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Therapeutic Apheresis in Transplantology

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Abstract

Background: The problem of organ transplantation is still far from being solved. Until now, to eliminate both acute and chronic rejection, medicines with many side complications are used.

Methods: At the same time, apheresis therapy methods aimed at removing antibodies from the body have not received enough proper and timely application.

Results: Among them plasmapheresis plays the leading role, which can be used to block both acute and chronic rejection of the transplanted organs as well as transplant-against-host reactions, giving less toxic doses of drugs.

Conclusion: The main aim of this work was to find evidence of the need for wider application of apheresis technologies in transplantation.

Keywords: Transplantation; Rejection; Graft-*vs.*-host response; Antibodies; Plasmapheresis

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Introduction

Despite all the achievements of modern transplantology, there is still a problem of acute or chronic rejection of the transplanted organs. These processes have many causes that not always can be eliminated. There is activation of the innate immunity elements against foreign microorganisms and of the antigenic structure disorders control of even their own cells (including the tumor ones) to perform their timely removal and cleansing of the body [1]. Humoral autoimmune mechanisms of antibody formation against the transplanted organ cell antigens are the main cause of graft rejection during the first year of the transplant [2,3]. T- and B-lymphocytes, natural killers, macrophages or polymorphonuclear leukocytes play a crucial role in rejection reactions [4]. At the same time, T-cells (T-killers) can affect the transplanted cells by release of cytokines (TNF-α, IL-2, etc.), contributing to the apoptosis of both their own damaged and foreign cells. On the other hand, they give a signal to the B-cells to form donor-specific autoantibodies [5].

Drug immunosuppression methods

Therefore, the main task after organ transplantation is to suppress these mechanisms of rejection by various immunosuppression methods. At the same time, it is necessary to immediately identify its potential dangers such as activation of microbial, viral, and fungal infection, up to the multiple organ insufficiency, as well as carcinogenesis [6-9]. Post-transplant children may develop lymphoproliferative disorders with high mortality rates [10]. Patients predisposed to coronary heart disease after transplantation may experience activation of atherosclerosis with symptoms of heart failure and even sudden death [11,12]. Therefore, it is necessary to avoid toxic side effects of such drugs. Modern immunosuppressive therapy consists of a combination of several drugs – cyclosporine, azathioprine, prednisolone, and in recent years – rituximab, tacrolimus, and mycophenolate mofetil. However, such treatment is fraught with a number of complications. Glucocorticoids in particular contribute to development Cushingoid syndrome, hypertension, diabetes, and osteoporosis. In addition in 30% of patients they do not prevent the transplant rejection [13]. It should be noted that the incidence of diabetes after transplantation of various organs reaches 40% [14]. Cyclosporine A has a pronounced nephrotoxicity [15,16]. One of the cyclosporin-A side effects is hypertriglyceridemia that develops after transplantation of bone marrow cells, which can be controlled with plasma exchange or double filtration plasmapheresis [17,18]. Azathioprine often causes pancytopenia and interstitial pneumonitis [19,20]. Methotrexate also contributes to development of lymphopenia, infectious and pulmonary complications [21]. Its nephrotoxicity

may lead to acute renal failure [22]. Calcineurin inhibitors (tacrolimus, sirolimus) are also widely used in transplantology but their use is also fraught with serious complications such as thrombotic microangiopathy with development of nephropathy (acute tubular necrosis), cholestasis, encephalopathy (headaches, seizures), and high rate of lymphoproliferative tumors [23-28]. At the same time, the rejection rate remains quite high [29,30]. Tacrolimus may also cause acute demyelinating polyneuropathy of the Guillain-Barré syndrome type [31]. In addition, it also has nephrotoxic and diabetogenic effects, causing apoptosis of β-cells [32-35]. This often negates the results of operations and leads to the most adverse consequences. In these cases, plasmapheresis helps relieve such toxic complications and save the organ [31].

