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Magdalena Jankowska

Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk

Immunosuppressive therapy following kidney transplantation in elderly recipients

Abstract

The benefits of kidney transplantation warrant the treatment being offered to a growing population of elderly patients with kidney failures. Kidney transplantation in recipients older than 65 is associated with some challenges due to the less optimal function of organs from older donors, age-related differences in immune response, pharmacokinetics, and pharmacodynamics of immunosuppressive drugs, comorbidities, and adverse events. Few clinical trials have evaluated the safety of modified immunosuppressive therapies in the elderly. Current recommendations are based on the immunological risk; however, further studies are needed to investigate immunosuppressive agents' safety, efficacy, and target levels in elderly kidney transplant recipients.

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INTRODUCTION

Compared to chronic hemodialysis, kidney transplantation is associated with longer survival and better quality of life in all age groups, including patients above 65 years of age [1, 2]. Patients within this age group are referred to as elderly patients. According to a forecast, by the year 2060, elderly individuals will comprise around 28% of all European population. In line with this forecast, a dynamic increase in the rates of kidney transplantations being carried out in recipients over 65 years has been observed in Europe in recent decades [3]. The results of observational studies support the suggestion that chronological age should not present a barrier to the first and subsequent kidney transplants [4]. This, however, does not change the fact that access to transplantations is still insufficient for elderly patients, which is particularly evident among those over the age of 74 [5, 6].

AGING OF THE KIDNEY

The results of transplantations from older donors are improving. The aging population of recipients forces a parallel increase in the age limit within the kidney donor population [7]. The observed shift in the donor age limits is justified because even the recipients over 65 years of age who had received a kidney transplant from a donor meeting the extended criteria have survived 4 years longer than patients on the transplant waiting list [8]. Still, the probability of 10-year survival of a transplant obtained from a deceased donor aged 50–70 years is 10% lower than the European average [9]. Despite the increased risk of failure of kidney transplants obtained from elderly donors, particularly in the younger group of recipients aged 20 to 50 years, elderly individuals will inevitably constitute an increasing percentage of donors, and the function of organs obtained from these donors may be suboptimal [10].

Age-related histopathological changes within the kidney reduce the total number and size of nephrons and cause tubular atrophy, interstitial fibrosis, thickening of the glomerular basal membrane, glomerulosclerosis, and arteriosclerosis [11]. While such lesions are present in approximately 2.7% of biopsies in donors under 30 years of age, their prevalence

Address for correspondence:
Magdalena Jankowska,
Department of Nephrology,
Transplantology and Internal Diseases,
Medical University of Gdańsk,
ul. Dębinki 7, 81–211 Gdańsk,
e-mail:
magdalena.jankowska@gumed.edu.pl

increases to 58% in donors aged 60–69 and up to 70% in donors over 70 [12]. Microscopic changes within the organ are accompanied by functional changes such as reduced glomerular filtration rate (GFR), reduced sodium reabsorption and potassium secretion in renal tubules, and reduced urine concentration [11]. Thus, the age of the recipient and the donor may be important elements to be considered when planning the treatment. The rate of biopsy-proven acute rejection (BPAR) of the transplant is known to be higher for organs from older donors [13]. One of the reasons for the poorer function and shorter survival of transplants from older donors is their increased sensitivity to ischemia/reperfusion injury, which increases the risk of acute rejection and impairment of distant organ function.

AGING OF THE IMMUNE SYSTEM AND ITS CONSEQUENCES

Aging and involution of the thymus are associated with depletion of the pool of naive T cells and accumulation of memory T cells [14]. The so-called T cell receptor repertoire is also decreased (including, for instance, the loss of CD 28), and increased release of pro-inflammatory cytokines (e.g., IL-2, -4, -6, -10, -17, TNF-α, IFN-γ) is observed, leading to the disturbed equilibrium of proinflammatory/anti-inflammatory mechanisms, autoimmunization, and generalized inflammation [15, 16]. Over-representation of memory T-cells reduces the number of virgin B cells, thereby reducing the turnover of mature B cells, decreasing the number of plasma cells within the bone marrow, and causing disturbances in the production of specific antibodies [17]. Due to the above-listed changes, an immune deficit is observed in elderly individuals, increasing the risk of infectious complications and death due to infection [18]. The opportunistic and non-opportunistic infections increase with age [19, 20]. The risk of infection is the key premise for reducing the strength of immunosuppression in this age group, particularly since another consequence of the aging of the immune system consists in reduced risk of acute rejection, which is up to 10% lower than in the younger age groups (19, 21, 22). Unfortunately, the reduced risk of acute rejection resulting from the impairment of the immune system does not apply to recipients of organs obtained from donors meeting the extended criteria, including elderly donors. In most transplantation centers, such donor-recipient selection is a rule.

