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Extracorporeal immunoparmacotherapy in rheumatoid arthritis

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Abstract
Worldwide, about 1% of population or 165 million people suffer from rheumatoid arthritis. And, despite all the achievements of modern medicine, the mortality rate is 1.6-2.0 times higher than in the general population. However, the treatment of rheumatoid arthritis remains a difficult problem to resolve. Disorders of both humoral and cellular immunity are involved in its pathogenesis. Therefore, it is difficult to choose the optimal drug therapy that does not always provide the desired effect, but, on the other hand, leads to additional complications. Extracorporeal immuno pharmacotherapy seems to be the optimal method, which allows not only to remove autoantibodies, immune complexes and other pathological metabolites, but also to suppress the activity of their producers such as T- and B- lymphocytes and macrophages, without affecting the whole body. This achieves a more stable remission with less toxic doses of drug therapy.

Keywords: rheumatoid arthritis, humoral and cellular immunity, apheresis therapy, extracorporeal immunopharmacotherapy, immunosuppression

1. Introduction

About 1% of the population or 165 million people have rheumatoid arthritis worlwide [1]. Women suffer to a greater extent-up to 1.2% to compare with 0.5% for men, as well as and elderly people, accounting for 43.3 per 100,000 of the population, while in some countries (Canada) it reaches 683 per 100,000 of population [2-4]. At the same time, the number of newly ill cases per year reaches 5-50 per 100,000 of population [5]. And, despite all the achievements of modern medicine, mortality rate in RA is 1.6-2.0 times higher than that in the general population [6-8].

Pathogenesis of RA

This disease causes inflammatory changes in the synovial membranes and periarticular structures associated with severe pain, joint stiffness up to ankylosis, and bone atrophy.

The blood serum of the patients with rheumatoid arthritis contains high titres of antistreptokinase and anti-plasminogen autoantibodies of class IgG and IgA, as a rule after streptococcal infection. There are also antineutrophil autoantibodies bothanti-nuclear and cytoplasmic. Plasminogen synthesized by the liver is distributed in the vessels both internally and externally. At activation plasminogen turns in plasmin, regulating extracellular proteolytic activity, activating proteases. In these patients fibrinogen level is increased, and insoluble fibrin is found on the synovial membranes. Plasmin, in turn, inhibits the cartilages proteoglycan. All of it leads to destruction of the joints and the synovial membranes proliferation. Besides, inflammatory processes are provoked by prostaglandins emitted by cyclooxygenase-2 and cytokines [9, 10].

RA also causes changes in the cellular component of the immune system. Both T- and B-lymphocytes as well as macrophages get into the synovial membranes of the joint surfaces and accumulate there, which promotes hyperplasia of these tissues structures. They also accumulate around the vessels, infiltrating to the stroma. T- and B-cells are often formed in the form of lymphoid follicles, forming granulomas with giant cells. Although B-lymphocytes play a secondary role, they also generate highly active antibodies [11].

Besides, in the serum of RA patients the extracellular DNA fragments are accumulated several times higher, than in healthy donors, and positively correlate with amount of C-reactive protein and the CIC [12]. It is to be considered that unlike nuclear DNA, extracellular DNA possesses immuno stimulating effect and can promote strengthening of autoimmune reactions that also raises a question of its elimination from the body.

In RA patients there are frequent combinations with damage of the blood vessels, myocardium, lungs, and kidneys. The risk of developing interstitial and obstructive pulmonary lesions increases significantly, which also increases mortality in such cases (from 14% during the year, 39% during 5 years and up to 60% after 10 years) [13-15]. Concomitant cardiovascular disease and metabolic syndrome also contributes to mortality rate increase [16-18].

Decreased physical activity due to joint pain and muscle weakness, treatment with glucocorticoids and a high level of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-7, IL-17) stimulate bone resorption processes with prevalence of osteoclasts that promotes development of osteoporosis with increased bone fragility up to fractures [19-21]. There is a higher frequency of mental disorders such as manic-depressive psychosis type [22].

Drug therapy

RA is a long-term (20 and more years) disease with progressing course and unstable therapeutic effect of non-steroid anti-inflammatory drugs, methotrexate, and hormonal therapy. Thus, it should be noted that *methotrexate* due to its liver and lung toxicity causes a number of complications, including increased incidence of concomitant infections and even lymphoma or myeloid leukemia development [23, 24]. Pneumonitis and pleurisies

develop approximately in 20% of patients; conjunctivitis and stomatitis are also possible [25]. After administration of other non-steroid anti-inflammatory preparation such as *ibuprofen* there is a high incidence of kidney damage [26-28].

