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Pharmacokinetics and pharmacodynamics of immunosuppressive drugs in elderly kidney transplant recipients

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A B S T R A C T

Elderly patients are a fast growing population among transplant recipients over the past decades. Both the innate and adaptive immune reactivity decrease with age, which is believed to contribute to the decreased incidence of acute rejection and increased infectious death rate in elderly transplant recipients. In contrast to recipient age, donor age is associated with a higher incidence of acute rejection.

Pharmacokinetic studies in renal transplant recipients show that CNI troughs are >5% higher in elderly compared to younger patients given the same dose normalized by body weight. This may impact the starting dose of tacrolimus and cyclosporine. Possibly in elderly patients the intracellular (in lymphocyte) concentrations are relatively high in relation to the whole blood concentration, resulting in a stronger pharmacodynamic effect at the same whole blood trough concentration. For cyclosporine this has been shown, but it is not clear if the same is true for other immunosuppressive drugs.

Pharmacodynamic studies have compared the inhibition of target enzymes, or more downstream effects of immunosuppressive drugs, in younger and older patients. Measurement of nuclear factor of activated T-cell (NFAT)-regulated gene expression (RGE), a pharmacodynamic read-out of CNI, is a promising biomarker of immunosuppression. Low levels of NFAT RGE are associated with increased risk of infection and non-melanoma skin cancer in elderly patients.

Clinical trials to evaluate the safety and efficacy of immunosuppression regimens in this specific patient population, which is underrepresented in published trials, are lacking. More studies in elderly patients are needed to investigate the impact of age on the pharmacokinetics or pharmacodynamics of immunosuppressive drugs, and to decide on the optimal regimen and target levels for elderly transplant recipients.

1. Introduction: aging in transplant recipients and donors

In the past decades, the number of elderly patients (those ≥65 years) with end-stage renal disease (ESRD) has grown rapidly [1,2]. Like in younger patients, renal transplantation provides a survival benefit and improves quality of life compared with dialysis, and is therefore the optimal renal replacement therapy for the elderly suffering from ESRD [3]. Since 2002, the total number of kidney transplants in patients ≥65 years old has doubled in the U.S. (Fig. 1) [1,4]. In Europe, the increase in the proportion of kidney transplant recipients ≥65 years between 1991 and 2007 is over 5-fold, from 3.6 to 19.7% [2].

Meanwhile, the imbalance between donor organ shortage and the growing waiting list has led to the increased utilization of kidneys from older living donors (OLD) and expanded criteria deceased donors (ECDs) [5,6]. Furthermore, the likelihood of receiving an OLD or ECD kidney increases with recipient age [7,8]. In the Eurotransplant Senior Program (ESP) kidneys from donors of 65 years or more were allocated to local transplant candidates above 65 years of age, without matching for HLA antigens. The rationale behind this policy was to expedite the change of the elderly to receive a transplant and to reduce cold ischemia time to prevent ischemic injury and hereby delayed graft function and the increased risk of rejection [9].

Transplantation of elderly recipients is more complicated compared to young transplant recipients because their graft function is often less than ideal, they have more comorbidities and a different immune response, suffer more from immunosuppression-related adverse events, and use more co-medication resulting in more frequent drug–drug interactions [10].

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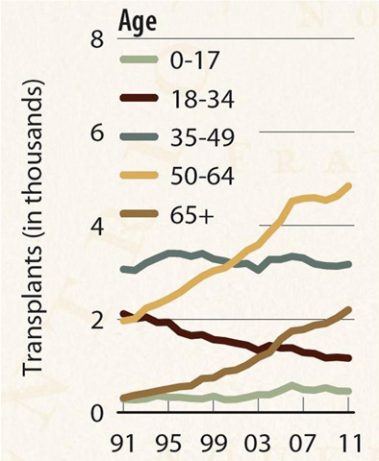

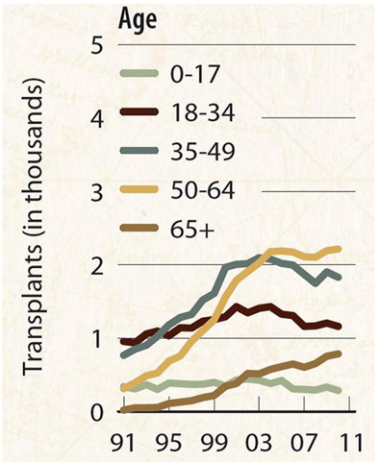

Fig. 1. 1.1 The number of deceased donor kidney transplants by age in the US. Includes kidney-alone and kidney–pancreas transplants. 1.2 The number of living donor kidney transplants by age in the US. Includes kidney-alone and kidney–pancreas transplants. Figure 1.1 and 1.2 are reproduced from the US Renal Data System. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government [1].

