Review

Personalized immunosuppression in elderly renal transplant recipients

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ABSTRACT

The number of elderly people has increased considerably over the last decades, due to a rising life expectancy and ageing populations. As a result, an increased number of elderly with end-stage-renal-disease are diagnosed, for which the preferred treatment is renal transplantation. Over the past years the awareness of the elderly as a specific patient population has grown, which increases the importance of research in this group.

Elderly patients often receive kidneys from elderly donors while younger donor kidneys are preferentially reserved for younger recipients. Although the rate of acute rejection after transplantation is lower in the elderly, these rejections may lead to graft loss more frequently, as kidneys from elderly donors have marginal reserve capacity. To prevent acute rejection, immunosuppressive therapy is needed. On the other hand, elderly patients have a higher risk to die from infectious complications, and thus less immunosuppression would be preferable.

Immunosuppressive treatment in the elderly is complicated further by changes in the pharmacokinetics and pharmacodynamics, with increasing age. Adjustments in standard immunosuppressive regimes are therefore suggested for this population.

An unmet need in transplantation medicine is a tool to guide a personalized approach to immunosuppression. Recently several promising biomarkers that identify injury to the graft at an early stage or predict acute rejection have been identified. Unfortunately, none of these biomarkers were tested specifically in the elderly. We believe there is an urgent need to perform clinical trials investigating novel immunosuppressive regimens in conjunction with biomarker studies in this specific population.

1. Introduction

Over the past decades the number of elderly people (in this manuscript defined as patients older than 65 years) has increased substantially and is expected to rise even further from 8% of the total world population in 2015 to 16% in the year 2050 [1–3]. This increase does not only affect health care in general, but also has a great impact on more specific issues, such as the increased number of patients with end-stage-renal-disease (ESRD) [1,2,4–6]. In younger patients (< 65 years), renal transplantation (RT) has been the preferred treatment option for ESRD for many years. The benefits of RT, however, have been less established for elderly patients. This, together with the poor availability of donor kidneys, is a reason why there has been reluctance to put the elderly on the waiting list for RT [7].

Over the past few years, research has focused more on the treatment of ESRD in the elderly. The results of these studies indicate that RT in elderly patients is also associated with reduced mortality compared to dialysis [8,9] We now see a gradual increase in the proportion of elderly patients in the total population of transplanted patients [10]. Not

surprisingly, transplantation of the elderly recipient is more complicated because of pre-existing comorbidities, frailty, changes in pharmacokinetics (PK) of (immunosuppressive) drugs, polypharmacy and changes in immunoreactivity (immunosenescence). In this paper, we will briefly review these topics and provide recommendations on how to increase the chances of success of RT in the elderly.

2. Benefits of transplantation in the elderly

Although RT is beneficial in elderly patients with a reduction in mortality rate and an improved quality of life compared to dialysis [1,8,9,11], mortality and quality of life only improve with a functioning graft. This applies to every transplant and recipient without taking age into account. It is therefore important to maintain allograft function. The 10-year renal allograft survival rate of deceased donor kidneys is close to 50%, and poorer long-term outcome is associated with several variables [12]. One of the risk factors for poor long-term outcome is acute rejection [13,14] Data from the United States indicate that transplantation from living donors to elderly recipients increased until

2010 and remained stable in the last couple of years, while transplantation from living donors to younger recipients decreased [10]. In Europe multiple organizations are involved in the allocation and exchange of deceased donor organs. There are big differences between European countries in the proportions of living and deceased donor kidney transplantation. For example, in the Netherlands the majority of patients (58%) are transplanted with a kidney from a living donor, but in countries where more deceased donor kidneys are available, such as in Belgium or Austria, living donation is a much smaller part of the transplant program (13% and 15%, respectively) [15].

