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Review Article

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Extracorporeal Immunopharmacotherapy of Autoimmune Diseases

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Abstract

The article aims to analyze pathogenetic mechanisms of autoimmune diseases development including disorders of both cellular and humoral immunity. The standard drug therapy with corticosteroids and cytostatic leads to a number of side effects such as lipid metabolism disorders (Kushing-syndrome), arterial hypertension, diabetes, and osteoporosis each of which is to be additionally treated. Chimeric monoclonal antibodies (rituximab, natalizumab, etc.) can also cause complications. Therefore apheresis therapy with removal of autoantibodies, circulating immune complexes and other pathological metabolites is pathogenetically justified. However, the greatest effect is reached by means of extracorporeal immunopharmacotherapy when, besides antibodies removal by means of plasmapheresis one performs selection of lymphocytes and their temporary incubation with corticosteroids and cytostatics, which are then returned to the patient. Such targeted immunosuppression is much more effective then "pulse therapy" with minimum negative consequences for the body. At the same time a supporting drug therapy can be carried out with half smaller doses.

Keywords: Autoimmune Diseases, Cellular Immunity, Plasma Exchange, Extracorporeal Immunopharmacotherapy, Immunosuppression, Fibrosing Alveolitis, Multiple Sclerosis, Rheumatoid Arthritis, Crohn's Disease.

Over the past four decades, there is an increased awareness that many human diseases are associated, at least partially, with the immune system disorders when the immune system instead of its inherent function to protect the health and life of the body triggers self-destructive immune processes.

Pathogenesis of autoimmune diseases

There are cell-dependent and humoral immunities. The main cellular components of the immune system are: CD_3 – all T-lymphocytes, CD_4 – T-helpers, CD_8 – T-suppressors, CD_{20} – B -lymphocytes, CD_{56} – natural killer T-cells, and CD_{16} – macrophages (neutrophils). Humoral immunity is determined by immunoglobulins such as IgA, IgG, IgE, and IgM.

There is a well-known specialization of T-helpers producing cytokines. Thus, type I T-helpers (Th-1) mainly affect the cellular immunity (hypersensitivity and cytotoxicity) and produce IL-2, TNF-α and interferon (IFN)-β. Cells of type Th-2 affect the humoral immunity (antibody formation) and secrete IL-4, IL-5 and IL-10, activating B-lymphocytes, stimulating organ-specific autoantibodies formation. Their interaction with antigens in the presence of complement leads to formation of circulating immune complexes (CIC) – "antigen+antibody+complement". Penetrating in the tissues, immune complexes contribute to attraction of macrophages, neutrophils and monocytes, eosinophils and lymphocytes in them associated with excitation of their enzymatic activity, and the released BAS cause different types of tissue reactions such as aseptic immune inflammation, granulomatosis, fibrosis or, on the contrary, destruction of the elastic framework, etc. Depending on the nature of these reactions, of tissues or organs type, certain diseases are developed referred to as autoimmune or immunocomplex diseases.

The humoral immunity depends on the cellular immunity, since T-lymphocytes are necessary both to trigger antibody production by B-lymphocytes and to regulate this process. In particular, T-helpers (CD_4) stimulate formation of antibodies, and T-suppressors (CD_8) suppress this process, and depending on the ratios between these subclasses (CD_4/CD_8), both hyper immune reactions and immunosuppression are possible. Cytotoxic T-lymphocytes (CD_{56}), releasing cytokines, aggravate the tissue damage.

But other leukocytes such as macrophages can trigger severe autoimmune reactions. There is a so-called "macrophage activation syndrome" (MAS) described, or hemophagocytic lymphohistiocytosis (HLH syndrome), when the latter release different active cytokines (IL-6, IL-18, IL-1β, TNF-α, and others), which damage various cells and tissues changing their antigenic structure, making them objects to form autoantibodies [1, 2].

Drug therapy

The most common tactics to treat autoimmune diseases is based on

drug therapy using corticosteroids and cytostatics, which should suppress the activity of both T- and B-lymphocytes; but the formed cytokirnes and autoantibodies, remain in the body and continue their destructive effect on the tissues and target organs. However, such therapy causes a large number of adverse reactions. Corticosteroids lead to Cushing's syndrome associated with hypertension, diabetes and osteoporosis, which will require additional treatment of these essentially iatrogenic diseases. Cytostatics lead to significant metabolic disorders, including healthy organs and systems. Often used in treatment of rheumatoid arthritis and other inflammatory diseases, methotrexate has been found to be toxic to the lungs and drug treatment of common combinations of various systemic diseases and lung fibrosis development is also to be performed with great caution [3].