Rituximab (anti-lymphocytic immunoglobulin) is able to stop acute rejection reactions, but it is less effective in chronic forms [36]. In particular, it is far from being the most "magic drug" in recurrence of nephrotic syndrome after kidney transplantation [37]. Its long-term use is associated with increasing endotoxicosis, contributing to neutropenia development followed by septic complications [38], and progressive leukoencephalopathy [39]. The use of mycophenolate mofetil is accompanied by persistent colitis and even colon ulcers [40-42]. The same complications occur with combined use with tacrolimus and mycophenolate mofetil [43]. According to the data of two transplantation centers chronic rejection processes of the transplanted lungs occurs in 60 to 80% of cases. The use of anti-lymphocytic antibodies during transplant rejection episodes is associated with activation of viral infections and lymphoproliferative diseases. In addition, in some cases, a graft-*vs.*-host reaction develops with the same consequences as after stem cell transplantation. In such cases, plasmapheresis enables to treat such complications [44]. Immune conflict after organ transplantation may result from anti-HLA antibodies appeared induced by isoimmunization due to previous transplants, blood transfusions or pregnancy. Despite cross-compatibility with the donor organ, presence of such HLA antibodies leads to early rejection. Growth of donor-specific alloantibodies occurs during the first few weeks [45]. In some cases, affected by natural autoantibodies IgG and IgM isotopes to endothelin-1 and angiotensin II and activation of the complement system and endothelial cells an ultra-acute rejection reaction may develop within the next few hours and even minutes [46]. However, it is to be taken into account that the cost of such drug therapy in acute crises is very high reaching up to $49,000-155,000 [47,48]. Mycophenolate mofetil therapy cost can vary from $638,018 to $752,107 in the course of a year [49].

Research Methodology

Methods of apheresis therapy

In cases of upcoming transplantation, without removing the remaining autoantibodies in the body, the transplanted kidney is at risk of the same autoimmune lesion as the removed one. Recurrence of focal segmental glomerulosclerosis in the transplanted kidney is observed in 30-80% of cases, and the transplant death within three years reaches 90% and only systematic conventional or cascade plasmapheresis after surgery prevents such complications [25,50-60]. A much higher incidence of rejection due to prior IgA nephropathy or focal segmental glomerulosclerosis is noted in cases of "live" kidney transplantation than in "cadaveric" one [61]. Sometimes this requires weekly plasmapheresis for almost four years [62-64]. The rise of hypoproteinemia with prolonged courses of plasma exchange forces to perform immunoadsorption instead [65]. Combination of plasmapheresis with rituximab or bortezomib enabled to achieve a longer remission of proteinuria [66-68]. However, it should be considered that rituximab itself can lead to severe complications, which also have to be treated with plasmapheresis [69,70]. Extracorporeal photopheresis, being quite efficient in cell-mediated rejection of the transplanted lungs and heart, is not applied in renal transplantation [71].

Immunoadsorption prior to transplantation improves outcomes and prognosis, even in cases of early rejection of the transplanted kidneys [72]. However, repeated procedures of plasmapheresis more reliably prevent rejection of the transplanted kidney than high-dose immunoglobulins [55]. High incidence of graft rejection in hemolytic-uremic syndrome also requires a preliminary course of plasmapheresis with eculizumab [73]. Plasmapheresis was necessary after transplantation, too [74]. After transplantation, a new situation arises when an antigenic signal comes from the transplanted kidney, in response to which new antibodies begin to form reaching the peak of acute "rejection crisis" in 1-2 weeks. In this case apheresis therapy can relieve these immune responses associated with lower level of immunosuppressive therapy. The course of plasmapheresis in such cases contributes to restoration of diuresis, reduction of creatinine level and gradual restoration of the graft function, which in 60% of patients enabled to avoid "graftectomy" [75]. Moreover, the transplanted organ, whether kidney, heart, lung, liver or bone marrow, is a constant driver of antibody reproduction during the whole life long, making this process one of the options of autoimmune diseases. Thus, anti-miosin antibodies are often found in case of the transplanted heart rejection [76]. Graft rejection can occur even after 10 years. Alloreactive antibodies are formed against the graft and they are also retained after its rejection, which reduces the chances of survival of the subsequent graft. Cells dysfunction is one of the causes of such resistant alloimmunization or hyperreactivity. In this case, uremia in renal failure plays the leading role even more than T-cell regulation [77]. Significant problems arise when kidney transplantation has to be performed in case of ABO-incompatibility. One of the reasons is the presence of A or B antigens, not only on the erythrocytes membranes, but also on the blood vessels walls, including the transplanted kidney [78]. In this case, the recipient antibodies begin to interact with antigens on the walls of the vessels, leading to microcirculation disorders and subsequent rejection of the transplanted organ ("high incompatibility"). "Low incompatibility" arises in the result of the donor lymphocytes production, being left in the transplanted organ as a kind of "passengers", against the recipient erythrocytes, causing their hemolysis [79]. In these cases, preliminary removal of anti-A or anti-B antibodies by plasma exchange significantly reduces the antibodies level, thereby minimizing the rejection reaction [80-82]. In organ

