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Immunosuppression in the past and today

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This article deals with evaluation of immunosuppressive drugs, the mechanism of their action and clinical application. The immune response to foreign tissue/organ is reminded. The classification of immunosuppressants based on their chemical structure described by P. Halloran in 2004 is presented. Peculiarities of the effects of immunosuppressive drugs on the immune system, their side-effects and toxicity, clinical application and differences among several immunosuppressive agents are discussed. Immunosuppression protocols more frequently used in clinical practice are mentioned. According to literature data and experience of Vilnius University Transplant Center we suggest that conventional immunosuppressants ought to have to be tailored in the following situations: 1) when the immunological risk of graft rejection is high; 2) graft quality is suboptimal; 3) nonimmunological risk for the recipient due to the toxicity of immunosuppressants in presence concomitant diseases (diabetes, cardiovascular diseases, etc.). So, standard immunosuppression must be tailored according to the clinical situation and resources of immunosuppressive drugs.

Key words: organ/tissue transplantation, immune response, immunosuppressive therapy, classification of immunosuppressive drugs

The first experimental transplantation of a kidney between dogs was performed in Vienna in 1902 by E. Ullmann. Ten years later Alexis Carrel developed the basic surgical techniques used to join the vessels, and the technical problems of transplantation were essentially solved (1). For this work he was awarded the Nobel Prize in 1912. But this surgical success in vascular anastomoses was thwarted by loss of the graft due to rejection. According to A. Carrel's words (1914) in his prescient lecture, until some method has been developed to prevent the reaction of the organism against the foreign tissue there would be no clinical application of organ transplantation (2). The first transplantation between humans was performed in Kiev by Voronoy (3, 4). This serious clinical attempt was technically successful, but the graft failed because of immunological reasons. In the period from the first human transplant to the time of the first successful allotransplantation between identical twins in Boston by Murray and Merrill in 1954 (5, 6), the immunological basis of events involved in kidney rejection was unknown. Any understanding of rejection and immunosuppression was rudimentary.

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An important milestone was Medawar?'s work on transplantation immunology. Medawar expressed a keen interest in the behaviour of skin homografts and how they were rejected (7, 8). Brent, Gorer, Medawar and many other workers, basing their studies primarily on the rejection of skin grafts in inbred mice, demonstrated by the mid 1940s that rejection was an immunologic response to genetically incompatible tissue (9). After many systematic experimental studies of skin grafts in rabbits the alloimmune response has proven to be a complex of the various immunologic mechanisms responsible for allograft rejection. Allografts can be damaged by immunologically specific cellular and humoral mechanisms and also by various nonspecific inflammatory mechanisms (10, 11).

So, a logical question was: Why not to protect the organ allograft by weakening the immune system? Subsequent progress focused largely on improvements in immunosuppression. Total body irradiation was used by Hamburger in Paris and Murray in Boston in 1959 with nonidentical twin transplants (12). By the early 1960s, it was clear that total-body irradiation was not the solution (13). During the same year Schwartz and Dameschek showed that 6mercaptopurine (6-MP) caused a dose-related delay of skin graft rejection in rabbits (14). In 1961 Calne, in

an extensive series of dog experiments, demonstrated that azathioprine, an analog of 6-MP, was effective and less toxic (15). Zukocki reported the use of large doses of corticosteroids to extend the survival of canine renal allografts in 1963 (2). Between 1963 and 1979, a significant advance in clinical immunosuppression was the introduction of heterologous antilymphocyte globulin (ALG) (16). Waksman and Woodruff experimented with a potent biological immunosuppressant, antilymphocyte serum, and in 1967 Starlz reported the first clinical application (3). In 1972, Turcotte and Feduska introduced "pulse" therapy, that is, the intermittent intravenous administration of pharmacologic doses of steroids as a potentially less toxic and more convenient method of reversing rejection. During the 1960s many other clinical and basic scientists made important contributions to improvements in renal transplantation. One of them was Terasaki's report of his microlymphocytotoxicity method in 1964 (17). This method was immediately introduced in a lymphocytotoxic crossmatch test. Terasaki's investigations began with a retrospective study of the influence of HLA matching on the quality of outcome in patients with long-surviving kidney allografts, followed by a prospective trial in live donor kidney recipients treated with azathioprine and prednisolone, with or without adjunct ALG (18).

Thus, the so-called azathioprine era lasted until the early 1980s and spawned early efforts at liver, heart, and pancreas transplantation. However, kidney graft survival at one year remained to be about 60%.

