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IMMUNOSENESCENCE AS A REASON FOR INDIVIDUALIZED IMMUNOSUPPRESSIVE THERAPY IN KIDNEY TRANSPLANTATION

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Transplantation in elderly patients is obviously more challenging due to existing underlying diseases, changes in pharmacokinetics of immunosuppressive drugs, polypragmasy, and transformation of immunoreactivity (immunosenescence). Our review presents data on modification of adaptive and innate immunity during aging. It also considers the possibility of both reduced and adapted immunosuppressive therapy in elderly renal transplant recipients in achieving an optimal balance between efficacy and complications.

Keywords: kidney transplantation, aging, immunosenescence, immunosuppression therapy.

INTRODUCTION

Kidney transplantation (KTx) remains the optimal treatment method for renal replacement therapy (RRT), providing the best patient survival [1].

Immediate and long-term transplant outcomes depend on several factors related to age, underlying disease, duration of dialysis, infections, duration of graft function and the cause of loss of first graft (for repeat transplantation), presence of preexisting antibodies, type and quality of donor organ, and co-existing diseases [2–5]. Some of these factors have a direct impact on the recipient's immune system prior to transplantation.

For example, it is known that young people under the age of 30 have a more reactive immunity; then, the T cell-mediated immunity suffers most of all with age. This is primarily associated with age-related thymic involution, starting from 15–20 years, and accompanied by a decrease in its mass, weakening of its function and synthesis of regulatory factors. This leads to a natural progressive suppression of this thymus-dependent immunity. The ratio of regulatory lymphocyte subpopulations changes against the background of general lymphopenia. Humoral immunity also undergoes negative changes: in the elderly there is a drop in normal antibodies, including isohemagglutinins, which should be taken into account when determining the blood group and organ transplantation in the elderly [6, 7].

Over the past decades, the number of elderly people has increased significantly and is expected to grow even more from 8% of the total world population in 2015 to 16% in 2050 [8]. Moreover, the fastest growing age group of recipients is patients over 65 years of age [9]. For example, in the United States, the number of operations on patients over 65 years of age increased from 17% to 33.3% of the total number of kidney transplants between 2012 and 2018 [10]. In Australia, 14% of kidney transplants performed in 2015 were in patients aged 65 years or older [11]. The 2012 European Kidney Transplant Registry report indicated that the prevalence of transplants was 22% in the age group over 65 years and 20% in the age group over 75 [12].

There is no age distribution of recipients in the Registry of the Russian Transplant Society; only data on kidney transplantation in minors are reported separately [13]. According to data from Sklifosovsky Research Institute of Emergency Care, the proportion of patients over 60 years of age on the kidney transplant waitlist is 9–13% of the total number of potential recipients, which is somewhat lower than in Europe and the United States [14].

This increase in the frequency of kidney transplantation in the elderly can be explained by the aging population, improved transplant outcomes, and introduction of expanded kidney donor criteria [15, 16]. However, transplantation in elderly recipients is obviously more challenging due to existing comorbidities, changes in the pharmacokinetics of immunosuppressive drugs, polypragmasy and transformation of immunoreactivity (immunosenescence).

Despite this, studies show that kidney transplantation in elderly patients is associated with reduced mortality compared to dialysis [9, 17]. Elderly recipients have a lower risk of acute rejection due to decreased immune reactivity, but they are the most likely age group to die with a functioning graft [18]. While the short-term outcomes in elderly transplant recipients are similar to those in younger recipients, the long-term graft survival and survival of elderly recipients is inferior to that of younger recipients. The most common causes of death in elderly

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recipients are infection, malignancy, and cardiovascular disease, each of which can be partially attributed to immunosuppressive agents [19–21].

Clearly, multifaceted modifications of adaptive and innate immunity with aging can justify both reduced and adapted immunosuppressive therapy in elderly kidney transplant recipients to achieve an optimal balance between efficacy and toxicity. By minimizing side effects, an individualized strategy can provide the optimal level of immunosuppression for elderly transplant recipients to minimize or prevent infections, malignancies and chronic kidney disease, as well as cardiovascular complications related to diabetes, hypertension and hyperlipidemia [22, 23].

