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Immune Response and Immunosuppressive Therapy in Elderly Kidney Transplant Recipients

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Abstract

The first series of nine patients older than 60 years of age treated successfully with renal transplantation was reported in 1976. Later reports confirmed the results and concluded that kidney transplantation in duly selected older patients is the treatment of choice for end-stage chronic renal disease as it is associated with a better survival and quality of life than treatment with dialysis. This has led to increased demand for kidney allografts in elderly patients. However, this population is more vulnerable to the effects of immunosuppression, as evidenced by the greater prevalence of infections and tumors and a lower incidence of acute rejection. This is due to the decline in the immune response caused by the reduction in the numbers of naive T lymphocytes, mature B lymphocyte precursors, clonal expansion of memory lymphocytes, dendritic cells, and phagocytic activity of the macrophages. This article analyzes the immune response and immunosuppressive therapy in elderly kidney transplant recipients. **(Trends in Transplant 2007;1:121-8)**

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Key words

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Introduction

Patients with end-stage renal disease older than 60 years of age who undergo renal transplantation have a 63% (nondiabetics) and 54% (diabetics) risk reduction for death compared with age-matched patients on the waiting list for a renal transplant[1]. This has led to increased demand for grafts in this population, but cadaveric renal transplantation is increasingly dependent on the use of elderly donors and these organs are associated with a high incidence of delayed kidney function as well as lower kidney function compared with organs from younger donors. Additionally, the reduction in the immune response in elderly patients causes a greater frequency of infections and tumors, two major problems for organ transplant recipients. Immunosuppressive therapy that does not take into account these data may induce a state of immunodeficiency that compromises the life of the patient.

Immune response and age – concept of immunosenescence

The immune response declines with age. A reduction occurs after puberty in naive lymphocytes and memory cells, but the adult adaptive response remains effective against most pathogens. At older ages, including what in renal transplantation is known as "elderly recipients", there is a progressive reduction in the immune response that gives rise to greater vulnerability to infectious agents[2]. These changes in the immune system affect both innate immunity[3] and adaptive immunity[4] and are grouped together under the term "immunosenescence"[5]. Innate immunity involves a progressive loss of efficacy of its cells against infectious agents (Table 1), and in the adaptive immune response there is a loss in the number of naive T and B lymphocytes, and the naive $CD4^+$ T lymphocytes require more intense stimuli to be activated, but with a reduced helper effect and altered cytokine secretion. Additionally, there is an increase in

Table 1. The main age-related changes in the innate immune system

Cell	Preserved	Reduced
Neutrophil	Number Phagocytosis GM-CSFR expression	Superoxide production Chemotaxis Signal transduction Apoptosis Molecule recruitment into the lipid rafts
Macrophage	Number	Phagocytosis Superoxide production Apoptosis Signal transduction Cytokine production MHC class II expression Chemotaxis
Dendritic cell	Antigen presentation	Number of Langerhans cells Langerhans cell migration
Natural killer cell	Cytotoxicity	Response to cytokines Cytokine production Cytotoxicity Signal transduction

Table 2. The main age-related changes in the adaptive immune system

Cell	Increased	Reduced
Lymphocyte T	$CD28^{-}$ $CD8^{+}$ Memory cells	Naive peripheral T-cells (from ~3 x 10^9 to ~7 x 10^8) Repertoire diversity (from ~10^8 to ~10^6) Loss of co-stimulatory receptor CD28 expression in $CD8^{+}$ cells Clonal expansion of memory cells Cytokine production
Lymphocyte B	Memory cells	Naive peripheral B-cells Immunoglobulin production

$CD28^{-}$ $CD8^{+}$ T lymphocytes[2]. The newborn lacks these cells, but in older persons they represent 80-90% of all circulating $CD8^{+}$ T lymphocytes, a similar situation to that caused by latent viral infections. The result is a reduction in naive $CD8^{+}$ T-cells with a consequent reduction in clonal expansion, leading to a lowered T-cell repertoire and, thus, less protection against new infections (Table 2).

The pathophysiologic factors associated with these alterations include:

– Involution of the thymus. This is one of the main reasons for the drop in naive T lymphocytes. Moreover, the permanent stimulus of the immune system, as occurs in latent infection with cytomegalovirus (CMV), produces an increase in $CD8^{+}$ memory effector cells, with the consequent reduction in the T lymphocyte repertoire with other receptors able to recognize other antigens. This is as if, as well as the reduced formation, the energy were used for their formation with a particular receptor to control the latent CMV infection[5].