The situation was transformed in the early 1980s with the introduction of cyclosporine. The discovery by Borel et al. of the drug cyclosporine A (CsA) in 1976 was to prove the next major advance in transplantation (19). The introduction of CsA into clinical practice opened the modern era, so-called cyclosporine era of transplantation (20). The early multicentre studies of CsA in kidney transplantation showed that it was capable of reducing acute allograft rejection and resulted in a 1-year graft survival 10 to 20% better than in patients immunosuppressed with azathioprine and steroids alone (21). The introduction of cyclosporine as the first "second generation" selective immunosuppressive agent was an important break-through, and its results dramatically improved kidney transplantation (22, 23). Biological agents, monoclonal and polyclonal antibodies which can be used for induction of immunosuppression and for the treatment of acute rejection, mark the dawn of a new era in transplantation. In 1985, OKT3, the first monoclonal antibody directed against T lymphocytes was introduced in clinical medicine, based on its capacity to treat first rejection episodes (24, 25). Since then, many other monoclonal antibodies against lymphocyte targets have been developed, but only those directed at the interleukin-2 receptor are in widespread use (26).

Immunosuppressive drugs exert a triple effect: they suppress rejection, undesired consequences of immunodeficiency (infection or cancer), and nonimmune toxicity to other tissues. The central issue in organ transplantation remains suppression of allograft rejection. Today our powerful battery of immunosuppressive agents allows us to treat successfully most of acute rejection episodes. Strategies to achieve this goal depend upon a thorough knowledge of basic immunologic principles and understanding of the immunological events involved in the immune response. It helps us to show how medications act.

Thus, let us briefly remind about alloimmune response. Lymphoid cells recognize antigens and participate in cell interactions through a wide variety of membrane receptors, all of which are attractive targets for immunosuppressive agents. Alloimmune responses involve naive and memory lymphocytes. In the graft and the surrounding tissues, dendritic cells of donor and host origin become activated and move to T-cell areas of secondary lymphoid organs. An antigen on the surface of dendritic cells, which triggers [with] cognate T-cell receptors, constitutes "signal 1" transduced through the CD3 complex. Dendritic cells provide costimulation, or "signal 2" delivered when CD80 and CD86 on the surface on dendritic cells engage CD28 on T cells. Signal 1 and signal 2 activate three signal transduction pathways: the calcium–calcineurin pathway, the RAS-mitogen-activated protein (MAP) kinase pathway, and the nuclear factor-kB pathway. These events induce the T cell to express CD40 ligand and many new molecules, including interleukin-2, CD154, and CD25. Interleukin-2 and other cytokines activate the "target of rapamycin" pathway to provide "signal 3," the trigger for cell proliferation. The interaction of CD40 and its ligand stimulates the B cell to become sensitive to the cytokines produced by the T cell. The B cell now undergoes clonal expansion and proliferation and produces an antibody for secretion. The graft is infiltrated by effector T cells, activated macrophages, B cells, and plasma cells, and increased chemokine expression, altered capillary permeability and extracellular matrix, and deterioration of parenchymal function becomes apparent. Thus, immunosuppression can be achieved by depleting lymphocytes, diverting their traffic, or blocking lymphocyte response pathways (2, 27, 28).

Classification of immunosuppressive drugs presented by F. Halloran in 2004 is based on the mechanism of action (2).

Corticosteroids

Small-molecule drugs

Immunophilin-binding drugs:

Calcineurin inhibitors: cyclophilin-binding drug Cyclosporine, FKBP12-binding drugs-Tacrolimus

Target-of-rapamycin inhibitors: sirolimus, everolimus

Inhibitors of nucleotide synthesis

Purine synthesis (IMPDH) inhibitors:
mycophenolate mofetil
enteric-coated mycophenolic acid
mizoribine

Pyrimidine synthesis (DHODH) inhibitors:
leflunomide
brequinar sodium

Antimetabolites: azathioprine

Sphingosine-1-phosphate-receptor antagonists: FTY720

Protein drugs

Depleting antibodies (*against T cells, B cells, or both*)

Polyclonal antibody: horse or rabbit antithymocyte globulin (ALG, ATG)

Mouse monoclonal anti-CD3 antibody (muromonab-CD3)

Humanized monoclonal anti-CD52 antibody (alemtuzumab)

B-cell depleting monoclonal anti-CD20 antibody (rituximab)

Nondepleting antibodies and fusion proteins

Humanized or chimeric monoclonal anti-CD25 antibody (daclizumab, basiliximab)

Fusion protein with natural binding properties: CTLA-4-Ig

Intravenous immune globulin.