Intravenous administration of large doses of immunoglobulins is often used, leading to a significant decrease in the content of pathological autoantibodies and inhibitors, and this effect exceeds the life of these immunoglobulins, indicating a more significant regulatory correction of pathological autoimmune processes in the body of the patients. However, this tactics besides its high cost has the risk of viral disease transfer.

In recent years, autoimmune diseases treatment using chimeric monoclonal antibodies to CD_{20}-antigen of B-lymphocytes (rituximab et al.) has become widespread, which should reduce the autoantibodies production [4, 5]. However, there are complications of such treatment up to multiple organ failure [6]. Cetuximab, rituximab, and panitumumab have direct nephrotoxic effect [7]. There are reports about development of interstitial pneumonitis due to rituximab, of atumumab, alemtuzumab therapy when they observe progressive decline in the lung diffusion capacity, including fatal outcome [8-10].

Ipilimumab may cause both acute and chronic demyelinating complications (Guillain-Barre syndrome, myasthenia gravis, polyneuropathy, transverse myelitis, myositis and occlusive colitis), which require plasmapheresis to treat such complications [11, 12]. Eculizumab can lead to severe kidney damage, up to anuria, with hemolytic uremic syndrome [13]. In the long-term period after *rituximab* therapy a patient can develop neutropenia with pneumonia and other infectious complications [14, 15]. Development of male infertility due to both gonadal dysfunction and appearance of antisperm autoantibodies is also described [16].

Selective inhibitors of adhesion molecules, which are represented by natalizumab – a recombinant monoclonal antibody, are also considered promising. However, such treatment has a flip side, which is progressive multifocal leukoencephalopathy development [17-19]. Moreover, in addition to natalizumab this complication is caused by treatment with other drugs based on monoclonal antibodies such as efalizumab, infliximab, adalimumab, etanercept, ibiritumab tiuxetan, bevacizumab, alemtuzumab, cetuximab, and brentuximab [20].

Given the severity of the disease and the difficulty of its treatment, the cost of it is very significant and is more than $34,000 per patient, and taking into account their total number in the US it reaches $6.8 billion. And in view of the approximate life expectancy of these patients, the total cost of their treatment is $2.2 million each [21].

In the most severe cases, a so-called "pulse therapy" is prescribed, when instead of the usual 4-20 mg of corticosteroids a single 1000 mg dose is administered. Of course, a significant inhibition of lymphocytes is achieved – both T-lymphocytes secreting cytokines (TNFa, IL-1-2, etc.) and stimulating B-lymphocytes to produce autoantibodies, and these B-lymphocytes being antibody producers. But the entire body suffers from it.

Apheresis therapy

In most cases, such drug therapy is symptomatic and is aimed at elimination of visible clinical manifestations; hormonal therapy only reduces the autoantibodies production, leaving them in the circulation and target organs "for the rest of life". Apheresis therapy is the only truly pathogenetic therapy, providing removal of autoantibodies, immune complexes and other pathological metabolites from the body. It is best achieved by plasmapheresis. However, it is just removal of autoantibodies and CIC while the cellular immunity is not affected.

In this case extracorporeal itmmunopharmacotherapy can be more valuable, when centrifugation removes plasma and isolate leukocytes, which are incubated at 37^0C for three hours with a minimal dose of corticosteroids (up to 8 mg of dexamethasone), and then returned to the patient intravenously. At the same time, within a small volume each lymphocyte is affected by dozens of times larger dose of corticosteroids (and in some cases of cytostatics) than in pulse therapy with minimal impact on the entire body. That is, there is a "targeted" immunosuppression of only immunocompetent cells, without affecting the whole body. The course of treatment consists of four such procedures performed every other day [22]. And patients in the most severe condition, having fibrosing alveolitis and sarcoidosis, now undergo such extracorporeal immunopharmacotherapy instead of pulse therapy. Its effectiveness is confirmed by a significant reduction in cytokine levels, which persists even after half a year (Table 1)

Table 1: Cytokine levels during and after the course of extracorporeal immunopharmacotherapy (n=59)

Stages	TNF-α picogram/ml	INF-γ picogram/ml	IL-2 picogram/ml
Before treatment	**35.3±3.36**	**103.4±8.45**	**45.6±3.6**
After treatment	**28.2±2.21***	**41.5±3.98***	**40.3±3.6**
In 6 months	**29.85±2.32**	**77.48±5.4***	**42.2±3.7**

• Change from baseline statistically significant ($p<0.05$)

In some cases, such extracorporeal immunotherapy is the most appropriate. We are talking about demyelinating diseases of the nervous system – different types of polyneuropathy, multiple sclerosis and the like. In this case, for some reason, the excited cytotoxic T-lymphocytes (killers), penetrating into the microglia, activate secretion and release of myelotoxic factors with direct damage to myelin [23]. Damage to the shells of the nerve structures contributes to translocation of myelin beyond them, which makes them visible to the immune system. Since myelin has never been in the field of view of the immune system before, it begins to be perceived as an alien protein and B-lymphocytes begin to form antibodies against myelin.

