after treatment with monoclonal antibodies. Sampling for analysis was carried out at INNOVA, a private medical research clinic in Samarkand, Uzbekistan. As part of our study patients were treated with biologics against systemic lupus erythematosus at the City Medical Association in Samarkand, in the Department of Cardio-Rheumatology, and at the 1st clinic of Samarkand Medical Institute in the Therapy Department #1.

Indications for the appointment of belimumab (benlist) for SLE:

1. Insufficient effectiveness of previous therapy with GC, GC and / or one of the CTs for at least 3 months.

2. High or medium SLE activity (> 6 points on SELENA – SLEDAI).

3. The need to prescribe GC (≥7.5 mg prednisolone per day) + GC and / or CT to maintain remission.

4. Contraindications for the appointment of one of the CTs or the need to prescribe CT in a dose exceeding the recommended dose.

5. High level of a-DNA, low level of complement.

6. Refractory to standard therapy lesions of the skin, joints, muscles, mucous membranes, thrombocytopenia ≤30,000.

7. Class III nephritis with a low degree of clinical and morphological activity.

8. Multiple organ refractoriness to standard therapy

Results and discussion. Belimumab (Belimumab, BLM, BENLYSTA, GlaxoSmithKline) are fully human recombinant mAbs (IgG1λ) that prevent the interaction of pBLyS with cellular receptors of autoreactive "transitional" and naive B cells [13], which in turn leads to suppression of SLE B characteristic -cellular hyperreactivity, in particular, the synthesis of autoantibodies [14]. In addition, BLyS blockade can reduce the survival of B cells in the growth centers of lymphoid organs, the differentiation of memory B cells into autoantibody-producing cells and the synthesis of "pro-inflammatory" cytokines (IL21, IL17, etc.), which play an important role in the immunopathogenesis of SLE [15]. Belimumab is administered by intravenous infusion. The half-life (T1 / 2) of the drug is 19–20 days, the volume

of distribution is small (69–112 ml / kg), and the clearance is slow (7 ml / day / kg). The pharmacokinetics of belimumab is not affected by concomitant therapy with non-steroidal anti-inflammatory drugs, antimalarial drugs, GC, methotrexate (MT), azathioprine (AZA) and MMF [16]. The duration of the infusion is 1 hour; the dose of the drug is 10 mg / kg. The first 3 infusions are performed every 3 weeks, and the subsequent ones - every 4 weeks.

BLM is the first genetically engineered biological preparations developed for the treatment of SLE. Clinical studies have proven its effectiveness. To date, about 5% of SLE patients in the United States have received one or more BLM infusions. 02.03.2012 BLM was registered in the Russian Federation. Over the past two years, some Russian experience of using BLM in real clinical practice has already been accumulated; there are several foreign publications showing the effectiveness of this drug 3, 12, 24 months and even 7 years after the start of treatment in patients with SLE. When should you use belimumab? In the studies conducted, the most frequent indications for its appointment were: polyarthritis, mucocutaneous syndrome, high immunological activity (increased concentration of antibodies to DNA, decreased levels of C3-, C4-complement components [17]. patients with insufficient efficacy of GC, GC and / or cytostatics, frequent exacerbations of the disease (relapsing-remitting course of SLE) J. Yazdany et al. [18], A. Askanase et al. [19], C. Collins et al. [20] prescribed BLM in 17% of cases in the presence of a combination of skin and mucous membrane lesions, polyarthritis and serositis in patients A. Doria et al. [21] used BLM not only in cases of joint damage and of serous membranes, but also with moderately active lupus nephritis. had all of the above Aspirations for the appointment of BLM. They had polyarthritis, lesions of the skin and mucous membranes, in all cases there was a high immunological activity. In one case, there were hematological disorders in the form of leukopenia, in the other - lupus nephritis with minimal proteinuria and a history of serositis. All patients had long-term GC therapy, insufficient effectiveness of previous therapy, and a relapsing-remitting course of SLE.