There are two broad classifications of immunoeuppressive agents: induction/anti-rejection agents and maintenance immunotherapy agents. Induction therapy is used in conjunction with maintenance agents for the purpose of minimizing the risk of early rejection episodes. Induction therapy is most often applied to recipients with "high risk" for rejection. For long-term immunosuppression, the majority of kidney recipients receive a combination of corticosteroids, a calcineurin inhibitor, and an antimetabolite.

Corticosteroids act by blocking cytokine gene transcription in and cytokine secretion from mononuclear phagocytes. Inhibition of IL-1, IL-2, IL-3, IL-6 and tumor necrosis factor (TNF) alpha, and gamma-interferon synthesis by corticosteroids has been demonstrated *in vitro* and *in vivo*. As a result, all stages of the T-cell activation process are inhibited. The diffuse effects of corticosteroids on the body reflect the fact that most mammalian tissues have glucocorticoid receptors within the cell cytoplasm and can serve as targets for the effects of corticosteroids (29). However, the use of steroids is associated with side-effects. The most important complications are cosmetic changes, hypertension, hyperlipidemia, glucose intolerance, impaired wound healing and resistance to infection, osteoporosis, obesity, hirsutism, acne, peptic ulceration, cataracts. Thus, the use steroid-free maintenance immunosuppression is a promising option that probably can be taken in a large fraction of patients (30, 31). The strategy of steroid withdrawal may be more successful today, because new and more potent drugs are now available for maintenance immunosuppressive therapy.

The calcineurin inhibitors differ from their predecessor immunosuppressive drugs by their selective inhibition of the immune response (32). They do not inhibit neutrophils' phagocytic activity as corticosteroids do, and they aren't myelosuppressive as azathioprine is. The introduction of *cyclosporine* (CsA) for immunosuppression has resulted in a striking decline of the early post-transplant rejection rate (33). With cyclosporine-based immunosuppression, one can currently expect a 1-year function rate of approximately 85% for primary cadaver kidney transplant (34). This drug is a cyclic peptide found as a natural metabolite in a species of fungus. CsA binds with high affinity to a ubiquitous small molecular size cellular protein called cyclophilin. The CsA–cyclophilin complex binds to the calcineurin–calmodulin complex and inhibits the phosphorylation of the cytoplasmic subunit of the NF-AT transcription factor which is required for transcription of the IL-2 gene and probably other "early" T cell activation genes. It is therefore a calcineurin inhibitor. Regardless of its precise mechanism of action, the consequence of CsA treatment is a profound inhibition of cell-mediated immunity. In the absence of adequate IL-2 and other cytokines, T cells fail to mount an effective immune response. IL-2 is essential for T cell growth and contributes to CTL differentiation. Consequently, the drug is highly lymphocyte- and particularly T-cell-specific. CsA is a widely used potent and selective immunosuppressant, and is usually prescribed in combination with steroids and azathioprine or mycophenolate mofetil (triple therapy). Nevertheless, CsA is not a panacea for transplantation, and it is not an ideal drug. This drug is regarded as a drug with a narrow therapeutic index, and the standards for proving the bioequivalence of generic forms need to be rigorous. The adverse effects of CsA, which are related to the concentration of the drug, include nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and tremor. Recent developments include monitoring of the peak cyclosporine levels two hours after administration to better reflect exposure to the drug. Cyclosporine therapy is associated with increased incidence of cholelithiasis. CsA enhances the expression of TGF-beta, which also inhibits IL-2 and the generation of cytotoxic T lymphocytes and may be responsible for the development of interstitial fibrosis, an important feature of calcineurin inhibitor nephrotoxicity (35–37). CsA can also induce the hemolytic-uremic syndrome and post-transplantation diabetes mellitus (38). An alternative to CsA therapy is FK506 (tacrolimus).

Tacrolimus is a macrolide molecule that binds to FKBP-12, and the complex inhibits the enzyme calcineurin, with blocking the transcription of IL-2 gene in T lymphocytes (39–41). Recent analyses suggest that in the current dosing strategy, the efficacy of CsA is similar to that of tacrolimus. FK506 is active at lower concentrations than CsA and may be less toxic: it is less likely to cause hyperlipidemia, hypertension, and cosmetic problems, and more likely to induce post-transplantation diabetes. FK monotherapy demonstrated its capacity to reverse steroid-resistant allograft rejection and this is the main difference between FK and CsA. This drug is widely used in heat and liver transplantation (42).