In this case, autoantibodies to myelin are included in the processes of demyelination at later stages of multiple sclerosis development

[24, 25]. Activation of microglial cells also leads to the production of pro-inflammatory cytokines, chemokines, which, in turn, excites lymphocytes. These processes also release TNF-α, nitric oxide and oxygen free radicals, IL-1, IL-12. Cytokines are found in the cerebrospinal fluid. It can be assumed that removal of such inflammation mediators by plasmapheresis should contribute to restoration of the immune cells tolerance to autoantigens [26]. However, such activated lymphocytes will still continue to damage the membranes of the nerve structures with release of myelin. All this requires not only to remove autoantibodies, but also to suppress the lymphocytes activity, which is best achieved by extracorporeal immunopharmacotherapy.

A similar pattern is observed in rheumatoid arthritis, when cytotoxic T-lymphocytes and macrophages penetrate into the synovial membranes of the joints; accumulate there with damage to the antigenic structure of such tissues. T- and B-cells are often formed as lymphoid follicles, forming granulomas with giant cells [27]. Although B-lymphocytes play a secondary role, they also generate highly reactive antibodies [28-30].

Rheumatoid arthritis is a long-term (20 years or more) condition with progressive course and unstable therapeutic effect from non-steroid anti-inflammatory drugs, methotrexate and hormone therapy. It should be noted that methotrexate due to its liver and lung toxicity is fraught with a number of complications. Use of ibuprofen is limited by its gastro- and nephrotoxicity [29, 30].

A number of biologicals are used that inhibit cellular activity. However, tocilizumab (an antagonist of IL-6 receptors) may lead to arterial hypertension with elevated cholesterol and triglyceride levels, respiratory infections, and acute pancreatitis [31]. Anti-TNF-α agents (abatosept, infliximab, adalimumab, etc.) are also effective in rheumatoid arthritis, but this is often combined with dose-related adverse reactions and a high cost of treatment [32-34]. In particular, certolizumab often leads to severe interstitial lesions of the lungs [35, 36].

Their use in combination with plasmapheresis reduces the risk of such complications [37]. Cascade plasmapheresis is also used to significantly reduce the level of rheumatoid factor, C-reactive protein and immunoglobulins [38, 39]. However, to reduce lymphocytes activity with simultaneous removal of antibodies extracorporeal immunopharmacotherapy is also justified [40].

There are no less difficulties in treatment of Crohn's disease and ulcerative colitis. The serum of these patients contains antibodies to antigens of the colon mucosa, as well as anti-neutrophil cytoplasmic antibodies [41]. Leukocytes releasing toxic cytokines play a significant role in the pathogenesis [42, 43]. That is why special methods of adsorption of leukocytes using column Ad column are suggested [44, 45]. It should consider that the cost of one such procedure exceeds €2,000 [46]. However, taking into account the autoimmune nature of the disease, there are indications for plasmapheresis with extracorporeal immunopharmacotherapy, since the isolated removal of lymphocytes only is not accompanied by removal of antibodies and other pathological metabolites.

For more than 20 years in reactions of graft-versus-host disease (GVHD) methods of extracorporeal photopheresis are used, although the mechanisms of its effects are still not clear [47]. At the same time, the isolated leukocytes are saturated with photosensitizers (psoralen) and exposed to ultraviolet radiation and then returned to the patient [48]. The dead T-cells are supposed to activate the antigen-presenting cells [49]. This method is used in T-cell lymphoma and in transplantation of some organs (heart, lungs) [50]. However, the weak point of this technique is the impossibility of simultaneous removal of the accumulated autoantibodies and other pathological metabolites, which makes it defective. The course of such treatment can reach €20,000 [51]. And here it is also advisable to combine plasmapheresis with extracorporeal immunopharmacotherapy performing targeted suppression of lymphocyte activity without killing them, but with simultaneous removal of autoantibodies and other pathological metabolites.

Conclusion

Thus, it is pathogenetically justified to carry out both conventional plasmapheresis with removal of autoantibodies and extracorporeal immunopharmacotherapy, when not only antibodies are removed, but also the activity suppression of the immune system cellular components is more targeted. This does not exclude drug therapy, but in much smaller and less toxic doses. Given chronic and progressive course of many autoimmune diseases, it is advisable to systematically conduct courses of plasmapheresis or extracorporeal immunopharmacotherapy, not waiting for aggravation crises but preventing their occurrence. In the most severe cases it is advisable to conduct one such session once a month.

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