2.1. Eurotransplant senior program

Elderly patients often receive kidneys from elderly donors, because kidneys of younger donors are mostly allocated to younger recipients. The Eurotransplant Senior Program (ESP) is a specially designed program that was set in place to solve the kidney shortage in the elderly. In this program, kidneys from older donors are preferentially allocated to elderly recipients without matching for HLA antigens and over a narrow geographic area [1,4] Because this process is less comprehensive than standard allocation, cold ischemia time is minimized whereby the chance of delayed graft function (DGF) and rejection are reduced [16].

The results of this program were evaluated by Peters-Sengers et al. who made a distinction in donors after brain death (DBD) or after circulatory death (DCD) [17]. They found less acute rejection in the elderly after receiving kidneys from young DBD and DCD donors (< 65 years) compared to younger recipients receiving kidneys from these same donors. Similar results were found in elderly patients who received kidneys from elderly DBD donors. The incidence of acute rejection was 13.5% in the elderly population compared to 17.9% in the group of younger recipients. This is most likely due to immunosenescence which will be explained later on. However, more acute rejection was seen in elderly recipients after receiving kidneys from elderly DCD donors. This is probably the result of more ischemia-reperfusion injury due to the longer warm ischemia time of older DCD kidneys [17].

Also research has shown that elderly patients with ESRD benefit from RT, even when kidneys from older donors are used [18]. Their immune system is less reactive and therefore they are less prone to acute allograft rejection and graft loss [19]. However, acute rejection in elderly recipients is still a major problem because it is associated with a dramatic decrease in long-term graft survival, especially when elderly patients have received a kidney from a marginal donor. A potential way to intervene is to apply the principles of personalized medicine (see below).

3. Pharmacokinetics and pharmacodynamics

After RT, combinations of immunosuppressants are prescribed to prevent renal allograft rejection. Worldwide, combined treatment with tacrolimus, mycophenolic acid (MPA), glucocorticoids and basiliximab induction therapy is most frequently used [19–21]. During ageing, significant changes in both the PK and pharmacodynamics (PD) of immunosuppressive drugs may result in different outcomes of transplantation.

3.1. Pharmacokinetics

Staatz et al. summarized all available published data on the PK of tacrolimus in a review and concluded that a lower dose of tacrolimus in elderly patients could still be effective and was possibly safer than the standard dose [22]. Over the last years several studies have confirmed this hypothesis with clinical trials (Table 1) [23]. The best evidence comes from the study by Jacobson et al. They found that older recipients had higher dose-normalized tacrolimus concentrations than young adults [24]. Comparable results were found for ciclosporin.

Despite receiving lower doses of ciclosporin and tacrolimus, elderly recipients often had higher predose concentrations of CNIs compared to younger recipients [24]. These findings indicate that adjustment of the starting doses of tacrolimus and ciclosporin in the elderly after RT is needed in order to avoid over-exposure.

However, these changes in PK of tacrolimus are not representative for all immunosuppressants. Tang et al. demonstrated that the PK of MPA is not affected by the physiological changes in the elderly. In this study, oral MPA was given to younger (43.7 ± 4.9 years) and elderly (65.8 ± 4.9 years) renal transplant recipients [25]. No significant difference was found in the PK of MPA [25]. Also elderly patients do not need dose adjustments for basiliximab as the PK does not change with age [26].