Table 1. Physiological age-related changes affecting the pharmacokinetics and pharmacodynamics of the immunosuppressive treatment

Delayed gastric emptying
↑ gastric pH
Slowed gastrointestinal peristalsis
Reduced visceral blood flow
Reduced small intestinal surface
Changes in glycoprotein P expression and activity
Reduced hepatic blood flow
Changes in CYP 450 expression
Reduced renal clearance
Reduced albumin levels
Changes in body composition with increased fat content

THE EFFECT OF AGE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF DRUGS

As a result of progressing age-related physiological changes listed in Table 1, the pharmacokinetics and pharmacodynamics of medications are also changed in elderly patients [22]. Drug absorption and distribution are reduced with age, for example, due to changes in the bodily water, muscle, and fat content. Distribution volumes increase for lipophilic drugs and decrease for hydrophilic medications. Liver size, liver blood flow, and kidney function are critical for the drug elimination process [17]. Although age is likely to have a negligible impact on the absorption of medicines by passive transport mechanisms, the increase in the stomach pH observed in elderly people can be crucial for bioavailability [23].

CALCINEURIN INHIBITORS

Despite the enzymatic clearance most likely remaining unchanged, the increase in the distribution volume affects the activity of calcineurin inhibitors (CNI), which may be further intensified by changes in albumin levels and anemia [24, 25]. A small study in 25 patients showed that the target level of cyclosporin (CsA) C2 was achieved in recipients over 65 years of age at lower doses than in younger patients [26]. Moreover, the drug level in T cells compared to the whole blood was 44% higher in elderly recipients [26]. Though it is possible to adjust an excessively high dose on

the basis of whole blood level monitoring, high lymphocytic CsA levels may remain unnoticed and exert toxic effects despite correct C0 and C2 values [22]. The results of the blockade of the calcineurin pathway are also observed beyond the immune system cells, namely in cardiomyocytes, skeletal muscle cells, and neurons [23].

Also, in the case of tacrolimus (TAC), the dose- and body weight-adjusted levels were 50% higher in elderly recipients than younger patients in two independent studies [27, 28]. Data available to date indicate that lower doses of calcineurin inhibitors are sufficient to achieve the target exposure in the elderly [23].

TAC metabolism can be measured by the drug concentration (C0) to dose ratio (C/D, with the dose being expressed in mg). Low C/D ratio values reflect rapid metabolism, which is associated with a higher risk of acute rejection and toxicity. The elderly age appears to be associated with higher C/D ratios and slower metabolism of tacrolimus [29].

An additional aspect of treatment involving TAC administration consists in the presence of preparations with different formulations: immediate release (IR-TAC), prolonged release (PR-TAC), and extended release MeltDose (LCP-TAC) formulations. IR-TAC is characterized by a narrow therapeutic index and high and inter-individually variable maximum concentrations, which may increase the risk of acute rejection and contribute to treatment toxicity, especially to neurologic complications and diabetes [27]. Compared to IR-TAC and PR-TAC, LCP-TAC is characterized by a flattened pharmacokinetics profile with less variation between maximum and minimum concentrations; at the same time, the formulation requires longer times to reach the maximum blood concentration of the drug [30]. LCP-TAC is gradually released within a distal segment of the colon, where the first-pass metabolism is minimized due to lower CYP3A activity. As recently demonstrated in a retrospective study, significantly lower doses of LCP-TAC are required to obtain the therapeutic effect in elderly recipients [31]. This may be the effect of the active substance being dispersed in the polymeric matrix, which increases its solubility and, therefore, bioavailability [32].

MYCOPHENOLATES

Available inosinomonophosphate dehydrogenase (IMPDH) inhibitor preparations are delivered in the form of prodrugs. The active substance is mycophenolic acid (MPA). Despite the large interindividual variability in doses required to achieve therapeutic levels of exposure to MPA, the available data suggest no age dependency in this regard [33, 34]. High IMPDH activity before and after transplantation is associated with a higher risk of acute rejection [35]. However, no data is available on IMPDH activity being age-dependent. The therapeutic index of MPA is not narrow, and, therefore, it is not necessary to monitor the blood concentrations of the drug.

mTOR INHIBITORS

No data is available on the pharmacokinetics of mTOR inhibitors in elderly recipients. The only known correlation is the inverse correlation between age and sirolimus clearance [36]. CYP450 metabolizes both mTOR inhibitor formulations, and, therefore, age may potentially affect the clearance of the drug due to changes in liver function. However, the target C0 values for mTOR inhibitor used with calcineurin inhibitors remain the same as those in younger recipients, namely > 3 ng/mL for everolimus and between 5–15 ng/mL for sirolimus [37]. The question of how the determined blood levels translate to actual inactivation of the p70S6 kinase, which is a biological equivalent to the efficacy of the treatment, remains a matter of dispute [22].