transplantation in the case of blood incompatibility according to the ABO system cascade plasmapheresis was successfully used [83,84]. At the same time, during 3-4 procedures of cascade plasmapheresis it was possible to reduce the anti-AB antibodies titer to the concentration ratio of 1:32, which is an acceptable criterion for subsequent kidney transplantation in ABO-incompatibility. The same problems with ABO-incompatibility arise in hematopoietic stem cells transplantation in hematology and the course of plasmapheresis before such transplantation to a large extent prevents crises of rejection [85]. In cases of incompatible ABO transplantation of relative's donor organs plasmapheresis is performed to reduce the relevant antibodies titer in ration of 1:2 to 1:4. At the same time in cases of the initial antibodies titer, up to 350-550% of the circulating plasma volume (CRV) has to be removed, and in case of the repeated increase of the antibodies titer up to 1:32 in the post-transplantation period it was necessary to resort to high-volume plasmapheresis with removal of up to 400% of the CPV [86]. Courses of plasmapheresis, both before and after the kidney transplantation in case of AVO-incompatibility, eliminated episodes of hyperactive antibody-dependent graft rejection [87]. Moreover, during the year, the transplanted kidneys were viable in 100% of cases. Positive results were also achieved when using immunoadsorption prior to ABO-incompatible kidney transplantation [88]. However, an increase in blood loss in such operations was observed [89]. More than 30% of potential kidney transplant recipients have a high level of anti-HLA antibodies, which can also be overcome by pre-transplant immunosuppression using plasmapheresis [90]. When it is needed to perform the kidney transplantation on the background of antiphospholipid syndrome, a preventive plasma exchange is also advisable due to the risk of early vascular thrombosis of the transplanted organ [91]. It should be considered that organ transplantation inevitably leads to a number of disorders, the treatment of which should require apheresis therapy. After all, almost all patients who require organ transplantation, by the time of the operation have very significant homeostasis disorders and endotoxicosis due to the organ failure. It's either renal, cardiac, pulmonary, or even multiple organ failure. The donor organ, which has just suffered hypoxia during the period of removal and transportation and before that it has suffered stress and pre-death endotoxicosis of the donor, does not get into the best conditions of the new host's internal environment after the transplantation, which hinders its adequate functioning on the new site. It was noted that content of average molecular weight toxins and malon dialdehyde even before the operation was higher than normal values and it continued to increase during the operation, reaching its maximum in 1 hour after the blood flow started in the transplanted kidney [92]. Therefore, apheresis therapy and detoxification of the recipient in the preoperative period seems relevant, and ideally, of the donor as well before his organ to be removed. It is believed that the graft dysfunction in the early postoperative period is due to hypoxia during preservation, immunological conflict, development of intravascular coagulation and microcirculation disorders in the transplanted organ, fraught with its functional failure [93]. Therefore, in 11 highly sensitized