Drug plasma/whole blood concentrations are affected by ADME (absorption, distribution, metabolism and elimination) of the drug. Most immunosuppressants are administered orally, and changes in gastrointestinal (GI) absorption are the first factor that may alter blood concentrations [27]. Oral absorption of medication by passive diffusion can be reduced by a decrease in gastrointestinal motility, reduced splanchnic blood flow, reduced gastric acid secretion and the diminished intestinal surface area [19,28,29] These changes may occur with increasing age. The effects of ageing on p-glycoprotein (p-gp) expression are largely unknown and no correlation could be found between p-gp expression in intestinal tissue and patient age (21–67 years).[22,30] Distribution of a drug is highly dependent on the lipophilic or hydrophilic character of a specific drug. With increasing age the body composition gradually changes, with a decline in muscle mass and an increase in body fat [28,29,31]. Although some studies indicate that due to this change in body composition the volume of distribution (Vd) of lipophilic drugs increases, a study of Jain et al. found that the Vd, adjusted for total body weight, in obese patients could not be predicted based on lipophilicity alone [32]. The Vd of ciclosporin for example was decreased in obese patients which is in contradiction with its lipophilic character. It was suggested that this was due to binding to lipoprotein or additional tissue distribution [32]. Increased body fat was also associated with a prolonged elimination half-life of tacrolimus and ciclosporin in patients with a mean age of 44 years [33–35]. Given the fact that elderly patients also have a higher amount of body fat, these results are likely to also apply to this group of patients. During a patient's lifetime drug-metabolizing capacity changes [28]. There is a reduction in liver volume and liver blood flow which is thought to be the main cause of changes in drug metabolism during ageing [36]. Moreover, phase I metabolism and activity of Cytochrome P450 (CYP) enzymes are both diminished by ageing [18,37].

In general, renal function deteriorates with age, and for drugs that are renally excreted doses need to be reduced in elderly patients [33]. Passey et al. identified age as a significant covariate towards tacrolimus clearance in a population pharmacokinetic model [38]. The role of the kidney in the excretion of the currently used immunosuppressive drugs is very limited, and a reduced renal function in elderly patients is unlikely to affect the PK of these drugs.

3.2. Pharmacodynamics

PD describe the efficacy and toxicity of drugs. For some immunosuppressants direct biomarkers are available that reflect their PD. Tang et al. measured 5'monophosphate dehydrogenase (IMPDH) activity in MPA treated elderly (± 65.8 years) and younger (± 43.7 years) recipients after RT [25]. As no changes between the two groups were found in IMPDH activity, the authors concluded that age does not affect the PD of MPA [25]. PD of CNIs can be measured by means of the calcineurin activity, which is associated with acute rejection [39]. However, no studies were carried out to link calcineurin activity to ageing.

The PD of immunosuppressive drugs may be influenced by comorbidities. Wu et al. used the Charlson Comorbidity Index (CCI) to

Table 1
Overview of published data on pharmacokinetic parameters of tacrolimus in elderly people (≥65 years).

Author	Year	Age of patients	Main findings
David-Neto et al. [23]	2016	Elderly: ≥65 years Control: 35 ± 6 years	• Mean TAC dose was lower in elderly (8.6 mg ± 4.8 vs 12.1 ± 5.1 mg). • Mean trough levels (C_{min}) were the same in both groups • Elderly vs control: Adj C_{max} [465 ± 271 vs 341 ± 235] (Adj for dose/body weight) • Elderly vs control: Adj TAC-AUC [2652 ± 1730 vs 2793 ± 1253] (Adj for dose/body weight) • Body clearance was lower in elderly [0.35 ± 0.31 vs 0.76 ± 0.42]
Melilli et al. [75]	2015	Elderly: ≥65 years (35%) non-elderly: < 65 years	• TAC level at 5–7 days was lower in elderly vs patients < 65 years (8.05 ng/ml vs 7.1 ng/ml) • At 1, 3 and 6 months the levels between the groups were equal.
Robertsen et al. [76]	2015	Elderly: 60–78 years	Differences between original and generic TAC formulations: • AUC_{0-12} of the generic formulation was 1.17 [90%-CI 1.10–1.23] • C_{max} ratio 1.49 [90%-CI 1.35–1.65]
Jacobson et al. [24]	2012	Elderly: 65–84 years Middle age: 35–64 years Young: 18–34 years	• Elderly had a higher normalized TAC trough with a lower median dose (1–2 mg/day lower) compared to middle and young age

TAC = tacrolimus, Adj = adjusted, CI = confidence interval, AUC = Area Under Curve.