BELATACEPT

Belatacept is a selective T-cell co-stimulation blocker characterized by dose-dependent binding of CD86 receptors [38]. The drug is a fusion protein administered as an intravenous infusion every four weeks. The pharmacokinetics of the drug is weight-dependent and characterized by small (< 30%) interindividual variability and negligible influence of demographic variables, including age [39]. The cumulative frequency of anti-belatacept antibodies development reached 5.3% over a three-year exposure period, with the impact of age on antibody production not being assessed [38].

OTHER PROBLEMS RELATED TO ELDERLY AGE IMPACTING THERAPEUTIC DECISIONS

Regardless of changes in the immune system and the pharmacokinetics and pharmacodynamics of medication, other problems related to elderly age should also be taken into account in treatment planning and customiza-

Table 2. Selected problems related to elderly age affecting the outcomes and potential complications of immunosuppressive therapy (modified from [40])

Organ or system	Age-related changes	Consequences
Central nervous system	Cognitive impairment	Mistakes in drug dosing, difficulty in understanding and remembering complex therapeutic regimens
Cardiovascular system	Vascular endothelial function disorders (pro-constriction and pro-aggregation changes)	Increased risk of vasoconstriction and thromboembolic complications
	Orthostatic hypotension	Increased risk of falls
Endocrine system	Reduced glucose tolerance, reduced insulin secretion	Increased risk of diabetes
	Reduced production of thyroid hormones	Increased risk of hypothyroidism
Musculoskeletal system	Reduced muscle tissue	Increased risk of falls, rhabdomyolysis, myositis
	Reduced bone mineral density	Increased risk of osteopenia, osteoporosis, and fractures

tion. These include reduced mobility, immobilization, postural instability, sphincter incontinence, cognitive impairment, depression, malnutrition, vision and hearing impairment, dependence on others, and polypragmasia. Age-related changes in the function of individual organs and systems affecting the outcomes and potential complications of immunosuppressive therapy are presented in Table 2.

Table 3. Different strategies for modification for immunosuppressive treatment as evaluated in elderly recipients

Reduction in the doses of medications
Delayed CNI introduction
Discontinuation of CNI and mTOR-based regimens
Belatacept
Early withdrawal of steroids
Steroid-free regimens
Induction: anti-IL-2R versus ATG
Use of medications with modified formulation

STRATEGIES FOR ADJUSTING IMMUNOSUPPRESSIVE TREATMENT TO THE AGE OF THE RECIPIENT

Paradoxically, elderly people who usually receive the largest number of medications are systematically excluded from clinical trials [17, 40]. This is due to the inclusion criteria, including age and comorbidities, limiting the chances for qualification to phase 2 and phase 3 studies. As a result, the knowledge about the safety and efficacy of drugs in this group of patients is insufficient and elderly individuals are often treated on the basis of results obtained in younger age groups; the excessively aggressive treatment contributes to the increased risk of complications [19, 22].

MINIMIZATION OF IMMUNOSUPPRESSION

The toxicity of immunosuppressive treatment is dose-dependent and directly related to its efficacy; however, secondary toxicity, independent of the therapeutic purpose, is also observed. Minimizing immunosuppressive treatment can reduce the complications associated with excessive immunosuppression, preventing its side effects and complications [41]. Over many years, attempts to minimize immunosuppressive treatment were a fundamental strategy for individualizing treatment in transplant recipients over 65 years of age [19, 42] (Tab. 3). However, the strategy involves a fundamental danger of insufficient immunosuppression and acute transplant rejection. Consequences of acute rejection, if it is encountered, are known to be far more damaging for elderly recipients than in the remaining age groups and involve a higher risk of transplant loss or even death [43, 44].

CALCINEURIN INHIBITORS

The only randomized studies carried out to date in the population of elderly recipients pertained to the strategies of delayed introduction of tacrolimus (post-transplantation day 7), with early withdrawal of steroids [45] and of discontinuation of tacrolimus (or MMF) 6 weeks after transplantation [46]. In both cases, attempts to reduce CNI were unsuccessful, partly due to the high discontinuation rate (38 out of 90 patients in the Meier et al. study).

The effect of the CNI dose level on the results of kidney transplantation in elderly recipients was the subject of an observational

study [47]. The study compared two TAC targets in a group of 88 patients over 60 years of age (10–12 ng/mL versus 8–10 ng/mL). Lower target levels were associated with improved transplant survival and? the same risk of acute rejection over two years of observation [47].

mTOR INHIBITORS

Recent reports indicate that blocking the mTOR pathway may have a protective effect on immunosenescence processes and the development of degenerative diseases typical for the elderly age [48]. The possibility of substituting a CNI with an mTOR inhibitor was assessed in retrospective studies in extended criteria kidney transplant recipients, including elderly patients [49] and dual kidney transplant recipients [50, 51] using a four-drug immunosuppressive regimen (baliximab or ATG induction). In the first study, all patients were treated without CNI, although conversion was later required in some patients due to the high rate of acute rejections [49]. Two other studies compared the treatment results with sirolimus vs ciclosporin [50, 51]. A lower risk of CMV infection but a higher risk of diabetes and proteinuria was observed in the mTOR group. The discontinuation rate in the sirolimus arm was as high as 24% [49].