patients with high antibody titer, 30-40% of CPV were eliminated immediately prior to the kidney transplantation and 40-50% of CPV – during re-transplantation (replacement of the removed plasma was carried out by albumin and fresh frozen plasma). In all cases, the graft began to function normally on the operating table with normalization of creatinine and urea levels on the 3rd – 4th days and without rejection crises. If necessary, repeated procedures of plasmapheresis were carried out in different postoperative periods [94]. One of such patients underwent a program plasmapheresis successfully for three years at 4 months intervals [95]. It was found that the level of the main proinflammatory cytokines (IL-6, IL-8, IL-10), toxins of the average molecular weight and lipid peroxidation products increases and reaches maximum by the end of the operation, which was the main indication for intraoperative plasmapheresis immediately after the inclusion of the transplanted kidney in the bloodstream [96]. Besides the reduction of such endotoxins in the blood, restoration of the initial nitrogen and water excretion function of the kidneys occurred much faster - by 5-6 days to compare with 12-18 days in cases without plasmapheresis [97]. Apheresis therapy is also advisable in the postoperative period for sanation of the internal environment from intraoperative stress agents, which should simplify the "inclusion" of the transplanted organ [98,99]. Plasmapheresis in the volume of 1 CPV in the next 2-3 hours after inclusion of the transplanted kidney in the bloodstream reduced the level of average molecules by 25% below the preoperative level, prevented oligoanuria, the need for hemodialysis, contributed to a faster normalization of creatinine and increased actuarial survival of the transplants [100]. Plasmapheresis, performed immediately after the liver transplantation also prevented its dysfunction [101]. The same tactics of intra- and postoperative plasmapheresis was used in the heart transplantation on the background of high antibody and tissue incompatibility [102]. It was possible to stop acute rejection, which occurred 10 days after kidney transplantation, using anti-CD3 mouse monoclonal antibodies in combination with intensive course of plasmapheresis (7 procedures with removal of up to 2.5-3 liters of plasma per procedure) [103]. In type I diabetes, the pancreas transplantation is also often used [104], although this does not always stop the diabetic foot syndrome development with the need for amputations of the lower limbs [105]. Plasmapheresis on the background of immunosuppressive therapy was able to block the rejection reactions after transplantation of the small bowel loops [106]. In case of the liver transplantation on the background of ABO-incompatibility, plasmapheresis was also used before the operation [107,108], as well as both before and after surgery [109]. The same course of plasmapheresis before the liver transplantation is used in the presence of autoantibodies against tissue antigens of the liver [110]. Preoperative administration of rituximab alone (without plasmapheresis) was not able to block the antibodies production [80]. Splenectomy in combination with rituximab is not reported to have positive results, too [111]. Plasmapheresis should be applied as soon as the first signs of organ rejection appear [112,113]. After the liver transplantation, ischemic parenchymal disorders may develop with formation of infarction, which can

