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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

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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