Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3802 - 3805
Received 20 January 2021; Accepted 08 February 2021.

Study of the Effectiveness of the Use of Monoclonal Antibodies in Rheumatological Diseases

Zarrina Bakhtiyarovna Babamuradova
PhD, Associate Professor
Head of the Department of Internal Medicine of Pediatric faculty
Samarkand State Medical Institute
140100, Samarkand, st. Amir Timur, 18.
Email:dr.zarrina.b.b@mail.ru

Gulandom Zikriyaevna Shodikulova
Doctor of Medical Sciences, Professor,
Head of the Department of Internal Medicine No. 3 and Endocrinology
Samarkand State Medical Institute,
140100, Samarkand, st. Amir Timur, 18.
Email:shodikulovagulandom@mail.ru

ABSTRACT

The study included 41 patients diagnosed with RA (24), Ankylosing spondylitis (3), Takayasu's disease (2), SLE (10), psoriatic arthritis (2), which were confirmed according to the ICD 10 classification. patients received basic therapy: methotrexate at a dose of 7.5–10 mg per week; three patients also received 7.5-10 mg of glucocorticosteroids per day. All patients also received non-steroidal anti-inflammatory drugs (NSAIDs) in adequate daily doses. Nevertheless, against the background of the therapy, a consistently high activity of the disease was noted. Twenty-one patients received Tocilizumab infusions.

The aim of the study was to study the effectiveness of using monoclonal antibodies in rheumatological diseases.

KEY WORDS: rheumatology, ankylosing spondylitis, Takayasu's disease, SLE, arthritis

INTRODUCTION

As our knowledge of the nature of adaptive immunity deepens, ideas are formed about those key points at which a malfunction of the immune system can occur, leading to the development of autoimmune diseases. The spectrum of autoimmune disorders is extremely wide and affects almost all tissues of the body. The pathogenesis of these diseases is due to both the appearance of autoimmune antibodies and the multiplication of effector T-clones that recognize their own antigens and, as a result, provoke inflammatory processes in a separate organ or in the whole system. Autoreactive T-clones may be present in the blood of healthy donors [1], but are in a state of immunological tolerance - anergy controlled by regulatory T-cells (Tregs). Violation of the number of Tregs or their functional activity is observed in many autoimmune diseases and may serve as one of the reasons for the development of inflammatory processes.

Systemic rheumatic diseases are pathologies that arise from the aggressive effects of immunity on their own tissues. Their development is based on an error of the immune system, which incorrectly recognizes the normal components of the human body - autoantigens. Immune cells mistake them for foreign agents, which they see as a threat to the body. The protective function is activated, and the "bombardment" of healthy cells with the factors of the immune system - autoantibodies – begins. Diseases associated with an autoimmune component are a serious problem in modern society. Their prevalence in the world population is approximately 5%. Diseases quickly become chronic, which reduces the quality of life of patients. Autoimmune pathologies often lead to disability of patients

Today, for the treatment of systemic rheumatic diseases, approaches are used that provide

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3802 - 3805
Received 20 January 2021; Accepted 08 February 2021.

general immunosuppression through drugs that directly or indirectly reduce inflammation. This paper considers the types of therapy for autoimmune diseases using monoclonal antibodies (MA). In the English-language literature, such MA, together with other genetically engineered drugs for clinical purposes, are called "biologics". A number of MAs are effectively used to treat various autoimmune diseases. Many drugs are still in clinical trials. Therapeutic MA can vary significantly in mode of action. They can bind to a soluble ligand, inhibiting its activity, or to a receptor on the membrane of a target cell, blocking the interaction of the receptor with the ligand, modulating the signal coming through this receptor, or causing apoptosis.

Over the past few years, the list of therapeutic antibodies related to disease-modifying drugs (DMT) and having a selective mechanism of action has expanded significantly.

In autoimmune diseases, it is possible to suppress the entire complex mechanism of immunity at once, which is what the drugs of classical therapy do. But this leaves a person without protection from enemy agents - bacterial infections, viruses and other pathogens. Therefore, it is preferable to preserve the activity of the immune system as a whole, saving a person from the auto-aggression of certain of its components. This is how new drugs work - monoclonal antibodies.