define comorbidities in RT patients [40]. Patients who were included in the high comorbidity group (CCI score > 5) had a crude hazard ratio of 1.42 [95%-CI 1.02–1.97] for kidney survival compared to patients with a low CCI score. Furthermore, crude hazard ratio for patient survival during a period of 80 months was 2.88 [95%-CI 1.90–4.37] between the low- and high CCI index patients. This implies that not only graft survival is diminished but comorbidities are also a risk for overall survival [40]. Elderly patients generally have more comorbidities such as diabetes and heart failure [41,42]. This does not mean that the presence of comorbidities should preclude the patient from having access to transplantation. In patients with chronic heart failure and RT, symptoms of heart failure even improved after receiving a donor kidney [43]. No studies were carried out to determine graft survival in this population, which is possibly due to the benefits of RT on the co-morbidity itself [37].

The classic immunosuppressive drugs have been selected based on inhibition of T-cell activation [19]. During ageing, a shift takes place towards the differentiation of memory cells, especially T_{EM} cells [44]. As a result the antigen-recognition repertoire is decreased and the immune system is therefore unable to protect the host properly against new pathogens [45]. This was observed in several studies which demonstrated that elderly patients had an increased susceptibility to infectious disease and cancer, but also a reduced response to vaccination [33,46–48]. Furthermore, a decline in T-cells during ageing was measured due to the loss of thymic tissue which is responsible for maturation of native T-cells [49,50]. This decline was also seen by Denecke et al. who investigated the activation of CD4+ T-cells in old recipient mice. [51]. They found an increase of early activated T-cells and memory T-cells, but this was not related to intracellular cytokine production. These findings were confirmed in humans as less acute rejection was seen in older recipients (> 50 years) compared to younger recipients (< 50 years). Older donor kidneys are more immunogenic, but the resulting higher incidence of acute rejection seen in younger recipients is less evident in the elderly recipient [52,53]. Because of the age-related changes in T-cell differentiation, the PD of immunosuppressants is also changed and one of the reasons why the dose of these drugs can be reduced (see Table 1).

Also, co-medication can lead to PD interactions in terms of adverse effects. It is well known that CNI's can cause acute and chronic nephrotoxicity [54]. A recent study from Khan et al. focused specifically on acute kidney injury in the elderly patient and the cumulative or synergistic nephrotoxicity of CNIs with nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, angiotensin-converting enzyme inhibitors (ACEi) and antimicrobial medication [55–58]. Because elderly patients are more prone to acute kidney injury after transplantation, it is necessary to minimize the use of nephrotoxic co-medication [55].

4. Frailty

Another factor that is associated with poor outcome after RT is frailty. Recently frailty was defined as a combination of diminished strength, reduced physiologic function and increased vulnerability to stressors [59,60]. Frailty is hard to diagnose because symptoms overlap with the overall decline of physiological systems in the elderly. [59]. Frailty was found to be an independent risk factor for mortality and it was associated with a poor outcome after RT [61,62]. This was also due to the surgical transplant procedure. Frailty scores pointed out that 19.8% of a population with an average age of 53 years was frail before RT. One month after surgery this increased to 33.3% and gradually declined over the months following transplantation to 17.2% [62]. Preoperative frailty was associated with a 1.94-fold increased risk of DGF [63]. This phenomenon was not related to the recipient's age, indicating that younger recipients diagnosed with frailty are at risk too. Because the elderly have several other risk factors that are of influence on graft failure, it is important to identify frailty at an early stage. Hereafter a more balanced decision can be made regarding RT.