– Telomere shortening. One of the characteristics of lymphocytes is their capacity to divide when faced with antigen stimuli, but this replicative capacity is finite and is conditioned by the length of the telomeres. Human telomeres are 10-15 kb long, tandem hexanucleotide (TTAGGG)n repeats and their binding proteins are located at the ends of chromosomes. Incomplete replication of chromosome termini shortens the telomeres with each cell division, and cells with shortened telomeres cease dividing[2].

– Reduced formation of calcineurin and transcription factors. T lymphocyte stimulation is produced by a sequence of phosphorylation reactions that lead to translocation of transcription factors from the cytoplasm to the nucleus to activate gene expression. One of these factors is nuclear factor of activated T-cells, which is phosphorylated by calcineurin. Rats show a reduction in the formation of calcineurin with age. If the same happens in humans, lower doses of calcineurin inhibitors (CNI) would be required to control the enzyme activity. Likewise, the activator protein 1 (AP-1) transcription factor requires c-jun and c-fos molecules for translocation to the nucleus, and these molecules decrease with age, resulting in reduced production of IL-2[6].

Age, cancer and immunosuppression

The incidence of cancer rises exponentially with age in the non-transplanted population. Persons of 65 years of age or older account for 60% of all cancers, which are responsible for almost 70% of all deaths in this population. This is thought to be mainly due to the decrease in the immune response.

Viruses cause most tumors in the older non-transplanted population (Epstein-Barr-lymphoma, herpesvirus 8-Kaposi, papillomavirus-vulval and skin cancer), as well as in renal transplant recipients.

Evidence suggests that the intensity of the immunosuppression rather than the agent itself has a greater impact on the prevalence of tumors in renal transplantation. The fact that the incidence of lymphomas in renal transplantation is greater in USA than Europe has been related with the greater use of induction with OKT3 or polyclonal antibodies, which induce a greater degree of immunosuppression[7]. These immunosuppressive agents therefore represent more risk in the older population and many complications in older recipients might be avoided by the use of modest immunosuppression.

Age and acute rejection

The incidence of acute rejection falls with age in corneal[8], liver[9], and heart[10] transplants, and in bone marrow transplantation the probability of engraftment and graft-versus-host-disease increases with recipient age[6]. Graft survival in renal transplantation falls with age, but it rises if the data are censored for death[11]. A multicenter analysis of 79,924 patients with a cadaveric renal transplant reported to the United Network for Organ Sharing (UNOS) showed that, after inclusion of variables known to favor acute rejection and exclusion of patients without acute rejection, while the risk of death increases with age, the risk of acute rejection declines exponentially[12]. The effect of age was independently stronger than all the other factors associated with acute rejection at one year. Immunosuppression was therefore recommended to be reduced in elderly recipients. Additionally, studies with an *in vitro* model of acute rejection have shown a lower number of alloimmune T-cells resistant to cyclosporin A (CsA) in elderly individuals than in newborns[13]. This suggests that a suppressor mechanism is active in the elderly, and that less-intensive immunosuppression is therefore indicated. Current data suggest that the incidence of acute rejection is of lower intensity and frequency in the older than the younger recipient. Nevertheless, given the current policy of transplanting the older recipient with a graft from an older donor, it is important to emphasize that these grafts are more immunogenic and can increase the incidence of acute rejection.

Age and infection – concept of "immune risk phenotype"

The SYMPHONY study found a significantly greater incidence of overall infections, pneumonia, sepsis, and urinary tract infection in renal transplant recipients older than 60 years of age, and more especially in the group with full doses of CsA[14]. Earlier studies showed that the elderly have a greater morbidity and mortality due to infectious diseases and they are associated with oligoclonal expansions of T-cells, especially $CD8^+$ T-cells, and that a positive serology for CMV is associated with many of the same phenotypic and functional alterations of T-cell immunity that were reported as biomarkers associated with aging[3]. Some authors consider CMV to be the prime driving force behind most of the oligoclonal expansions and altered phenotypes and functions in $CD8^+$ T-cells[15]. At the same time, longitudinal studies of a free-living population of the very old have led to the emerging concept of an "immune risk phenotype", predicting mortality, which was itself found to be associated with CMV seropositivity and specific T-cell populations[2].