The study of indicators such as cytokine production, lymphocyte proliferation or activation antigen expression on T cells as biomarkers can be used to monitor and evaluate immune system activity, since for some of them there is a statistically significant association with the frequency of acute rejection or immunosuppressant toxicity, and this is an obvious unmet clinical need [24].

IMMUNOSENESCENCE AND ORGAN TRANSPLANTATION

Immunosenescence (immune aging or deterioration of the immune system, derived from the Latin term senescere, meaning "to grow old") is a gradual suppression of immune reactivity in the elderly due to a decrease in the number of naive T lymphocytes, accumulation of memory T cells and changes in B cells, causing a reduced antibody response [18]. Immune aging is characterized by impaired function of both adaptive and innate immunity and can affect all immunological components and cause a shift in both regulation and function of the entire immune system [25, 26]. Obviously, the mechanisms underlying transplant rejection differ in young and elderly transplant recipients, and clinical outcomes in elderly recipients should be accompanied by individualization of immunosuppression [27].

Immunosenescence is a complex and continuous remodeling of certain cell subpopulations, rather than uniform changes [28]. The effect of aging on T cell-mediated immunity is most prominent, while the changes in B cells are considered by scientists to be less pronounced [29].

T cells play a key role in both the development of tolerance and transplant rejection. In an aging population, the dynamics of T cell-mediated immunity includes internal and systemic changes in T cells with a change in the ratio of naive T cells and memory T cells and thymic involution, which certainly entails clinical significance [30].

Thymic involution begins as early as 1 year of age, with the naive T cell count decreasing by 50% over any 15 years of life and leading to significant decrease in the production of naive T lymphocytes in the thymus in the population over 60 years of age [31]. Remarkably, memory T cells are long-lived, and memory T lymphocyte responses show a half-life of 8–15 years. The lifespan of memory T cell subsets is mainly due to self-renewal rather than the lifespan of individual T cells [32]. Naive T cells can divide and generate daughter T cells with a naive phenotype. Such increased homeostatic proliferation can compensate, at least partially, for the decreased thymic activity with aging. However, this new T cell population, consisting mainly of memory T cells, has a reduced ability to recognize and eliminate new pathogens [27]. Thus, the response of elderly T lymphocytes is mainly based on less effective memory T cell responses, which lack the ability of young T cells to migrate and naïve de novo production [28].

A major review by Russian authors substantiates the need to introduce into clinical practice a comprehensive monitoring of immune blood cells and cytokines in patients with transplanted organs in order to be able to select individual immunosuppressive therapy tactics, assess its effectiveness and predict the outcomes. It is emphasized that special attention should be paid to the characteristics of CD4+ T lymphocytes and determination of the ratio of their individual populations in the peripheral blood, since they are the main players in the immune system response to the graft [33].

The ratio of CD4+ (T-helpers) to CD8+ (T-suppressors) cells in peripheral blood is called the immunoregulatory index and in most elderly people undergoes an inversion along with increased activated T cells and T lymphocytes expressing NK-cell markers [34]. Schaenman J.M. et al. showed that older kidney transplant recipients demonstrated decreased frequency of naïve CD4+ and CD8+ T cells, and increased frequency of terminally differentiated, immune senescent, and NK T cells. The authors also observed a trend towards increased frequency of T cell immune senescence in patients experiencing infection in the first year after transplantation, which reached statistical significance. They noted the potential for risk stratification and customization of immune suppression to prevent infection and rejection after transplantation [35].

Aging of T cells is also accompanied by loss of costimulatory molecule CD28 on CD4+ and CD8+ T cells [36]. CD28 is a key costimulatory surface receptor that plays a crucial role in antigen-dependent activation, proliferation and survival of T cells and prolongs graft survival. Virtually all human T cells express CD28 during birth. In contrast, by age 80, 10–15% of CD4+ T cells in peripheral blood and 50–60% of CD8+ T cells lack CD28 expression. As an alternative and compensatory pathway for classical T cell receptor/CD28 activation, aging T cells increase de novo expression of cytotoxic NK cell receptors [37]. These changes indicate that in-

creased NK-cell receptor expression will influence alloimmune responses in the elderly, potentially reflecting the relevance of an enhanced innate immune response. Although the overall significance of NK cell receptors in kidney transplantation remains poorly understood, recent work has demonstrated phenotypic changes in the NK cell repertoire induced by immunosuppressive treatment [38]. Such age-related changes in T cells provide grounds for exploring the potential of new immunosuppressive approaches [28].