Mycophenolat mofetil (MMF) is an antiproliferative drug that inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), a key step in *de novo* pathway of purine synthesis (43, 44). It differs from azathioprine by its selective effect on lymphocytes. In contrast to the effects of azathioprine, MMF selectively interrupts synthesis of DNA, it inhibits just a single enzyme non-competitively (in contrast to azathioprine which inhibits many enzymes). Thus, it might be expected to be less mutagenic to DNA. Both T and B lymphocytes rely on the *de novo* pathway, and MMF is therefore equally effective against B cells as T cells. Thus, it inhibits both cell-mediated immunity and humoral immunity. Numerous clinical studies showed that MMF was more effective than azathioprine in preventing acute rejection in recipients of cadaver kidney transplants when used in combination with cyclosporine and prednisone (45). MMF may also exert a preventive effect on the development and progression of proliferate arteriolopathy, a critical pathologic lesion in chronic rejection (46). The drug has largely replaced azathioprine and is widely used, because it is effective in combination with many other agents, simple to use without monitoring, and free from organ toxicity and cardiovascular risk. The most common adverse events are related to the gastrointestinal tract, with diarrhea occurring in up to one third of patients and varying degrees of nausea, bloating dyspepsia, and vomiting in up to 20% Most of these symptoms respond promptly to transient reduction of drug dosage.

Mizoribine (*Bredinin*) is an antimetabolite, and like both azathioprine and mycophenolate mofetil is an inhibitor of purine metabolism (47). Its biological action is rather similar to the action to MMF although it is less lymphocyte-elective (48). Mizoribine has been known for many years, but its use in human transplantation is somewhat limited. The majority of the clinical studies have been undertaken in Japan (49).

Brequinar sodium (*BQR*) is one of the unique immunosuppressives, being the only agent that is an antiproliferatively active against pyrimidine nucleotides. The drug is active against both T and B cells and may have a particular role in the situation of high antibody levels (highly sensitized patients and xenotransplantation) (50, 51). Toxic effects included severe ulcerative mucositis, dermatitis, nausea, vomiting, anorexia, diarrhea and thrombocytopenia.

Leflunomide (*LFM*) acts through the inhibition of dihydroorotate dehydrogenase (DHODH) and like brequinar it inhibits the synthesis of pyrimidine nucleotides (52). As a consequence of its site of action, leflunomide has been shown to reverse experimental ongoing acute allograft rejection some days after it has started (53). The main side-effects are gastrointestinal, allergic skin reactions, and rarely hepatic dysfunction.

Rapamycin (*Sirolimus*) is the most recent antirejection drug. Like CsA and tacrolimus it is a fungal product. It binds to the immunophilin, FKBP-12, and inhibits the mammalian target of rapamycin molecule (mTOR) implicated in the proliferation induced by different interleukins (IL-2, IL-4, IL-7, IL-15). Although the immunophilin of sirolimus is the same as tacrolimus, sirolimus exerts its immunosuppressive effects via a different pathway (54). Through TOR inhibition, sirolimus blocks the postreceptor IL-2 signals that mediate T-cell proliferation, a key immune response to foreign tissue. This prevents cell cycle progression from G_1 to S phase. However, sirolimus does not block the IL-2 signals that lead to T-cell apoptosis (55), it promotes apoptosis and improves graft tolerance. Sirolimus has no effect on calcineurin; no effect on kidney function or blood pressure has been reported in experimental animals or humans. Sirolimus has two possible advantages. First, unlike CsA and tacrolimus, it is non-nephrotoxic in humans, although work in experimental animals suggests that it might enhance cyclosporine nephrotoxicity (56, 57). Secondly, sirolimus inhibits growth-factor-triggered proliferation of smooth muscle cells, endothelial cells, and fibroblasts. Sirolimus may also afford protection against chronic rejection by blocking proliferation of vascular endothelium. The major side-effects of sirolimus are thrombocytopenia and hyperlipidemia, both are dose-dependent and can be controlled by reducing the dose or adding lipid-lowering agents.