Depending on the point of application of the drug, monoclonal antibodies are divided into groups:

1. TNF (tumor necrosis factor) inhibitors - infliximab, etanercept, certolizumab, golimumab, adalimumab.
2. Interleukin receptor blockers - tocilizumab (IL-6R), canakinumab (IL-1R), secukinumab (IL-17R).
3. Anti-B-cell antibodies (antibodies to membrane molecules CD20) - rituximab, belimumab [17].
4. Anti-T-cell antibodies (antibodies to CD80 and CD86 molecules) –abatacept

In the spectrum of cytokines involved in the pathogenesis of rheumatological diseases, much attention is paid to the study of the role of interleukin-6 (IL6). The influence of interleukins is one of the "triggers" of the inflammatory process. Therefore, blocking their activity improves the condition of patients with autoimmune diseases. It is possible to suspend the work of interleukins if you bind their receptors - molecules that transmit a signal to immune cells. This is the basis of the mechanism of action of monoclonal antibodies from the group of inhibitors of interleukin receptors. Tocilizumab is a drug that blocks IL-6 from working.

The aim of the study was to study the effectiveness of using monoclonal antibodies in rheumatological diseases.

MATERIALS AND METHODS

The study included 41 patients diagnosed with RA (24), Ankylosing spondylitis (3), Takayasu's disease (2), SLE (10), psoriatic arthritis (2), which were confirmed according to the ICD 10 classification. patients received basic therapy: methotrexate at a dose of 7.5–10 mg per week; three patients also received 7.5-10 mg of glucocorticosteroids per day. All patients also received non-steroidal anti-inflammatory drugs (NSAIDs) in adequate daily doses. Nevertheless, against the background of the therapy, a consistently high activity of the disease was noted. Twenty-one patients received Tocilizumab infusions.

All patients had extra-articular manifestations (rheumatoid nodules - 20, polyneuropathy - 2, keratoconjunctivitis dry - 5, weight loss and subfebrile condition - 35, Raynaud's syndrome - in 38 patients).Tocilizumab was administered once with an interval of 4 weeks: 8 mg / kg in 200 ml of physiological solution intravenously for 2.5 hours. Treatment was carried out according to the standard scheme.Evaluation of clinical and laboratory parameters of the therapeutic effect was carried out before the start of the administration of Tocilizumab, before the second administration of the drug, and 8, 16, 24 and 48 weeks after the first infusion. Treatment efficacy was assessed according to clinical ACP criteria and DAS 28 (EULAR) disease activity index.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3802 - 3805
Received 20 January 2021; Accepted 08 February 2021.

RESULTS

All 21 patients on the registry received 4 infusions of Tocilizumab and were followed up for 24–48 weeks. The positive effect of Tocilizumab therapy was observed in all patients. By the 8th week of treatment, there was a significant improvement, reaching a maximum by the 16th week. There was a decrease in pain on a visual analogue scale (VAS, mm), the duration of morning stiffness, the number of painful and swollen joints, the need for NSAIDs decreased up to complete cancellation ($p < 0.05$). Two patients completely stopped taking glucocorticosteroids, one patient reduced the dose to 5 mg per day. A significant ($p < 0.05$) decrease in ESR and C-reactive protein was revealed. The effectiveness of therapy according to the ACR criteria was 50% in 10 and 70% in 14 patients, according to DAS 28, the effect was considered satisfactory - in 6, good - in 9 patients, in 6 patients complete clinical and laboratory remission was achieved by 16 weeks.

By the 24th week, the effect obtained in two patients weakened, which was expressed in the deterioration of clinical and laboratory parameters. In this regard, a repeated course of drug therapy was carried out - two infusions with an interval of 3 weeks. By the 32nd week of observation, one patient showed a significant improvement in clinical and laboratory data.

Thus, the use of Tocilizumab in rheumatological patients, including those with an inadequate response to basic drugs, has a pronounced long-term clinical and laboratory effect. Despite all the possible difficulties, monoclonal antibodies have firmly entered the register of drugs used in rheumatology. But even now, we can say that the development of therapeutic monoclonal antibodies is an important step towards the victory over autoimmune inflammation, such therapy can reduce the risk of early disability, improve the quality of life of patients and the long-term prognosis of the disease.