In our 2020 study, interesting age-associated cellular immunity features were also noted – in healthy volunteers, the functional activity of peripheral blood mononuclear cells was statistically insignificant but gradually decreased with increasing age. Meanwhile, in patients with chronic kidney disease (CKD) undergoing dialysis, this dependence was of the same direction, but expressed significantly stronger and was statistically significant. It can be concluded that older CKD patients after kidney transplantation are subject to significant changes in the morphofunctional state of peripheral blood mononuclear cells and subpopulation composition of lymphocytes, while the severity of changes in the functional state of these cells is strongly related to age, which is not observed in healthy volunteers. This should be considered when choosing immunosuppressive therapy in older kidney transplant recipients [39].

Additional in vitro studies have shown that loss of CD28 is accompanied by increased expression of its antagonist gene, the CTLA-4 receptor, which potentially enhances the already inhibitory effect [40].

Some authors found a very significant correlation between age and the percentage of CTLA-4+ in CD4+ cells, as well as between age and mean CTLA-4 fluorescence intensity. CTLA-4 levels also correlated with immune system activation as determined by CD3+ HLA-DR+ cell levels. Consequently, age-related immune system aging is in part caused by chronic immune system activation with a corresponding decrease in CD28 costimulatory molecules and increase in CTLA-4 inhibitory molecules [41].

It is important to note that immune aging should be viewed as a multitude of complex modifications of immunological functions and regulations with broad implications for alloimmune responses. There is little evidence for the effect of age on B cell function. Reports demonstrate that older age affects humoral immune response through decreased naïve B cell count combined with decreased T cell count, which are integral to B cell activation [42]. In contrast to T cells, B cell homeostasis is maintained in the periphery by decreased turnover of mature B lymphocytes. Despite this, a decrease in B cell count causes a change in antibody specificity and a decrease in plasma cells in the bone marrow [26]. However, a number of authors, on the contrary, believe that aging apparently leads to decreased diversity of naive B cells rather than to significant changes in peripheral B cell count, which suggests that the effect of aging on the B cell component may be primarily qualitative [43].

The narrowing of the B cell repertoire with age correlates with susceptibility to infection. A correlation has been reported between Epstein–Barr virus seropositivity and B cell clonal expansion in the very elderly (80 years and older) without association with persistent cytomegalovirus (CMV) infection [44]. It remains clinically unclear whether humoral response is age-dependent and whether humoral rejection requires a different therapeutic approach in the elderly. Most humoral immune responses require the assistance of related T lymphocytes, and, as noted above, immunosenescence is associated with changes in the CD4+ compartment. However, how immune age-associated changes in CD4+ cells initiate changes in B cells in older adults has not been directly investigated.

Several reports also associate aging with a decrease in the Th1/Th2 cytokine ratio, whereas the total number of type 1 and 2 cytokine-producing T cells appears to increase with age [45]. Impaired IL-2 production in older T cells may also be associated with age-related loss of CD-28, since costimulatory signaling is critical for T cell activation and their subsequent IL-2 production [46]. One study showed that both IL-2 cytokine capacity and CD4+ T cell sensitivity decline with age, at least in mouse models [45]. Maintenance immunosuppression relies heavily on calcineurin inhibitors specifically targeting IL-2 production in T cells. Taken together, loss of CD28 and decreased IL-2 production may represent critical factors in impaired alloimmune response in the elderly, affecting immunosuppression and tolerance protocols.

Regulatory T cells (Tregs) play a crucial role in maintaining immune tolerance and preventing exacerbation of immune responses to foreign antigens. Numerous studies have proved that $FoxP3^+$ Tregs accumulate with age [47, 48]. As a result, immune response activity or formation of immunological tolerance depends on the balance of T-helpers (Th) initiating active immune response and triggering rejection, and on Tregs having the opposite effect.