also be stopped with help of plasmapheresis courses [114]. In addition, development of cholestatic fibrosing hepatitis is also described, for the relief of which cascade plasmapheresis was used [115]. Since in such autoimmune processes practically the only and truly pathogenetic treatment is the apheresis therapy and among its methods the most effective is plasmapheresis, the principle of periodic courses of plasmapheresis aiming to remove antibodies against the transplanted organ should be introduced in transplantology [116-118]. At the same time, of course, immunosuppressive therapy remains relevant, but plasmapheresis will help to carry it out in subtoxic doses without the risk of side effects. The best effect was achieved by combining courses of plasmapheresis with intravenous administration of immunoglobulins [119]. Reduction of organ dysfunction after the liver transplantation by both conventional plasmapheresis and MARS (molecular adsorbent recirculating system) was equally effective [112].

After the heart transplantation, even in cases where the cause of transplantation was not ischemic heart disease, but dilated cardiomyopathy, immunosuppressive therapy leads to significant disturbance of the blood lipid composition and the occurrence of ischemic disorders in the transplanted heart. Since plasmapheresis is one of the most effective methods of treatment of hyperlipidemic conditions, it was included in the treatment program of 8 patients who underwent orthotopic heart transplantation 2-7 years after the operation. After courses of plasmapheresis, conducted twice a year, there was a pronounced positive dynamics in the state of hemorheology and lipid metabolism. Blood levels of total cholesterol and low-density lipoproteins were significantly reduced without significant changes in the concentration of immunosuppressors. Scintigrams showed significant improvement in myocardial perfusion in the ischemic areas [120]. It is especially important to conduct plasmapheresis to relieve acute crisis of rejection, even with unstable hemodynamics [121]. And it was emphasized that after 7 episodes of rejection in 7 patients treated without plasmapheresis, only 2 survived, and after 11 such episodes in 6 patients with plasmapheresis all of them survived [122]. At Birmingham University (Alabama, USA) plasmapheresis method is considered first-line method to overcome the crises of the heart rejection [123]. Plasmapheresis has been successfully used in crises of rejection of the transplanted heart even in children, starting from the age of 3.5 months [124]. Plasmapheresis was also effective after combined heart and liver transplantation in the presence of donor-specific antibodies [125]. Taking into account HLA-antigen allosensitization development in "candidates" for heart transplantation, it is advisable to carry out plasmapheresis before transplantation [126]. In addition, removal of antibodies with help of plasmapheresis is used during extracorporeal blood circulation during the heart transplantation [127]. Currently, the optimal tactics to prevent graft rejection is considered to be a combination of plasmapheresis with intravenous introduction of immunoglobulins (sometimes with addition of retuximab) [82,128,129]. Along with plasmapheresis, immunoadsorption is also used [118]. Cascade plasmapheresis is also an effective and safe treatment method to relieve the crises of the transplanted organ acute rejection [130]. The lung transplantation has the lowest median survival rate compared to other organs [131]. Therefore, such preventive apheresis therapy is particularly relevant here, especially in cases of allosensitization to HLA-antigens [90]. First, the donor lung, in principle, cannot be "normal", because at the time of death, the donor should develop such endotoxicosis, which can lead to of respiratory distress development in their lungs, and ischemia with hypoxia at the time of the organ removal and its transportation can add additional damage, too. This was shown in the research of the experimental pathology laboratory, Institute of Pulmonology by E.N. Danilov, G.M. Kudryashov and E.D. Shekhunov back in 1980-1990-ies [132]. In addition, as the period of ischemic tissue increases, release of such toxic substances as "large histocompatibility complex" class II, and IL-2 and IFN-γin content increases in the bronchoalveolar lavage fluid, which significantly increases the rejection risk [133].

Secondly, immediately after the transplantation and inclusion in the bloodstream, pathological metabolites of the recipient, who has been in the state of severe respiratory failure for a long time, together with intraoperative BAS overwhelms them. Everything abovementioned also requires detoxification in the earliest postoperative, and maybe even in the intraoperative period [134]. This is especially true in lung transplantation for emergency indications on the background of severe respiratory distress syndrome, when only with help of plasmapheresis it is possible to ensure the normal function of the transplanted lungs [135,136].

The risk of acute rejection of the transplanted lung during the first year is 55% [137]. Even if the transplanted lung avoid the rejection reaction a significant number of patients (up to 60-80%) develop a progressive obliterative bronchiolitis, which is not less difficult to treat [138,139], including in children [140]. The risk of death often forces the patient to resort to repeated lung transplantation [141]. It is detected by reduction of the forced exhalation volume for 1 second to less than 80% compared to the early (basic) post-transplantation period. This syndrome can be considered a kind of chronic rejection reaction. It is characterized by a progressive fibroproliferative process of *lamina propria* of the small bronchi wall with lumen narrowing down to 2 mm with a relatively normal surrounding parenchyma [142]. Conducting plasmapheresis with subsequent administration of immunoglobulins or rituximab can prevent not only the rejection crisis, but also obliterative bronchiolitis [134,137,143,144], including in children [145]. When thrombotic microangiopathy develops, especially with tacrolimus administration or Guillain-barré syndrome, a more intensive course of plasmapheresis is required [28,31,146]. Extracorporeal photopheresis is also used [147]. In some cases, in highly sensitized patients particularly in those with ABO-incompatibility it is advisable to perform preoperative courses of rituximab and plasmapheresis [148,149], although it may pose a risk of infectious complications in the postoperative period [150].