BELATACEPT

Belatacept, a drug currently unavailable in Poland, is another therapeutic option for eliminating CNI toxicity. The experience with the use of the medication in elderly recipients is limited as only 15% of the participants in the BENEFIT and BENEFIT-EXT studies were over 65 years old [52, 53]. Improvements in kidney function and reduced complication rates were demonstrated in both studies, including in extended criteria kidney transplant recipients, in patients treated with belatacept as compared to ciclosporin. Unfortunately, the results of tacrolimus substitution are far less favorable [54].

GLUCOCORTICOSTEROIDS

Limitation of glucocorticosteroid use in the form of steroid-free treatment regimens, steroid induction (5–7 days), and early (within up to 3 months) withdrawal of steroids are particularly attractive potential strategies for improving the treatment of elderly transplant recipients, mainly due to the reduction of the risk of diabetes, osteoporosis, sterile bone necrosis, cataract, depression, or deterioration of cognitive functions. Despite long-lasting attempts to apply this strategy, it is still uncertain whether the benefits outweigh the risk of transplant loss and the associated high mortality rate in elderly recipients. A retrospective study assessing early discontinuation of steroids in transplant recipients aged under and over 60 revealed no differences between groups in achieving the composite endpoint involving patient survival, transplant survival, biopsy-proven acute rejection, and creatinine levels [55]. Recipients at increased immunological risk were excluded from the study, the CNI dose was optimized, and patients were subjected to extensive observation [55].

INDUCTION TREATMENT

The decision to use medicines resulting in lymphocyte depletion (polyclonal antibodies or monoclonal anti-CD-25 antibody) depends on the immunological risk assessment regardless of the recipient's age [56]. No evidence suggests longer persistence of lymphocytopenia following administration of depletion antibodies to elderly individuals [22]. Until recently, it was believed that interleukin 2 receptor blocking antibodies (IL2RA) were preferred in elderly recipients due to their better safety profile as compared to anti-thymocyte antibodies [22]. However, recent data indicate that even in low-immunological risk patients aged above 65, ATG is not associated with increased risk of complications and facilitates a reduction in the incidence of post-transplant diabetes mellitus by reducing tacrolimus doses [57].

MEDICATIONS WITH MODIFIED FORMULATION

In an aggregate analysis of transplant recipients aged 65 and above participating in two clinical trials comparing different tacrolimus formulations, a subgroup of 32 patients treated with LCP-TAC had a lower risk of transplant failure (defined as BPAR, transplant loss, death, or being lost to follow-up) compared to a subgroup of 52 patients receiving IR-TAC (0% vs. 13%) [58]. In a recent retrospective study, elderly recipients required significantly lower LCPT-TAC doses to achieve therapeutic drug levels [31].

RECOMMENDATIONS OF THE POLISH TRANSPLANTATION SOCIETY

The recommendations of the Polish Transplantation Society for immunosuppressive therapy after kidney transplantation in

Table 4. Immunosuppression in elderly recipients: recommendations of the Polish Transplantation Society [59]

Low immune risk	IL2RA induction + MMF + minimization of CNI + minimization of glucocorticosteroids
High immune risk	Induction with depletion antibodies + CNI + MMF + Glucocorticosteroids

elderly recipients (Tab. 4) are in line with the proposal for immunosuppression regimens developed by the Working Group of the ERA-EDTA DESCARTES Developing Education Science and Care for Renal Transplantation in the European States) [59]. The authors of the recommendations stress the particular need to individualize treatment in this patient population, with the high risk of concomitant diseases in the recipient being taken into account and the risk factors associated with the donor.

CONCLUSION

Kidney transplantation in elderly recipients may pose a particular challenge due to the suboptimal function of the transplanted organ that is usually collected from a suboptimal donor, but also due to the significant comorbidity burden in the recipient, aging of their immune system, significant susceptibility to complications and polypragmasia. Pharmacokinetics and pharmacodynamics of drugs change with patients' age leading to increased toxicity and associated complications. The aging of the immune system is associated with a lower incidence of acute rejections. Still, it increases the risk of infection and cardiovascular, autoimmune, cancer, and neurodegenerative diseases. In the absence of conclusive evidence from large randomized trials, current recommendations are based mainly on expert opinions. They suggest that immunological risks are addressed when deciding on depletion antibodies and minimizing the doses of calcineurin inhibitors or steroids in this group of recipients.

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