Biologic immunosuppressive agents can be used for induction immunosuppression and for the treatment of acute rejection; they are not used for maintenance immunosuppression. Induction therapy refers to the blocking of molecules involved in transplant immunity by an antibody or a soluble receptor during the peritransplant period. The critical biological event that characterizes the immediate post-transplant period is the increased expression of adhesion and co-stimulatory molecules, such as selectins, ICAMs, VCAMs and B7, throughout the graft as a consequence of the ischemia/reperfusion injury. This may have two deleterious consequences. First, adhesion molecules are able to recruit and activate polymorphonuclear cells, a

process which contributes to the development of delayed graft function. Second, the inflamed allograft may also promote the early migration and activation of alloreactive T cells, which may trigger acute rejection (58, 59). The possible actions of monoclonal antibodies or soluble receptor molecules are: (i) to maximally inhibit T cells during the initial weeks after transplantation, when the graft is most immunogenic; (ii) to target the adhesion molecules involved in the pathogenesis of delayed graft function; (iii) to help to achieve transplantation tolerance through the blockade of T-cell co-stimulation (60–64).

Polyclonal antithymocyte globulin (ATG, ATGAM) is produced by immunizing horses or rabbits with human lymphoid cells, harvesting the IgG, and absorbing out toxic antibodies (*e.g.*, those against platelets and erythrocytes). Currently, there are four different preparations in use: the horse ALG Lymphoglobulin produced by Pasteur-Merieux, the horse ATG, ATGAM from Pharmacia & Upjohn, the rabbit ATG Thymoglobulin marketed by IMTX/Sangstat, and the ATG Fresenius is a rabbit anti-human T-cell antibody raised against the Jurkatt cell line. In addition to immunodeficiency complications, toxic effects of polyclonal antithymocyte globulin include thrombocytopenia, the cytokine-release syndrome, and occasional serum sickness or allergic reactions. Muromonab-CD3, a mouse monoclonal antibody against CD3, binds to T-cell-receptor-associated complex and triggers a massive cytokine-release syndrome before both depleting and functionally altering T cells. Prolonged courses of muromonab-CD3 increase the risk of post-transplantation lymphoproliferative disease (65).

Rituximab, an anti-CD20 monoclonal antibody, eliminates most of B cells and is approved for treatment of refractory non-Hodgkin's B cell lymphomas, including some post-transplantation lymphoproliferative disease in transplant recipients. Rituximab is used in combination with maintenance immunosuppressive drugs, plasmapheresis and intravenous immune globulin to suppress deleterious alloantibody responses in transplant recipients (66).

The anti-CD25 monoclonal antibodies daclizumab (Zenapax) and basiliximab (Simulect) are widely used in transplantation for induction in patients who are at low-to-moderate risk of rejection (67, 68). Both antibodies target the α chain of the trimeric IL-2R complex present only on activated T cells. Therefore, in contrast to OKT3/ATG Abs, anti-IL2R Abs should block only activated T cells, such as those engaged in the alloreactive response. A similar 35% reduction in the renal rejection rates at six months was observed with both antibodies in patients that received CsA-Neoral as primary immunosuppression (69–77). Because expression of CD25 requires T-cell activation, anti-CD25 antibody causes little depletion of T cells. Both drugs are remarkable for the absence of significant side effects. Their largely human origin accounts for the absence of anaphylaxis or a first-dose reaction.

A wide range of immunosuppressants are becoming available, and the challenge facing the transplant community is to introduce the drugs in a manner which will improve short- and long-term results without incurring the side-effects of overimmunosuppression (78). Infection, cancer, cardiovascular diseases are the leading causes of patient's death in the late posttransplantation period, and immunosuppression plays a major role in the pathogenesis of each of these complications (79–81). Each immunosuppressive agent has both immune and nonimmune toxicity. Immune toxicity is the result of the total amount of all immunosuppression over a given period of time and is usually nonspecific. Immunodeficiency leads to infections. Viral infections are the major problem in allograft recipients, particularly one to six months after transplantation. Cytomegalovirus (CMV) infection is the most frequent viral infection affecting transplant recipients; more than 50% of seronegative and about 10% of seropositive transplant patients may develop a symptomatic CMV disease (80). Within the first month after Tx, the risk of infection follows the surgical complexity of the transplantation procedure. About 80% of infections in kidney transplant recipients are bacterial: urinary tract infection, superficial or deep wound infections, primary bacteremia, pneumonia, vascular catheter and site infections. Thus, the introduction of newer immunosuppressive agents, more selective drugs with a better therapeutic index reduces the need for powerful aggressive immunosuppression to treat acute rejection, and reduce the rates of infection and cancer. The major nonimmune toxic effects are nephrotoxicity, hypertension, hyperlipidemia, diabetes mellitus, and anemia. For example, posttransplantation diabetes mellitus develops after three years in 24% of patients who have undergone kidney transplantation (38). The toxic effect of calcineurin inhibitors is an important contributor to the problem of graft failure (36). The availability of multiple immunosuppressive agents has stimulated attempts to minimize or avoid the most toxic components of the standard protocol. Several studies have shown that it may be possible to withdraw these drugs or reduce their dose in some stable patients (30, 31).