Results

The bone marrow cell transplantation often results in acute or chronic graft-*vs.*-host disease (GVHD) with rate of up to 46% [151]. In acute GVHD, cells and tissues of the body are recognized to be "foreign" for the transplanted donor cells, which contributes to the launch of pathological reactions involving effector T- and B-lymphocytes, natural killer cells with release of a number of proinflammatory cytokines (IL-1β, IL-6, IL-17, IL-18, TNF-α) and this "cytokine cascade" activates other effector cells – natural killers and macrophages, leading to direct tissues damage of the skin, liver, and gastrointestinal tract [152-154]. GVHD plays the leading role in complications and deaths after the bone marrow or stem cell transplantation [155]. The gastrointestinal form of GVHD is the most severe and is the leading cause of death [156,157]. It is especially severe in children when the mortality rate reaches 60% [158]. The liver damage appears to be rather common consequence caused by veno-occlusive liver disease, chronic viral or fungal infection, and cholestatic disorders [159,160]. In GVHD acute lung damage develops in the form of severe respiratory distress syndrome showing 28-day mortality of 46.6% of patients, and by the end of the year it reaches 66.9% [161]. It is aggravated by activation of viral-bacterial and fungal infection associated with leukopenia [162]. However, GVHD can develop after transplantation of solid organs and it is rather severe in such cases with fatal outcome. In particular, it occurs after the liver transplantation, when after interaction of the donor T-lymphocytes with cellular antigens of the patient (recipient), they proliferate and clonally expand leading to the liver, skin, bowels, bone marrow lesions and subsequent development of sepsis, multiple organ failure with fatal outcome [163]. All this are indications for plasmapheresis and we are convinced of its effectiveness in the treatment of GVHD [164,165]. It should be noted that chronic GVHD can develop in 50% of such patients with mortality up to 25% [166], which once again emphasizes the urgency of this problem and the need for more active treatment involving plasmapheresis.

Discussion

A frequent complication of stem cell transplantation is thrombotic microangiopathy associated with intima edema and fibrinoid necrosis of the vascular walls. This is due to high doses of conventional chemotherapy drugs, radiation therapy, calcineurin inhibitors (used for prevention and treatment of GVHD) and infection [167,168]. The kidneys are primarily affected and the renal insufficiency appears to be a poor prognostic factor with 44-90% mortality rate [169,170]. Plasma exchange, carried out daily until the positive effect appers, can control this complication [164,171,172]. In case of the lungs lesions ECMO may be required [173,174]. However, attempts are also made to directly suppress T- and B- lymphocytes hyperactivity (producers of cytokines and antibodies), with help of extracorporeal photopheresis, when irradiation of the isolated cells with ultraviolet rays is carried out [175]. After ingestion of methoxalen - photosensitizer drug in a dose of 1 mg/kg to achieve the blood plasma concentration of more than 50 mg/DL, 90 minutes later leukopheresis is performed with extracorporeal irradiation of thin layer of white blood cells with long-wave ultraviolet rays followed by subsequent reinfusion of these cells in apoptosis state. The latter are photoactive and covalently bind to pyridine bases of leukocyte molecules of the membrane and cytoplasm, which leads to their lethal damage. These cells then reinfused to the patient and die within 1-2 weeks, but during this interval they stimulate autosuppression reaction, partly directed against T-cells, but also damaging the non-irradiated clones of T-cells. This method made it possible to reduce the frequency of both rejection crises and infectious complications [176]. Although such procedures have been successfully carried out for more than 20 years, the mechanisms of their therapeutic effect are still not fully understood [177,178]. Of course, it would be tempting to affect this way the specific T-cells that damage the graft, but such a reaction is not selective and possible lethal damage due to ultraviolet irradiation of other lymphocytes clones can lead to the most unpredictable consequences for the body as a whole. Besides, photopheresis does not remove the formed autoantibodies, which makes this procedure incomplete, since the remaining autoantibodies continue their damaging effect on the tissues and organs of the patient. That's why plasmapheresis was successfully performed weekly before each photopheresis procedure [179-182]. And we also think photopheresis and plasmapheresis to be the most appropriate combination.

Conclusion

The problem of organ transplantation is still far from being solved. Until now, to eliminate both acute and chronic rejection of the transplanted organs they use drugs with many side effects. At the same time, apheresis therapy methods, aimed at removing antibodies from the body, have not received enough proper and timely application. Indications to remove pathological agents that caused organ damage arise even in the preoperative period. It is advisable to use them even in the intraoperative period and immediately after the transplantation for faster and optimal restoration of the transplanted organs functions. The simplest and safest method of apheresis therapy is plasmapheresis, which removes gradually formed autoantibodies. Performing it regularly enables to prevent rejection crises, using drugs in less toxic doses. Russian equipment with "Rosa" or "PFM-500" plasma filters allows conducting membrane plasmapheresis even in outpatient settings.

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