Current trends in immunosupression

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INTRODUCTION

The improvement observed in the past decade in graft and patient survival has focused the challenge of clinical research on long-term immunosuppression-induced complications in renal transplantation. New immunosuppressive agents have decreased the incidence of acute rejection and improved survival a year after the transplant[1,2] which, combined with the improvement observed in renal allograft function[2,3], should increase the number of patients in whom an excellent evolution can be expected. However these advances have had very little impact on long-term graft survival[4].

The side effects of new immunity agents with an increase in the development of infections or tumors[5], and non immune-related infections such as nephrotoxicity[6] or increased cardiovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus and anemia[7], are factors that limit any improvement in the results.

Chronic transplant nephropathy (CTN) is currently the main cause of graft loss[8]. Furthermore, even though the relative risk of patient death has decreased in recent years[5], patient death with graft function is the second cause of graft loss[8]. Both factors contribute to the loss of over 80% of transplanted grafts[5,8]. Defining strategies that reduce CTN and patient death with graft function has become the main challenge in renal transplantation[9].

CURRENT IMMUNOSUPPRESSIVE AGENTS AND PROTOCOLS

Immunosuppressive agents used today in organ transplants can be classified in five categories: calcineurin inhibitors (CNI) (cyclosporin —CsA—, tacrolimus —TAC—), antiproliferative agents (azathioprine, mycophenolate mofetil —MMF—, sodium mycophenolate), mTOR inhibitors (sirolimus –SRL-, everolimus), steroids and polyclonal or monoclonal antibodies (antithymocyte and antilymphocyte globulins, muromonab-CD3, basiliximab and daclizumab)[10]. The immunosuppressive protocol most frequently used today is therapy with three agents— a calcineurin inhibitor, an antiproliferative agent and steroids —with or without induction with poly— or monoclonal antibodies[10,11].

An analysis of changes in immunosuppression occurring in a decade (1993-2002) in the United States has shown the following findings[11]: 1) Induction with mono- or polyclonal antibodies has increased from 11% in 1993 to 65% in 2002, and rabbit antithymocyte globulin, basiliximab and daclizumab were the agents most used in the last year. 2) The use of CsA as a CNI has dropped from 90% to 30% with a TAC increase from 2% to over 60%. 3) In 1993 the only antiproliferative agent was azathioprine, and it was used in 86% of recipients. In 2002 only 2% of the patients continued treatment with azathioprine, with a progressive increase of MMF since it came about in 1995 up to 79% in 2002. 4) 99% of the patients took steroids in 1993 compared to 91% in 2002, which indicates the increasingly growing trend to avoid or suppress steroids in renal transplantation. 5) In 2002 15% of the patients continued treatment with SRL.

EVIDENCE ON THE USE OF DIFFERENT IMMUNOSUPPRESSIVE AGENTS

The previously mentioned changes in immunosuppression trends are mainly based on evidence accumulated with the different immunosuppressive agents briefly described below:

Mono- or polyclonal antibodies: The use of basiliximab or daclizumab compared to a placebo both in dual therapy (CsA and steroids) and triple therapy (CsA, azathioprine and steroids) in randomized, double blind multicenter clinical trials have shown a significant decrease in the incidence of acute rejection after 6 or 12 months[12-16]. In contrast, a study of these characteristics with basiliximab, using triple therapy

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with CsA, MMF and steroids, showed no significant differences[17]. A meta-analysis of the use of basiliximab or daclizumab has shown a significant reduction in the incidence of acute rejection with no improvement in graft survival at least up to the third year of follow-up[18]. However, an analysis of the UNOS Registry with a large number of cases showed that the use of basiliximab or daclizumab compared to patients without induction or with other monoclonal or polyclonal antibodies significantly reduces the risk of graft loss and patient death[19]. Though the role of continuous induction is still considered controversial, the use of basiliximab or daclizumab is recommended in patients with a moderate risk of acute rejection, and the use of polyclonal antibodies (rabbit antithymocyte globulin) is recommended in high risk patients[20].