On the other hand, *penicyllamine* that is administered quite often is also of considerable danger to the patients with rheumatoid arthritis for it can cause severe damages of the skin (pemphigus vulgaris) and even Goodpastur's syndrome [29, 30].

Treatment with glucocorticoids and, especially, biologically modified antirheumatic drugs increases the risk of cancer and lymphoma [31, 32].

It also uses a number of biologicals that inhibit cellular activity. Anti-TNF agents (*abatocept, inaliximab, adalimumab,* etc.) are also effective in rheumatoid arthritis, but it is often combined with dose-dependent adverse effects at the high treatment cost [33-35]. However, *tocilizumab* (an IL-6 receptor antagonist) can lead to hypertension with elevated cholesterol and triglycerides, respiratory infections, and acute pancreatitis [36, 37]. In particular, *abatocept* and *certolizumab* quite often leads to severe interstitial lung disease [38-39].

In recent years, *Rituximab* is actively used that is chimeric monoclonal antibodies against protein receptors CD-20 (B-lymphocytes) inhibiting their activity, but the cost of such treatment reaches $45,900 - $70,223 [40]. However, in some cases, not all B-cells are removed, and after 4 weeks their more dominant and more mutated clones may appear [41]. In addition, T-lymphocytes remain not inhibited, and it is they that secrete cytokines, which primarily damage the synovial membranes, which makes such treatment not quite complete.

Their use in combination with plasmapheresis reduces the risk of such complications [42].

Therapeutic apheresis allows eliminating pain syndrome and, thereby, to restore the joints mobility, to slow down organic damages progression, especially when plasma exchange procedures are repeated two times a year. The lasting positive clinical effect after a course of plasma exchange was reached in 88.7-93.9% of patients with rheumatoid arthritis [42, 43].

Besides the considerable improvement of clinical indicators there was also a marked decrease of fibrinogen, Villebrand's factor, fibronektin complexes, C-reactive protein, sialic acid, and α-2 globulins. More stable results were achieved by combined use of plasma exchange and laser radiation of the blood [44]. Immuno sorption with staphylococcal Protein A is also used (Prosorba columns); however it is fraught with damage of the kidneys due to the immune complexes deposition in their vessels leading to vasculitis [45]. In particular, when ANCA vasculitis occurs, acute renal failure may develop. A course of plasmapheresis in this case, even on the background of hemodialysis, helps to cope with such a complication and restore the kidney function [26].

Cascade (double-filtration) plasma exchange on the background of the disease progression, using hormones and cytostatics only, leads to normal level of C-reactive protein, anti-nuclear antibodies and rheumatoid factor with stabilization of the clinical picture as well [46, 47].

Given the significant role of the cellular factors in the pathogenesis of rheumatoid arthritis, leukocytapheresis methods are also applied [48, 49]. However, according to the biology laws, the removed white blood cells are replaced by the same white blood cells with the same properties, being thrown into the circulation from the depot. Therefore, the effect of such procedures cannot be long-lasting.

Extracorporeal immunopharmacotherapy

Since humoral and cellular mechanisms take place in the RA pathogenesis, it is advisable to manage all these factors, which can be best done using extracorporeal immunopharmacotherapy that we have described earlier [50]. In this case, plasmocytapheresis is performed with the plasma removal including all the antibodies, immune complexes and other pathological metabolites, and the allocation of the entire pool of leukocytes with their subsequent incubation with a minimum dose of corticosteroids for three hours and their subsequent return to the patient. In this case, targeted immunosuppression of leukocytes occurs without affecting the entire body. And leukocytes subjected to such treatment remain longer in the circulation. Control studies show a significant decrease in the levels of cytotoxic cytokines (TNF-αand IL-2) and interferon. This achieves a more stable and long-term remission with a lower level of drug support.

Conclusion

Thus, it should be recognized that the treatment of rheumatoid arthritis remains an intractable problem. In many ways, it is determined by rather complex mechanisms of its pathogenesis, when disorders of both humoral and cellular immunity are involved. Therefore, it is difficult to choose an optimal drug therapy. Since many pathological products are of large molecular nature, which do not allow them to be excreted by the kidneys, the methods of therapeutic apheresis are justified. Extracorporeal immunopharmacotherapy seems to be the optimal method, which allows not only to remove autoantibodies, immune complexes and other pathological metabolites, but also to suppress the activity only of their producers – T- and B-lymphocytes and macrophages, without affecting the entire body. This enables a more stable remission with less toxic doses of the supportive drug therapy.