Data support the influence of CMV in molding immunity. Firstly, differences exist between CMV-specific T-cell populations and antigen-specific T-cells, which are infrequently present. The former are highly differentiated,

have shorter telomeres, and are functionally defective, secreting very little interferon-gamma and with a lower pool of memory cells. This favors the presence of opportunistic infections and explains why CMV disease is associated with other viral and bacterial infections. Less frequent antigen-specific T-cells, however, are more differentiated, have longer telomeres, and do not evolve towards senescence[11].

Immunosuppressive therapy in the elderly recipient

The above data support a reduction in immunosuppression in the elderly recipient, though the limits have yet to be clearly established.

Induction therapy

Experience regarding the safety of antibody induction therapy in elderly patients is scarce. Arguments limiting its use have been the greater prevalence of infections and tumors. Others, however, recommend its use because elderly receptors often receive a suboptimal graft, which is more immunogenic and sensitive to the adverse effects of CNI. The use of induction therapy combined with mycophenolate mofetil (MMF) may offer sufficient protection to delay the introduction and reduce the dose of CNI, or even replace it by a mammalian target of rapamycin (mTOR) inhibitor. Anti-CD25 monoclonal antibodies are the most frequently used form of induction therapy.

A prospective, multicenter study of 133 renal transplant recipients with a mean age of 61.6 (± 6.0) years with cadaveric kidney donors of 64 (± 5) years treated with two doses of daclizumab 1 mg/kg (pre-renal transplant and on day 14), delayed introduction of tacrolimus (TAC) (started before day 7 and adjusted to a target level of 5-8 ng/ml), MMF 2 g/day and low doses of steroids showed that, at one year, the incidence of acute rejection was 13.4% and *de novo* diabetes mellitus 5%. Patient and graft survival were 97 and 95.5%, respectively, and the mean serum creatinine and creatinine clearance were 1.5 mg/dl and 52.4 ml/min, respectively. Eighty-six percent of patients had at least one episode of infection (60.3% bacterial, 13.5% viral and 2.6% fungal). Nearly half the patients had urinary tract infections, but only one patient died from infection as a result of acute pyelonephritis[16].

Another prospective, randomized, single-center trial of kidney and kidney-pancreas transplants which included a subgroup of 31 patients aged ≥ 60 years treated with induction with a single dose of 30 mg of alemtuzumab vs. thymoglobulin on alternate days and TAC, MMF and prednisone found the incidence of acute rejection at one year was 7 vs. 17%, graft survival 93 vs. 84% and patient survival 93 vs. 100%. Comparison of the elderly population with another group younger than 60 years (range 28-59 years) showed no differences in the incidence of infections, but the younger patients had received greater doses of TAC and MMF[17].

Calcineurin inhibitors

Calcineurin inhibitors form the basis of immunosuppressive therapy. However, their nephrotoxic effect has stimulated the search for immunosuppression regimens that permit their minimization or suppression, though they still remain necessary. No data exist suggesting that age alters their pharmacokinetics[18] or about the recommendable doses and levels.

The CAESAR study analyzed the one-year results in renal transplant patients who followed an immunosuppression regimen with MMF and prednisone randomized to three arms according to the CsA dose: continued low dose (to maintain blood levels of 50-100 ng/ml),

low dose with suppression at 4-6 months, and standard dose. The first two groups received induction with daclizumab. Ceasing CsA presented no improvement in renal function, blood pressure or lipid levels, but it was associated with an increase in episodes of acute rejection. The patients who ceased CsA had 12.6% ($p = 0.027$) more episodes of acute rejection than those on low doses of CsA and 10.5% more than those on standard doses ($p = 0.04$). The study conclusion was that withdrawal of CNI in patients treated with daclizumab, MMF and prednisone during the first six months increased the risk of late acute rejection with no other benefits[19].

The SYMPHONY study compared four arms of immunosuppression, formed by standard doses of CsA to maintain levels of 150-300 ng/ml (100-200 ng/ml with effect from the fourth month) with MMF and prednisone, and the three remaining arms with induction with daclizumab, MMF and prednisone with low doses of CsA to maintain levels of 50-100 ng/ml or TAC (3-7 ng/ml) or sirolimus (SRL) to maintain levels of 4-8 ng/ml. Renal function and graft and patient survival were significantly better in the group with low doses of TAC[20].