Calcineurin inhibitors: The choice of CsA or TAC for maintenance treatment in renal transplantation has been the topic of debate in recent years. In a meta-analysis comparing it to non-microemulsion CsA, TAC showed a lower acute rejection rate in the first year without affecting graft survival[21]. Multicenter randomized studies comparing the new formulation of CsA (Neoral) with TAC in patients with steroids and azathioprine provided similar results[22,23]. On the other hand a similar incidence of acute rejection has been observed when TAC or CsA (Neoral) is associated to MMF and steroids, though graft survival was significantly higher in patients with delayed renal function who received TAC[24]. A recent meta-analysis shows that compared to CsA, in addition to reducing the acute rejection rate, TAC significantly decreases graft loss between 6 months and 3 years after the transplant, although it does so at the expense of a higher incidence of diabetes mellitus[25]. The inclusion of a considerable number of patients with non-microemulsion CsA and azathioprine means that it is necessary to be cautious when assessing these results. According to existing evidence, TAC offers a lower acute rejection rate and better graft function with a greater risk of developing diabetes mellitus; therefore the choice of the agent to be used must be made individually[26].

Antiproliferative agents: Clinical trials with MMF have shown a decreased incidence of acute rejection compared to azathioprine both in patients with CsA and with TAC, but they have not shown better graft survival[27,28]. However, analysis of registries with a large number of cases have shown better graft and patient survival in renal transplant recipients treated with MMF in comparison to azathioprine[29].

mTOR inhibitors: The emergence of sirolimus, and more recently everolimus, has undoubtedly increased therapeutic options in renal transplantation[30,31]. Clinical trials in patients with CsA and steroids have shown that compared to azathioprine or placebo, SRL decreases the incidence of acute rejection[30,32]. On the other hand, compared to Cs, in patients treated with steroids and azathioprine or MMF, SRL improves the glomerular filtration rate with a similar incidence of acute rejection[33-35]. In comparison to Cs, the association of basiliximab with MMF and steroids in patients with SRL further showed a trend towards a lower acute rejection rate[36]. Two prospective, randomized multicenter studies evaluated the use of SRL in early CsA withdrawal[37,38]. One year later the calculated glomerular filtration rate was significantly higher in patients with CsA withdrawal without a greater incidence of acute rejection. An extension of one of the studies to 4 years showed better graft survival[39].

mTOR inhibitors have become the basic immunosuppressants in regimens aiming to prevent or eliminate CNI (see below).

NEW IMMUNOSUPPRESSIVE STRATEGIES

With the ample number of immunosuppressive agents available today, there are multiple possible combinations. There are several developmental therapeutic approaches for the purpose of increasing long-term renal transplant survival. The reduction of nephrotoxicity and of other adverse effects aggravating the cardiovascular risk are developed strategies that can be summarized as:

- *Avoidance or absence of drugs:* do not introduce an agent with an unwanted adverse effect
- *Eliminating drugs:* withdrawal of an agent at a given time to prevent its adverse effects.
- *Minimizing drugs:* reducing the dose of an agent for the purpose of decreasing adverse effects.

ABSENCE OR ELIMINATION OF STEROIDS

Despite its universal use for decades in transplantation, its mainly diabetogenic and proatherogenic adverse effects have necessarily led to strategies with the absence or elimination of steroids[40,41].

After 6 months, a randomized multicenter study comparing TAC/MMF/steroids and TAC/MMF/daclizumab (2 doses) showed a similar incidence of acute rejection and graft survival with a significant decre-

ase in the incidence of diabetes mellitus and blood cholesterol levels[42].

Though in a meta-analysis by Kasiske et al.[43], the elimination of steroids showed a considerable acute rejection rate and greater risk of graft loss, a more recent meta-analysis with new immunosuppressants and triple therapy, worse graft survival was not observed although a greater risk of acute rejection was, showing decreased cholesterol levels as the beneficial effect[44].