5. Optimization of therapy

Based on the fact that the elderly patient has a reduced immune response to the transplanted organ, it may be possible to reduce the overall immunosuppressive load. As prospective randomized trials comparing different regimens in elderly patients have not been performed, one can only speculate on which drug should be reduced or stopped. One could propose to leave out basiliximab induction therapy in elderly patients, as the benefits of induction therapy may be less because they have a reduced IL-2 response [34]. Furthermore, in elderly patients, one may encounter severe infectious complications for which a rapid reduction of the immunosuppressive load might be needed. Obviously, the effects of basiliximab, with its long elimination half-life of approximately one week, are long lasting [64]. Another option would be to taper glucocorticoids more rapidly in elderly patients. There is an ongoing debate regarding the safety of glucocorticoid avoidance or tapering strategies. In elderly patients the balance between risks and benefits of glucocorticoid minimization may be different compared to younger patients, also in view of their higher risk of developing diabetes, cardiovascular disease and osteoporosis after transplantation [65–67]. There is only little evidence that tapering or withdrawal of glucocorticoids after RT in elderlies is beneficial, but long-term survival could be prolonged if comorbidities are prevented [68].

Recent research suggested that everolimus-based therapy has the potential to improve outcome after transplantation as it allows for CNI-free or minimized CNI-based treatment [69,70]. A major advantage of using everolimus in elderly patients would be the avoidance of the

nephrotoxic effects associated with tacrolimus treatment. Elderly patients often receive ECD kidneys from elderly donors, and as a result, renal function after transplantation is often disappointing. In order to reduce the proportion of patients with an eGFR below 30 mL/min per 1.73 m^2, an everolimus-based immunosuppressive regimen may be beneficial. Also, because IL-2 production is decreased in the elderly, tacrolimus could be less effective [71]. In patients with lower IL-2 concentrations, it may therefore be attractive to replace tacrolimus by everolimus. In a recent study of David-Neto et al. everolimus was given to elderly patients in combination with tacrolimus and prednisone [72]. No differences were seen in the PK of everolimus during the first 6 months after transplantation compared with younger recipients. However, the sample size was small (n = 16) and the association between the use of everolimus and acute rejection was not investigated.

6. Potential biomarkers

For the management of transplanted patients, and to reach true individualized therapy, biomarkers would be very helpful. Instead of dosing immunosuppressive drugs based on a pharmacokinetic measurement, an immunological biomarker would better reflect the activity of the drug (or drug combination), rather than its mere concentration. In a recent and comprehensive review of the use of biomarkers in transplantation by Brunet et al., three types of biomarkers are discussed: [1] those associated with the risk of rejection (alloreactivity/ tolerance), [2] those reflecting individual response to immunosuppressants, and [3] those associated with graft dysfunction. Brunet et al. conclude that it is likely that in transplanted patients, in whom many factors influence the outcome, multiple predictive biomarkers will need to be integrated with parameters such as time after transplantation, previous rejections and infectious complications. Increased use of integrated PK-PD modeling will allow for balanced decision making [73].

No specific biomarkers have been identified for elderly patients. Since elderly patients appear to be especially vulnerable to the toxicity of immunosuppressive therapy, such biomarkers are of special importance in this population [55,73].

7. Conclusions

Two decades ago, Meier-Kriesche et al. pointed out that transplanted elderly patients are at risk for death due to severe infectious complications, while they are less likely to reject their kidneys. Although this observation advocates for a tailored immunosuppressive regimen for this growing patient population, in daily practice elderly patients are still treated with the same immunosuppressive regimens and with the same doses and maintained at the same target concentrations as non-elderly patients [74]. Another factor to consider is the preferential allocation of kidneys from elderly donors to elderly recipients. These ECD-kidneys are more sensitive to the nephrotoxic effects of CNIs, and thus a CNI-free or low-CNI exposure immunosuppressive regimen could be of benefit for these patients.

Besides a modified immunosuppressive regimen there is also an unmet need to develop biomarkers that reflect the PD effect of the immunosuppressive drugs. A so-called "immunometer" would be able to identify patients that are either under- or over-immunosuppressed, and in these patients the dose of the immunosuppressive medication could then be adapted to prevent rejection or manifestations of over-immunosuppression. Ideally such a test should reflect the overall state of immunosuppression, taking into account both the physiological reduced immune reactivity of the elderly patient, the alloreactivity towards the allograft, and the biological effect of the immunosuppressive drug combination.

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