Mycophenolate mofetil and mycophenolate sodium

Mycophenolate mofetil is currently the most used immunosuppressive agent, in most cases in association with a CNI[21]. The use of MMF reduces the incidence of acute rejection and is associated with better graft survival. Additionally, during the primary phase, it enables the doses of CNI to be reduced and even suppressed during the maintenance phase, when impairment of renal function is the result of CNI nephrotoxicity, with a significant improvement in renal function in a high percentage of cases. The elderly population is probably the most suitable for a significant reduction in CNI dosage.

In patients with progressive worsening of renal function due to interstitial fibrosis and tubular atrophy, the introduction of MMF results in a significant reduction in loss of glomerular filtrate, independently of the dose of CNI[22].

Sequential, prospective, protocol kidney biopsies in patients treated with CsA, prednisone and MMF or azathioprine showed that MMF was associated with lower interstitial fibrosis, striped fibrosis and periglomerular fibrosis, mesangial matrix accumulation, chronic glomerulopathy score and glomerulosclerosis in patients with or without acute rejection. In addition, MMF was associated with delayed expression of CNI nephrotoxicity, less arteriolar hyalinosis, striped fibrosis and tubular microcalcification. These effects suggest a direct action of reduced fibrinogenesis[23]. Furthermore, the treatment with MMF was not associated with an increase in lymphoproliferative disorder[24,25].

mTOR inhibitors

The mTOR inhibitors have been used as primary therapy in renal transplantation and during the stable phase as substitutes for CNI. No generalized consensus exists for their use as initiating therapy and the excellent results seen by some, in both the general population[26] and in elderly patients with induction with basiliximab[27], were not confirmed by others. The outcome of 2040 kidney transplant recipients between 2000 and 2005 reported to the UNOS and treated with SRL/MMF was recently evaluated and the results compared with patients treated with TAC/MMF and CsA/MMF. Overall graft survival was significantly lower in patients on SRL/MMF and this immunosuppression was associated with twice the hazard for graft loss relative to TAC/MMF, the data being consistent for both living donor transplants and expanded criteria donor transplants. The comparative analysis at six months of patients who continued the discharge im-

munosuppressive regimen showed a significantly lower graft survival than those treated with CNI[28].

The SYMPHONY study also failed to confirm the use of mTOR inhibitors as basic primary immunosuppressive therapy and this conclusion included middle-aged recipients, as shown in the subgroup analysis of Spanish patients with a greater percentage of older recipients and donors. Another important point is that in most comparative studies of different primary immunosuppression therapy regimens, the SRL without CNI arm was suspended because the incidence of acute rejection was greater than in those treated with CNI. Furthermore, the side effects, such as delayed wound healing and recovery of delayed graft function, more common in elderly patients, do not favor their use as primary therapy, which supports the concept that CNI are necessary during the early phase of renal transplantation, when the immunologic risk is greater.

The current indications for the use of mTOR are oriented towards conversion, either as replacement therapy in patients with complications induced or exacerbated by CNI, or as preventive therapy against their nephrotoxic effect. However, data on their use in conversion are limited, as most studies involved small nonrandomized series, which hinders their interpretation. Nevertheless, some contraindications to conversion are known, such as the presence of proteinuria and very deteriorated renal function[29]. If the aim is to avoid interstitial fibrosis and tubular atrophy, conversion does not make sense when irreversible damage already exists; thus, mTOR are indicated when the lesions are not very advanced. They have also been recommended in patients with neoplasms, after confirmation of the lower incidence of tumors in patients treated with mTOR inhibitors as compared with CNI[30], and this may benefit the elderly population with a greater prevalence of tumors.

Steroids

The dose of steroids, their withdrawal, and the time of withdrawal are permanently under debate in organ transplantation. The new immunosuppressive agents favor dose reduction and early withdrawal in low immunologic-risk patients without increasing the incidence of acute rejection. The association of MMF and CNI, especially TAC, permits safe withdrawal, generally with good medium-term results, provided the patients are duly selected, as well as a marked reduction in the starting dose. As older persons have a reduced immune response and are more sensitive to certain adverse effects of steroids, they may well benefit from early withdrawal. Most adverse effects of steroids, once begun, continue their course despite withdrawal. Early withdrawal is therefore recommended in elderly recipients with an acceptable renal function who have not had any episodes of acute rejection[31].

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