REFERENCES

1. Arroyo-Avila M., Vila L.M. Cardiac tamponade in a patient with mixed con-nective tissue disease // J. Clin. Rheuma-tol. 2015. Vol. 21, № 1. P. 42-45.
2. Babamuradova Z. B., Shodikulova G. Z., Mirzaev O. V. Treatment of patients with undifferentiated connective tissue dysplasia in mitral valve prolapse with varying degrees of mitral regurgitation //European science review. – 2018. – №. 3-4. С.140-143
3. Bennett R. Overlap syndromes. In: Firestein G, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors. Kelley's Textbook of Rheumatology. 9th ed. Philadelphia, PA: Elsevier Inc; 2013. pp. 1431–1451
4. Castori M., Morlino S., Ghibellini G., Celletti C., Camerota F., Grammatico P. Connective tissue, Ehlers-Danlossyn-drome(s), and head and cervical pain // Am. J. Med. Genet. C. Semin. Med. Ge-net. 2015. Vol. 169, № 1. P. 84-96.
5. Conti V, Esposito A, Cagliuso, et al. Undifferentiated connective tissue disease-An unsolved problem: Revision of literature and case studies. InternationalJournalofImmunopathologyandPharmacology. 2010;23(1):271–278.
6. Deng Y., Wei S., Hu S., Chen J., Tan Z., Yang Y. Ehlers-Danlos syndrome type IV is associated with a novel G984R COL3A1 mutation // Mol. Med. Rep. 2015. Vol. 12, №1. P. 1119-1124.
7. Guerrero LF1, Rueda JC, Arciniegas R, Rueda JM. Undifferentiated connective tissue disease in a rheumatology center in Cali, Colombia: clinical features of 94 patients followed for a year. RheumatolInt. 2013 Apr;33(4):1085-8.
8. Hajas A, Szodoray P, Nakken B, Gaal J, et al. Clinical Course, prognosis, and causes of death in mixed connective tissue disease. J Rheumatol. 2013;40(7):1134–1142.
9. Jensen S.A., Aspinall G., Handford P.A. C-terminal propeptide is required for fi-brillin-1 secretion and blocks premature assembly through linkage to domains cbEGF41-43 // Proc. Natl. Acad. Sci USA. 2014. Vol. 111, №28. P. 10155-10160.
10. Mosca M., Tani C., Vagnani S., Bom-bardieri S. The diagnosis and classifica-tion of undifferentiated connective tissue diseases // J. Autoimmun. 2014. Vol. 48-49 P. 50-52.

11. Shodikulova G. Z. Effect of L-arginine on endothelial dysfunction in patients with congenital mitral valve prolapse //Kazan medical journal. – 2014. – Т. 95. – №. 3. – С. 326-331.
12. Shodikulova G. Z., Toirov E. S., Babamuradova Z. B. Clinical biochemical features in patients with undifferentiated connective tissue dysplasia //European science review. – 2016. – №. 1. – С. 129-131.
13. Shodikulova G. Z. Special features of clinical and functional disorders in patients with undifferentiated connective tissue dysplasia //European science review. – 2017. – №. 3-4. – С. 72-74.
14. Shodikulova G. Z. Value of matrix metalloproteinases and their tissue inhibitors in the diagnosis of undifferentiated connective tissue dysplasia //The First European Conference on Biology and Medical Sciences. – 2014. – С. 111-116.
15. ShodikulovaGulandonZikrievna, BabamuradovaZarrinaBakhtiyarovna. “Occurrence of Clinical Options of Undifferentiated Connective Tissue Dysplasia in Uzbek Population” //International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 02, 2020 ISSN: 1475-7192
16. ShodikulovaGulandonZikrievna, MirzaevOzodVohidovich, BabamuradovaZarrinaBakhtiyarovna “Assessment of extracellular matrix condition in persons with undifferentiated connective tissue dysplasia”// International Journal of pharmaceutical Research / Jan-Jun 2020/ vol.12/ supplementary Issue 1
17. Tani C., Carli L., Vagnani S., Talarico R., Baldini C., Mosca M. et al. The diagnosis and classification of mixed con-nective tissue disease // J. Autoimmun. 2014. Vol. 48-49. P. 46-49.
18. Sung Y.K., Chung L. Connective tissue disease-associated pulmonary arterial hypertension. Rheum // Dis. Clin. North. Am. 2015. Vol. 41, №2. P. 295-313.
19. *Ueshima K.* Magnesium and ischemic heart disease: a review of epidemiological, experimental, and clinical evidences //Magnes Res.- 2005.- Vol.18 (4).- P.275–284.
20. Wang X.L., Mahaney M.C., SimA.S.,Genetic contribution of the endothelial constitutive nitric oxide synthase gene to plasma nitric oxide levels // Arterioscler. thromb. vasc. biol. – 1997. – Vol. 17. – P. 3147–3153.
21. Yosefy C., Ben Barak A. Floppy mitral valve/mitral valve prolapse and genetics //J. Heart Valve Dis.- 2007.- Vol.16 (6).- P.590-595.
22. Zacchigna L., Vecchione C., Notte A., Cordenonsi M., et al. Emilin1 links TGF–beta maturation to blood pressure homeostasis //Cell.- 2006.- Vol.124(5).- P.929–942.