References

1. Wasserman A. Rheumatoid arthritis: common questions about diagnosis and management. Am Fam Physician. 2018; 97(7):455-462.
2. Charles J, Britt H, Pan Y. Rheumatoid arthritis. Aust Fam Physician. 2013; 42(11):765.
3. Nair B, Taylor-Gjevre R, Wu S. Incidence and prevalence of rheumatoid arthritis in Saskatchewan, Canada: 2001-2004. BMC Rheumatol. 2019; 3:28.
4. Safiri S, Kolahi AA, Hoy D. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis. 2019; 78(11):1463-1471.
5. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010; 376(9746):1094-1098.
6. Turkiewicz A, Neogi T, Björk J. All-cause mortality in knee and hip osteoarthritis and rheumatoid arthritis. Epidemiology. 2016; 27(4):479-485.
7. Cleveland RJ, Nelson AE, Callahan LF. Knee and hip osteoarthritis as predictors of premature death: a review of the evidence. Clin Exp Rheumatol. 2019; 37(5):24-30.
8. Løppenthin K, Esbensen BA, Østergaard M. Morbidity and mortality in patients with rheumatoid arthritis

compared with age-and sex-matched control population: a nationwide register study. J Comorb. 2019; 9:2235042-19853484.
9. Bellucci E, Terenzi R, La Paglia GM. One year in review 2016: pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol. 2016; 34(5):793-801.
10. Veale DJ, Orr C, Fearon U. Cellular and molecular perspectives in rheumatoid arthritis. Semin Immunopathol. 2017; 39(4):343-354.
11. Diaz-González JF, Ferraz Amaro I. [The B cell in the pathogenesis of rheumatoid arthritis]. Rheumatol Clin. 2007; 3(4):176-182.
12. Neumann E, Hasseli R, Lange U, Müller-Ladner U. The Role of Extracellular Nucleic Acids in Rheumatoid Arthritis. Curr Pharm Biotechnol. 2018; 19(15):1182-1188.
13. Hyldgaard C, Hilberg O, Pedersen AB. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017; 76(10):1700-1706.
14. Bendstrup E, Møller J, Kronborg-White S. Interstitial lung disease in rheumatoid arthritis remain a challenge for clinicians. J Clin Med. 2019; 8(12):E2038.
15. Ma Y, Tong H, Zhang X. Chronic obstructive pulmonary disease in rheumatoid arthritis: a systematic review and meta-analysis. Respir Res. 2019; 20:144.
16. Adawi M, Firas S, Blum A. Rheumatoid arthritis and atherosclerosis. Isr Med Assoc J. 2019; 21(7):460-463.
17. Bernardes M, Madutreira A, Oliveira A. Coronary artery calcium score in female rheumatoid arthritis patients: associations with apolipoproteins and disease biomarkers. Int J Reum Dis. 2019; 22(10):1841-1856.
18. Naidu G, Bhilave N, Sharma K. Prevalence of metabolic syndrome in rheumatoid arthritis patients: a case control study from a tertiary care center in North India. J Assoc Physicians India. 2019; 67(7):22-24.
19. Maruotti N, Corrado A, Cantatore FP. Osteoporosis and rheumatic diseases. Rheumatismo. 2014; 66(2):125-135.
20. Adami G, Fassio A, Rossini M. Osteoporosis in rheumatic diseases. Int J Mol Sci. 2019; 20(233):E5867.
21. Li G, Chen M, Cesta A. Frailty and risk of osteoporotic fractures in patients with rheumatoid arthritis: data from the Ontario Best Practices Research Initiative. Bone. 2019; 127:129-134.
22. Charoen ngam N, Ponvilawan B, Ungprasert P. Patients with rheumatoid arthritis have a higher risk of bipolar disorder: a systematic review and meta-analysis. Psychiatry Res. 2019; 282:112484.
23. Sakai T, Tamura S, Miyosi T. Development of myeloid sarcoma after long term metotrxate use for rheumatoid arthritis. Int J Hematol. 2014; 99(4):493-498.
24. Agarwal S, Kaelev N, Gupta P. A fatal case of acute myeloid leukaemia-methotrexate related or primary autoimmune disease related: a rare case report. J Clin Diagn Res. 2016; 10(3):6-7.
25. Pérez-Dórame R, Mejía M, Mateos-Toledo H, Rojas-Serrano J. Rheumatoid arthritis-associated interstitial lung disease: lung inflammation evaluated with high resolution computed tomography scan is correlated to rheumatoid arthritis disease activity. Rheumatol Clin. 2015; 11:12-16
26. Foray N, Hudali T, Papireddy M, Gao J. A case report describing a rare presentation of simultaneous occurence of MPO-ANCA-associated vasculitis and rheumatoid arthritis. Case Rep Nephrol. 2016, 9340524.
27. Geith S, Renner B, Rabe C. Ibuprofen plasma concentration profile in deliberate ibuprofen overdose with circulatory depression treated with therapeutic plasma exchange: a case report. BMC Pharmacol Toxicol 2017; 18:81.
28. Solomon DH, Husni ME, Libbi PA. The risk of major NSAID toxicity with celecoxib, ibuprofen, or naproxen: a secondary analysis of the PRECION trial. Am J Med. 2017; 130(12):1415-1422.
29. Gholizadeh N, Zeniuz AT, Eslami H. Pemphigus vulgaris associated with rheumatoid arthritis in a patient not taking penicillamine. J Dent Res Clin Dent Prospects. 2012; 6:33-35.
30. Sharma R, Jain S, Kher V. ANCA-associated Goodpasture's syndrome in a patient with rheumatoid arthritis on penicillamine. Indian J Nephrol. 2012; 22:45-47.
31. De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. Best Pract Res Clin. Rheumatol. 2018; 32(6):869-886.
32. Klein A, Polliack A, Gafter-Gvili A. Rheumatoid arthritis and lymphoma: incidence, pathogenesis, biology, and outcome. Hematol Oncol. 2018; 36(5):733-739.
33. Van Herwaarden N, den Broeder AA, Jacobs W. Down-titration and discontinuarían strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2014; 9:CD10455.
34. Tarp S, Eric Furst D, Boers M. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology (Oxford). 2017; 56(3):417-425.
35. Salmon JH, Peritin JM, Morel J. Serious infusion-related reaction after rituximab, abatacept and tocilizumab in rheumatoid arthritis: prospective registry data. Rheumatology (Oxford). 2018; 57:134-139.
36. Flaig T, Douros A, Bronder E. Tocilizumab-induced pancreatitis : case report and review of data from the FDA Asdfverse Evernt Reporting System. J Clin Pharm Ther. 2016; 41(6):718-721.
37. Hoffman E, Rahat MA, Feld J. Effects of tocilizumab, an anti-interleukin-6 receptor antibody, on serum lipid and adipokine levels in patients with rheumatoid arthritis. Int J Mol Sci. 2019; 20(18):E4633.
38. Lager J, Hilberg O, Løkke A, Bendstrup E. Severe interstitial lung disease following treatment with certolizumab pegol: a case report. Eur Respir Rev. 2013; 22(129):414-416.
39. Markatseli TE, Papagoras C, Nikoli A. Certolizumab for rheumatoid arthritis. Clin Exp Rheumatol. 2014; 32(3):415-423.
40. Ahmadiani S, Nikfar S, Karimi S. Riruximab as first choice for patients with refractory rheumatoid arthritis: cost-effectiveness analysis in Iran based on a systematic review and meta-analysis. Rheumatol Int. 2016; 36(9):1291-1300.
41. Pollastro S, Klarenbeek PL, Doorenspleet ME. Non-response to retuximab therapy in rheumatoid arthritis is