The indications for prescribing belimumab for SLE: moderate / high disease activity, the presence of severe serological abnormalities (positive results for the determination of ANF and / or anti-dsDNA) and insufficient effectiveness of standard therapy (in accordance with the instructions, the drug is prescribed in the presence of all three indications in one patient). Against the background of treatment with belimumab at a dose of 10 mg / kg after 52 weeks, an improvement in the SRI index was noted significantly more often than in the PL group (43.2% versus 33.8%), although no statistically significant differences were obtained after 76 weeks. Thus, in both studies, the primary endpoint (higher response rate according to the SRI index) was reached during treatment with belimumab, which indicates the effectiveness of the drug. Other important secondary endpoints were HA dose reduction and improvement in patient quality of life (QOL). Of particular interest is the positive dynamics of immunological parameters, which is consistent with clinical data during treatment with belimumab. Normalization of biomarkers reflecting the activity of SLE was observed: hypergammaglobulinemia, autoantibody titers (a-DNA, a-Sm, anti-ribosomal antibodies and a-CL), as well as an increase in the concentration of C3 and C4 components of complement. In addition, there was a decrease (by 20-25%) in the total number of B-cells and certain subpopulations of B-lymphocytes (naive and activated B-cells and plasma cells), indicating a pronounced immunomodulatory effect of the drug. According to R.F. van Vollenhoven et al. [22], the efficacy of belimumab in patients with an initially high SELENA – SLEDAI index (≥10), hypocomplementemia and an increase in anti-dsDNA levels (compared with PL) was significantly higher than in the general population of patients receiving belimumab. In addition, in patients of this subgroup, there was a significant improvement in such long-term outcomes as the frequency of exacerbations, the need for GC and QOL. This is consistent with the data of previous studies, which showed that the number of plasma cells correlates with the activity of SLE [23], and a high level of anti-dsDNA and a decrease in the concentration of complement - with the activity of SLE and the risk of exacerbations [24].

We also observed a relative normalization of the levels of antibodies to DNA and complement components in only two out of three patients. It is quite possible that the complete normalization of these parameters will be observed over a longer period, as, for example, in the group of patients by E. Ginzler et al. [25], who noted the normalization of immunological activity 7 years after the start of BLM therapy. A great advantage of prescribing BLM is the ability to reduce the dose of HA. In 449 patients with SLE on the background of BLM treatment, the GC dose was reduced by 25% after 2 years and by 55% after 7 years [26]. We also got the opportunity in two cases to reduce the HA dose by 50% within 6 months of therapy.

According to the RCT, belimumab is well tolerated, the most common AEs were infectious complications, joint pain, headache, diarrhea, nausea, infusion reactions, neutropenia and thrombocytopenia were occasionally observed.

Conclusion. In conclusion, it should be emphasized that despite the moderate efficacy of belimumab in SLE, primarily in patients with an immunologically active variant of the disease, but without severe potentially fatal manifestations (lupus nephritis, CNS damage), the creation and introduction of the drug into clinical practice is an important step towards improving the pharmacotherapy of the disease. Currently, only against the background of treatment with belimumab have been obtained reliable positive results of the RPKI, which made it possible to register this drug for the treatment of SLE. At the same time, the place of belimumab in real clinical practice requires clarification. Taking into account the data of clinical studies and the mechanism of action of the drug (suppression of the accumulation of pathological autoreactive B cells and synthesis of autoantibodies), it seems that belimumab is promising for slowing the progression and maintaining remission of SLE induced by high doses of HA, CP or RTM, optimizing HA maintenance therapy, reducing the risk of irreversible damage to internal organs. A clear relationship between the effectiveness of belimumab and the indicators of immunological biomarkers of SLE activity, as well as the ethnic characteristics of patients opens up new prospects for personalized therapy for this disease.

The emergence of belimumab marked a new era in the treatment of SLE, associated with the beginning of the widespread use of genetically engineered biological preparations and the creation of a new class of drugs - BLyS inhibitors, which can play an important role in the treatment of not only SLE, but also a wide range of autoimmune diseases.

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