EFFECT OF IMMUNE AGING ON KIDNEY TRANSPLANT OUTCOMES

Elderly renal transplant recipients have a higher overall mortality rate, and nearly 50% of graft losses are associated with death in a working graft, compared with 15% in younger recipients. Immunosuppression complications such as cardiovascular disease, infection, or malignancy, especially among older patients, represent important components of morbidity and mortality [20]. Nevertheless, predicted life expectancy has increased to

10 years in kidney recipients older than 65 years compared to the control group of corresponding age remaining on dialysis [49].

Weaver-Pinzon O. et al. conducted a retrospective study of 52,995 adult kidney transplant recipients and came to logical conclusions: mortality among recipients aged over 60 years was significantly higher, mortality among younger recipients was due to acute rejection, coronary vasculopathy and graft failure, while mortality among older recipients was due to infection, malignant tumors and kidney failure [50]. Another large study also confirmed a decrease in both innate and adaptive immune reactivity with age, which contributes to a lower incidence of acute rejection and increased infectious mortality in older recipients [51].

Jackson-Spence F. et al. conducted a retrospective single-centre analysis of 1140 consecutive patients receiving kidney-alone allografts in different age groups. They noted that elderly kidney transplant recipients had increased risk of complications associated with immunosuppression, but rejection rates and death-censored graft losses were similar. Therefore, the authors consider clinical trials of age-adapted immunosuppression to be necessary [52].

In a study by Tullius S.G. et al., elderly recipients (>50 years) had a lower incidence of acute rejection compared to younger recipients, despite the more obvious immunogenicity of elderly donor kidneys [53].

Other authors also note that in kidney transplants, less than 25% of failures in older recipients are due to rejection, compared to 50% in recipients younger than 45 years of age. However, acute rejection in the elderly has a more pronounced deleterious effect on patient and graft survival. Age-related internal organ changes and immunogenicity aspects may be relevant in this context, since older recipients are more likely to receive organs from older donors [49].

Thus, in transplant recipients, aging of the immune system probably reduces the risk of acute rejection but increases the risk of side effects associated with immunosuppression, especially infections and malignancies [54].

The relevance of metabolic disorders also increases with aging. Indeed, recurrent diabetes mellitus is more common in the elderly and is associated with the immunosuppression used. For example, the risk of its occurrence after kidney transplantation increases 1.5-fold during each decade of life. Incidence of pre-transplant diabetes mellitus also increases from 7% to 31% with age, as shown in a study of over 12,000 liver transplant recipients [55]. In turn, the presence of diabetes mellitus is associated with increased incidence of acute rejection, infections, late cardiovascular complications, and poor outcomes.

The risk of death from infection increases exponentially with age among renal transplant recipients, while among kidney and lung recipients older than 60 years, infection is the leading cause of increased mortality seen in the first postoperative year [54]. Cytomegalovirus infection is considered an environmental contribution to immunosenescence, as the CMV-specific CD8 T cell count is highest in the elderly. It has been suggested that filling the "immunological space" with CMV-specific T cells may narrow the T cell repertoire and strongly influence the memory component. The peripheral naïve T-cell population in people not infected with CMV showed a higher naïve T cell count and a lower immunoregulatory index [56].

Cancer incidence is known to increase steadily with age, reaching its highest level in transplant recipients over the age of 50. Skin cancers and lymphoproliferative diseases are the most common malignancies among transplant recipients. In addition, de novo malignancies are a major cause of death, accounting for one-third of deaths among liver transplant recipients, unrelated to liver disease [57].

DISCUSSION

Aging induces a series of modifications in T cell-mediated immunity. In general, T cell compartments undergo a shift toward a less effective response throughout life. In organ transplantation, impaired T cell-mediated immunity with aging is associated with less acute rejection and improved graft survival. At the same time, older transplant recipients are more likely to experience side effects of immunosuppression with higher rates of infections and malignancies.

The complex balance between under- and over-immunosuppression becomes even more vulnerable in older recipients due to changes in pharmacokinetics and pharmacodynamics of drugs [58]. Also, existing rejection treatments can have detrimental effects in the elderly and often lead to over-immunosuppression. It is becoming apparent that immunosuppression protocols for elderly transplant recipients must balance the risk of acute rejection with the risk of adverse cardiovascular, infectious and other complications.

