see original article in page 287

Immunosupressive strategies in elderly recipients

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Over the past 15 years, coinciding with increased transplantation activity and organ use in Spain, mean donor age has markedly increased from 34.5 years in 1992 to a little over 50 years in 2006. This has naturally resulted in an increase in the percentage of donors aged over 60 years from barely 10% in 1992 to 38.6% of all donors in 2006.[1-2]

Organs from elderly donors are mostly used for recipients over 65 years of age. Therefore, the elderly transplanted population currently represents a not negligible proportion of patients.[3-4]

Elderly transplant recipients have been reported to have an increased risk of developing acute tubular necrosis, a greater probability of chronic graft nephropathy, and a higher risk of death from infectious and cardiovascular causes, and some studies also suggest that they may have a higher incidence of acute rejection.[5-7]

As stated, risk of ATN is higher in patients receiving organs from elderly donors. In this regard, it has been reported, based on data from the UNOS registry, that the risk of ATN linearly increases with a donor age over 13 years and an OR of 0.17 for every 10-year increase in donor age. ATN has also been reported to be an independent risk factor for patient and graft survival and for occurrence of acute rejection. It is therefore important to take measures to decrease ATN incidence, particularly in the elderly.[4,5]

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Moreover, final graft function is determined by the characteristics of organs used. Again, data from the UNOS registry, this time reported by Woo Y.M. et al., are of great value by showing that patients receiving kidneys from donors over 55 years of age have a poorer renal function at six months and one year than recipients of organs from younger donors. In addition, other studies conducted with donor biopsies have reported a direct relationship between the rate of glomerulosclerosis and donor age, and between the rate of glomerulosclerosis of transplanted kidneys and the glomerular filtration rate achieved by the graft at one year of transplant.[8-10]

It has been experimentally shown that elderly kidneys are more immunogenic than young kidneys, and though an increased acute rejection rate has not always been seen in elderly recipients, published data from the UNOS registry show that in Caucasian populations the risk of chronic graft nephropathy is 29% higher for donors aged 50-65 years and 69% higher for older donors as compared to the group aged 18-49 years.[6-11]

Based on the foregoing, the great clinical interest of developing specific immunosuppressive strategies for elderly donors and recipients is easily understood.

However, most clinical trials exclude recipients over 65 years of age, and available data about immunosuppression in the elderly population usually come from uncontrolled short series or small randomised studies.[12-16]

Two main strategies have been proposed to address the problem of immunosuppression in elderly kidneys.

Some groups suggest benefits from use of induction therapies using antibodies against the IL-2 receptor and low doses of calcineurin inhibitors, while others suggest calcineurin inhibitor-free regimens either combining proliferation signal inhibitors and MMF or separately using each of these immunosuppressants.[12-16]

Data from the Symphony study, conducted in 1,645 patients aged 18-75 years, were recently reported. This study allowed for reaching significant conclusions about immunosuppression in the transplanted population.[17]

The study compared three immunosuppression arms with daclizumab induction (associated to low dose calcineurin inhibitors in two arms only) to a fourth arm given standard immunosuppression, defined as high doses of cyclosporin associated to MMF and steroids.

The best results were achieved in patients treated with induction with basiliximab, low dose tacrolimus, and MMF, in whom rejection rate was 12.3%.

In the arm with no calcineurin inhibitors, including rapamycin at levels ranging from 4 and 8 ng/mL associated to MMF and steroids, acute rejection rate was higher and, strikingly, renal function of grafts at one year of transplant was also poorer.

A subsequent analysis of this study selecting only 296 patients over 60 years of age, who would theoretically benefit in the short term from an immunosuppression with no nephrotoxicity, found these same results, with an acute rejection rate of 13.6% in the induction arm with basiliximab, low dose tacrolimus, and MMF, and a renal function at one year of transplant of 50.9 mL/min, as measured according to Cockcroft-Gault.[18]

In the Niza study conducted in several Spanish centres, no differences were seen in acute rejection rate in the group with late onset of calcineurin inhibitors.[19]

In the multicentre study published in this issue, the Spanish group for the study of kidney transplant from elderly donors assesses the results of an immunosuppressive regimen with late start of

KEY CONCEPTS

1. Age of kidney transplants donor and recipients in increasing in recent year.
2. Older recipients have a high risk of immunological and non-immunological complications.
3. Elderly recipients have a worse graft sruvival and an increased infectious and cardiovascular mortality.
4. Immunosuppressive strategies in elderly recipients are still to be defined because this patient group is usually excluded from clinical trials.
5. The substudy on recipients aged over 60 years of the Symphony study found an immunosuppressive strategy based on induction with daclizumab, MMF, and low dose tacrolimus to have the best rejection rate.
6. Data reported by Gentil and colleagues in this issue show that with late onset of tacrolimus, acute rejection and complication rates are similar to those reported in the Symphony study.

tacrolimus in a significant number of recipients older than 50 years who were carefully followed up for one year and received grafts from donors older than 55 years.[20]

The immunosuppressive regimen used consisted of daclizumab 1 mg/kg on post-transplant days 0 and 14, mycophenolate 2 g/24 hours until day 45 after transplant with subsequent reduction, and tacrolimus started between days 5 and 7 after transplant with the objective of achieving drug levels ranging from 4-8 ng/mL.

The acute rejection rate with this immunosuppressive regimen was 13.5%, virtually identical to the rate in the arm with best results of the Symphony study. Patients achieved an acceptable renal function at one year of follow-up, with no significant associated infectious complications.

Based on these results, late onset of tacrolimus with low subsequent levels of the drug may be considered to have an acceptable acute rejection rate and, as concluded by the study authors, could be considered a good therapeutic option for elderly recipients with a low immunological risk.

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