Associated with incomplete disruption of the B cell receptor repertoire. Ann Rheum Dis. 2019; 78(10):1339-1345.
42. Cheng Y, Yang F, Huang C. Plasmapheresis therapy in combination with TNF-α inhibitor and DMARDs: A multitarget method for the treatment of rheumatoid arthritis. Mod Rheumatol. 2016; 27(4):576-581.
43. Korach JM, Guillevin L, Petitpas D. Apheresis registry in France: indications, techniques, and complications. Ther Apher, 2000; 4(3):207-210.
44. Voinov VA. Therapeutic apheresis. Constanţa: Celebris, (Romania), 2016, 403.
45. Deodhar A, Allen E, Daoud K, Wahba I. Vasculitis secondary to staphylococcal Protein A immuno adsorption (Prosorba column) treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2002; 32:3-9.
46. Matsuda Y, Tsuda H, Takasaki Y, Hashimoto H. Double filtration plasmapheresis for the treatment of a rheumatoid arthritis patient with extremely high level of C-reactive protein. Ther Apher Dial. 2004; 8(5):404-408.
47. Yu X, Ma J, Tian J. A controlled study of double filtration plasmapheresis in the treatment of active rheumatoid arthritis. J Clin Rheumatol. 2007; 13(4):193-198.
48. Kitagaichi M, Kusaoi M, Tsukahara T. Safety and efficacy of the leukocytapheresis procedure in eighty-five patients with rheumatoid arthritis. Transfus Apher Sci. 2016; 55(2):225-232.
49. Hidaka T, Hashiba Y, Kubo K. Leukocytapheresis in rheumatoid arthritis. Transfus Apher Sci. 2017; 56(5):698-702
50. Voinov VA, Ilkovich MM, Isaulov OV, Novikova LN, Karchevsky KS, Baranova OP, *et al*. Extracorporeal Immunopharmarcotherapy of Autoimmune Diseases. Journal Clinical & Experimental Immunology. 2019; 4:1-5.