The late (3-6 months)[45,46] or early (< 1 week)[47,48] elimination of steroids has been analyzed in randomized multicenter studies in regimens with CsA[46,47] or TAC[45,48] and MMF. Induction therapy with basiliximab[47] or daclizumab[48] was used in patients with early withdrawal. Steroid suppression did not show a greater incidence of acute rejection in follow-up between 6 and 24 months, and some cardiovascular risk factors (lipids, blood glucose and blood pressure) improved with no differences in graft survival[45-48]. Treatment with TAC/MMF/basiliximab or TAC/SRL/basiliximab with two days of steroids allowed the non-reintroduction of steroids in 100% of patients, excellent patient and graft survival and a low incidence of acute rejection[49]. In said study serial biopsies done at 1, 6, 12 and 24 months showed a lower incidence of subclinical acute rejection and moderate/severe CTN in the SRL group.

Although more long-term follow-up is required, steroid suspension seems advisable in patients with no immunological risk who are treated with CNI and MMF or SRL. Early suppression may be the preferred strategy. The beneficial effect of steroid suppression is greater in the pediatric population[50].

ABSENCE, MINIMIZATION OR ELIMINATION OF CALCINEURIN INHIBITORS

Despite the effectiveness of these agents in renal transplantation, their nephrotoxic effect and their relation to the development of CTN (6, 8, and 51) have led to designing protocols that reduce these effects. New antiproliferative agents and mTOR inhibitors have favored this.

Randomized prospective studies with CNI-free regiments based on SRL associated to azathioprine or MMF have shown better graft function compared to the use of CsA, with no significant differences in the acute rejection rate or graft survival[33-35]. In these cases the association of basiliximab allows for a very low incidence of acute rejection[35].

A prospective study on minimizing CsA the first year after the transplant in patients with stable renal function and who are treated with MMF and steroids showed an improved glomerular filtration rate, lower blood pressure, triglycerides and uric acid in comparison with maintenance with standard CsA doses[52]. CNI minimization immediately after the transplant, associated to SRL or MMF (TAC), or SRL (CsA), with daclizumab showed a low incidence of acute rejection in the 3 arms but significantly lower in patients with TAC compared to CsA[53]. However, TAC levels during the first year showed values that were close to those considered to be standard.

CsA elimination in patients treated with azathioprine and steroids in a systematic review of 13 clinical trials proved an increase in the risk of acute rejection with no repercussion on graft survival[43]. More recently a randomized prospective study in three treatment arms compared the effectiveness of combined treatment with Cs, MMF and steroids compared to the withdrawal of steroids or CsA after 6 months. CsA suppression improved renal function without an increase in the acute rejection rate, but it did show a greater incidence of chronic rejection proven by biopsy[46]. Most recent randomized prospective studies on CNI elimination have been based on immunosuppression with SRL[54]. A systematic review of SRL-based clinical trials has proven that CsA or TAC suspension improves renal function and blood pressure figures, although it increases the risk of acute rejection with no differences in graft survival after one year[54]. It is important to stress the results of a large multicenter study in patients treated with CsA, SRL and steroids who were randomized after 3 months to CsA elimination or maintenance, which showed better graft survival after 4 years in the CsA suppression group (91.5% vs 84.2%; $p<0.024$)[39]. Furthermore, the calculated glomerular filtration rate and blood pressure levels significantly improved in said study, showing no differences in the incidence of acute rejection[39,55]. The protocol biopsies conducted a year after the transplant in a group of 64 non-selected patients of this study showed an improvement in chronic interstitial and tubular lesions with no increase of subclinical rejection in patients with CsA suppression[56].

There is no long-term evidence of the existence of the benefit of regimens with the absence or minimization of calcineurin inhibitors. However the association of SRL and MMF does not increase the short-term risk of acute rejection in patients with no immunological risk, and induction with basiliximab or daclizumab is advisable. CsA elimination after 3 months in regimens with SRL does not increase the acute rejection rate, and after one year renal histo-

logy, glomerular filtration rate and midterm graft survival improve. The problems of SRL associated to a delayed recovery in acute tubular necrosis, healing of the surgical wound and development of lymphoceles[57] require specific approaches for decreasing these adverse effects.

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