In this paper, we will review the evidence that elderly patients differ from younger patients in pharmacokinetics (PK) and pharmacodynamics (PD) of immunosuppressive medications. Studies performed in adult kidney transplant patients are the main focus in this review.

2. Immunosuppression in elderly patients

2.1. Aging and immune response

The immune response, like the function of all organs and biological systems in the human body, is significantly affected by aging [11]. Both innate and adaptive immunity decrease with age but cell-mediated immunity is most clearly affected [11–13]. Thymic output of naive T cells decreases exponentially, resulting in a decline of T-cell diversity and a low CD4/CD8 ratio in the older immune system [14–16]. Experimental transplantation models indicate that $CD4^+$ T-cell function and proliferation is impaired, while regulatory T-cell responses remain intact in older recipients [17]. Other changes include increased numbers of memory T-cells and overproduction of pro-inflammatory cytokines [11,13,18].

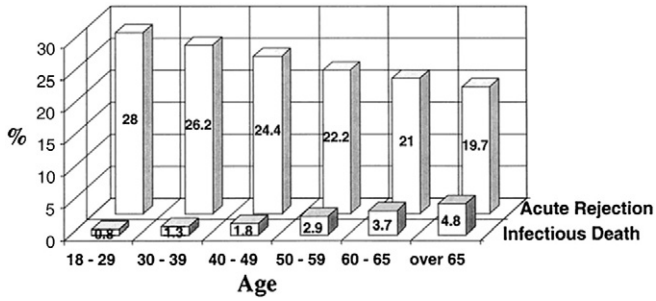

Fig. 2. Acute rejection rate and death from infection by age categories. Reproduced from Meier-Kriesche and colleagues with permission of Wolters Kluwer Health [19].

2.2. Aging and rejection

The age-related decline in immune reactivity is believed to contribute to the lower acute rejection risk of elderly transplant recipients. Studies from individual centers and registry data analyses show that the incidence of acute rejection decreases steadily with increasing recipient age (Fig. 2) [19–22]. In a recent analysis of more than 100,000 renal transplant recipients from the United Network for Organ Sharing (UNOS) database, Tullius and Milford [23] confirmed these findings. Acute rejection rates in patients above 65 years of age were about 10% lower than those in patients between 20 and 30 years [23]. Older renal transplant recipients may therefore benefit from a less aggressive immunosuppressive regimen.

However, this lower risk of acute rejection may not apply when grafts are transplanted from older donors. Organs from elderly donors are particularly susceptible to ischemia–reperfusion injury and associated with a higher incidence of acute rejection and delayed graft function (DGF) [11,24]. De Fijter et al. [25,26] reported that the cumulative incidence of biopsy-proven acute rejection (BPAR) was significantly higher in older than in younger donor (<50 years of age) kidneys, a phenomenon that was observed in both younger and elderly recipients. Interestingly, the increased rejection incidence in older donor kidneys was largely due to an increase in rejections of the tubulo-interstitial type, whereas the incidence of acute vascular rejection was not different from younger donor kidneys [26]. Using the recent data from UNOS, Tullius and Milford [23] confirmed that higher donor age is associated with more frequent acute rejection. Wiebe et al. [27] studied the development of de novo donor-specific antibodies and the risk factors for its development in 315 consecutive renal transplants without pre-transplant donor-specific antibodies. A stepwise logistic regression analysis identified HLA-DR mismatches and non-adherence, but not donor or recipient age, to be predictors of de novo donor-specific antibodies [27].

Acute rejection has a stronger negative impact on long-term graft survival of older renal transplant recipients compared with younger recipients [28]. In an analysis of 48,821 transplant recipients from the United States Renal Data System (USRDS) database, Meier-Kriesche et al. found that acute rejection had a strong negative impact on death-censored graft survival in older renal transplant recipients [28]. This strong effect of acute rejection could not be explained by the fact that more marginal and therefore more vulnerable grafts are transplanted in the elderly [29].

2.3. Aging and infection

While the risk of acute rejection is reduced, the risk of death due to an infection is increased in elderly transplant recipients [30,31]. Meier-Kriesche et al. showed that the risk of death due to infectious complications increases with age (Fig. 2) [19,32]. Both opportunistic, as well as non-opportunistic infections are more frequent with