Current immunosuppressive drugs, although the best option available, are far from being ideal agents. The ideal therapy for the prevention of graft rejection would be short-term one to achieve life-long tolerance without incurring side effects or diminishing immunocompetence to infectious agents. Tolerance is defined as a state where there is no rejection of a foreign graft even in the absence of immunosuppression. There have been a number of strategies advanced to promote the induction of tolerance in human transplantation; however, the mechanisms of tolerance continue to be the subject of much debate

and many theories. Induction of immunological tolerance by intensive manipulation of recipient immunity during the very early weeks after Tx remains the ultimate goal (82–85). Despite the development of tolerance, the refusal of immunosuppression leads to graft loss. Unfortunately, most patients will reject their grafts if immunosuppression is completely withdrawn. For example, according to investigators from the University of Alabama, 35% of all graft losses after the first six months were thought to be due to noncompliance. Thus, noncompliance was suspected to be the major cause of late graft failure and should be considered as a relative contraindication in selecting a recipient for transplantation.

The ideal immunosuppressive therapy does not exist. However, modulation of existing regimens is necessary. An immunosuppressant must be tailored if: 1) the immunological risk is high (responder, young age of recipient, presensitization, retransplantation, low degree of histocompatibility), 2) the quality of the graft is suboptimal (donor age >50, the cause of his death is cardiovascular disease, cold ischemia time >20 h), 3) there is a non-immunological risk due to other diseases (diabetes mellitus, cardiovascular disease, etc.). It is necessary to take into account the toxicity of immunosuppressive drugs when the recipient's damaged organs are targets to toxicity (86, 87). There are many protocols and algorithms of immunosuppression therapy, but immunosuppression should be individualized.

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Tatjana Rainienë

IMUNOSUPRESIJA PRAEITYJE IR DABAR

Santrauka

Straipsnyje apþvelgiama transplantologijos ir imunosupresantø sukûrimo bei klinikinio pritaikymo raida. Trumpai aprašomas imuninio atsako á svetimà audiná/organà mechanizmas. Pateikiama visø klinikoje vartojamø imunosupresantø klasifikacija (pagal P. Halloran, 2004), paremta vaisto chemine struktûra. Aprašomas jø veikimo mechanizmas: imunosupresinis poveikis transplantatui, poveikis imuninei sistemai atsakant á infekcijà bei toksinis poveikis tam tikriems organams/sistemoms, vadinamiesiems taikiniams. Paminëti daþniausiai klinikinëje transplantacijoje vartojami imunosupresiniø vaistø deriniai. Palyginami imunosupresantø poveikio mechanizmai ir jø efektyvumas klinikai. Remdamiesi literatûra bei Vilniaus transplantacijos centro patirtimi manome, kad esami vaistø vartojimo algoritmai turëtø bûti modifikuojami, ypaè tais atvejais, kai: 1) didelë transplantato atmetimo grësmë (recipientas responderis, recipientas jaunas, presensitizuotas, pakartotinai transplantuojamas, bloga recipiento ir donoro audiniø dermë), 2) bloga transplantato kokybë (donoras vyresnis nei 50 metø, mirties prieþastis – ðirdies ir smegenø kraujagysliø ligos, ðaltosios iðemijos trukmë – daugiau nei 20 val.), 3) neimunologinë rizika dël kitø recipiento ligø (diabeto, ðirdies kraujagysliø patologijos ir t. t.) Bûtina ávertinti taikomø imunosupresantø poveiká pakenktiems recipiento organams. Taigi standartizuotà imunosupresijos terapijà bûtina individualizuoti pagal klinikinæ situacijà bei turimus resursus.

Raktaþodþiai: audiniø / organø transplantacija, imuninis atsakas, imunosupresinë terapija, imunosupresiniø vaistø klasifikacija