Decisions to adjust immunosuppressant doses are based on clinical experience, and patients often deviate from target concentrations, being exposed to alternative risks of toxicity and graft rejection. A five-year survival rate of 78% has been achieved for recipients using this strategy, but these success rates only indicate that there is still room for improvement [59]. Current data on recommended standard immunosuppressive therapy are mostly derived from studies in which elderly patients were excluded or were a minority. To date, there have been only a few well-designed prospective studies in the elderly that demonstrate the need to correct immunosuppression in the first months after transplantation [49].

Many authors emphasize the need to reduce maintenance doses of immunosuppressive drugs in elderly recipients to possibly minimize side effects and consider further research in this direction necessary. For example, it is suggested that a reduced dose of thymoglobulin or IL-2R antibody is preferable as an induction treatment for this group of recipients, a reduced dose of tacrolimus or immunosuppression without a calcineurin inhibitor (CNI) can be considered as maintenance therapy. Based on experimental data, mTORi (in particular, Betalasept) appears to be a promising candidate to replace CNIs in elderly patients [28].

Because of age-related changes in T cell differentiation, the pharmacodynamics of immunosuppressants also change, and this is one reason why the dose of these drugs may be reduced. In addition, simultaneous administration of several drugs can lead to the side effects of pharmacodynamic interactions. It is well known that CNIs can cause acute and chronic nephrotoxicity. A recent study by Khan S. et al. focused on acute kidney injury in elderly patients and the cumulative or synergistic nephrotoxicity of CNIs with nonsteroidal anti-inflammatory drugs, aminoglycosides, angiotensin-converting enzyme inhibitors and antimicrobials. The authors concluded that the use of nephrotoxic drugs should be minimized, since elderly patients are more prone to acute kidney injury after transplantation [60].

Amelia R. Cossart et al. in their 2019 review also examined currently known evidence on the pharmacokinetics and pharmacodynamics of commonly prescribed immunosuppressants (tacrolimus, cyclosporine, mycophenolate, and prednisolone) in older kidney transplant recipients and noted that older recipients may have higher dose exposure or lower clearance of calcineurin inhibitors. There have also been reports of a 50% reduction in the efficacy of tacrolimus in the elderly, a lack of increased mycophenolic acid dosing on the graft of elderly recipients, and unclear effects of aging on the pharmacokinetics of prednisolone [19].

Meier M. et al. believe that individualized immunosuppression strategies, such as calcineurin inhibitor withdrawal and mycophenolic acid withdrawal, can improve patient and graft survival in the case of an aged recipient. The authors consider the benefits of steroid withdrawal less obvious, but perhaps more important in the elderly, in whom age-associated bone mass loss, glucose intolerance, and other metabolic changes complicate steroid therapy [61].

It is becoming apparent that the aging immune system may not only require reduction, but also individualization of immunosuppression. Thus, clinical trials evaluating graft and recipient survival are urgently needed to implement age-adapted immunosuppressive protocols to meet the needs of this vulnerable group of kidney transplant recipients [62].

The use of minimum drug concentrations as the current "gold standard" for monitoring immunosuppressive therapy levels is also a disadvantage of modern immunosuppressive drug therapy for the elderly. However, monitoring blood concentrations may not adequately reflect the effects of aging immune system or age-associated organ dysfunction. Consequently, diagnostic use of biomarkers is necessary to adjust drug therapy for age-related changes. Scientists are beginning to think about finding pharmacodynamic, pharmacogenetic or immunological markers of individualized immunosuppression. Instead of dosing immunosuppressive drugs based on pharmacokinetic measurements, an immunological biomarker would better reflect the activity of the drug (or combination of drugs) rather than just its concentration [54]. Indeed, monitoring of peripheral blood cells and cytokines in the pre- and post-transplant period reveals changes in the processes of developing organ rejection or engraftment, which may provide grounds for individualization of immunosuppressive therapy [63].

Coming up with and implementing a comprehensive individualized immunotherapeutic strategy in kidney transplantation will allow to minimize the complications of immunosuppressive drugs used, their nephrotoxicity, various infectious and cancer diseases, and post-transplant diabetes, thereby improving kidney transplant outcomes and reducing the transplant waitlist with simultaneous rational use of expensive immunosuppression.

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