Steroid sparing strategies in renal transplantation

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Introduction

In the last few years, the aim in the majority of immunosuppressive regimens has been to reduce the incidence and severity of acute rejection, because acute rejection is considered a prognostic factor for poor graft outcome. In the last decade, many renal transplant centres have used triple therapy consisting of a calcineurin-inhibitor (CNI), an antimetabolite, and steroids as induction and maintenance regimens. In this period, nearly all kidney transplant recipients received corticosteroid therapy prior to discharge, although the proportion of patients receiving steroids declined slightly at the end of this period [1]. This trend may reflect concern in the transplant community about the importance of steroid-related morbidity in transplanted patients. As a consequence, different attempts have been made to spare steroids in order to reduce co-morbidity. However, steroid sparing strategies may increase the risk of acute and chronic rejection that in turn may jeopardize transplant outcome. In this article we will first review the attempts to spare steroids in renal transplantation in the so-called cyclosporine (CsA) era, and subsequently discuss the strategies tried after the introduction of new xenobiotic immunosuppressants and biological agents.

Steroid-sparing protocols in the CsA era

The main questions raised by steroid-sparing protocols are patient selection, the timing after transplantation and the concomitant immunosuppression.

Initial reports in the CsA era pointed to the increased risk of acute rejection after steroid withdrawal in patients with renal grafts treated with CsA and azathioprine (AZA) [2]. In paediatric patients receiving CsA, stopping steroids was followed by a 56% rate of acute rejection episodes [3]. In a single centre experience with 100 patients, early discontinuation, black race and renal function were identified as risk factors for subsequent rejection episodes after steroid withdrawal [4]. In a multicentre randomized and double-blind, placebo controlled Canadian trial in 523 patients under CsA therapy, prednisone discontinuation at 90 days after transplantation significantly reduced actuarial 5 year graft survival rates.
to 73% in comparison to 85% in patients who remained on prednisone [5]. Results of a meta-analysis suggested that avoiding steroid therapy from the time of transplantation or withdrawing steroid therapy at some time after transplantation increased the risk of acute allograft rejection but without adversely affecting patient or graft survival [6]. As expected, beneficial effects of maintenance immunosuppression were catch-up growth after discontinuation of steroids in children [7] and reduced incidence of hypertension, improved glycaemic control, as well as reduced total levels of serum lipids. Nevertheless, the long-term consequences of steroid-free CsA-based immunosuppression in renal transplantation were clarified by these early studies reported in the mid-nineties [8]. In a prospective and randomized trial, 100 patients were included 1–6 years after transplantation. They were treated with CsA and AZA. Discontinuation of steroids over about 4 months caused a rise in mean plasma creatinine at the end of the withdrawal period and at 2–3 years from trial entry. Changes in several clinical and metabolic indices were also observed in association with steroid withdrawal. Blood pressure declined, but the reduction was not sustained: lowering of blood pressure was more evident immediately after steroid withdrawal than after 1 year. The data from this trial indicated that (i) steroid withdrawal was feasible in most patients with stable graft function on triple immunosuppression and (ii) had potentially beneficial metabolic effects, but (iii) was associated with reduced graft function in a substantial proportion of patients. Clearly there was a need for caution with respect to the long-term outcome [9]. Another prospective trial compared CsA monotherapy with AZA-prednisone maintenance therapy starting 3 months after transplantation. The incidence of rejection within 3 months of steroid withdrawal or after conversion from CsA to AZA was 30 and 25%, respectively. Two years after transplantation, however, serum creatinine levels were significantly lower in the AZA-prednisone group than in the CsA group. Yet the graft survival was no different 5 years after transplantation [10]. Late steroid withdrawal in patients on CsA with stable renal function at least 1 year after kidney transplantation showed that acute rejection was the main cause of withdrawal failure (26%), although no grafts were lost due to rejection [11]. Beneficial effects were found regarding hypertension, hypercholesterolaemia, hyperglycaemia and Cushingoid. An Italian prospective study [12] compared CsA monotherapy with AZA as an adjunct to CsA at the time of steroid withdrawal 6 months after transplantation. The endpoint was acute rejection. The need to start again with steroids because of acute rejection was significantly more frequent in the group on CsA monotherapy than in the group on CsA–AZA (57 vs 29%). Nevertheless, serum creatinine values did not differ and graft survival was similar in both groups. In contrast, studies assessing gradual withdrawal of steroids in the course of 6 months in patients receiving therapy with CsA and AZA found that this procedure was associated with a low rate of acute rejection [13]. The above results suggest that the addition of an antimetabolite to a CNI may allow patients to remain steroid free. A meta-analysis on randomized, controlled trials of immunosuppression withdrawal comprised more than 1400 patients investigated in studies reported during the nineties. The conclusion was that prednisone withdrawal entailed a 14% higher risk of rejection and a 40% higher risk of late graft failure [14], thus raising concerns about the safety of steroid-sparing strategies. In accordance, the published European Best Practice Guidelines for Renal Transplantation on late steroid or CsA withdrawal emphasized that steroid withdrawal is safe only in a proportion of graft recipients. It is recommended only in low-risk patients, and the efficacy of the remaining immunosuppression must be taken into consideration (B). Moreover, the Guidelines also recommend that after steroid withdrawal, graft function has to be monitored very carefully because of the risk of a delayed, but continuous, loss of function due to chronic graft dysfunction. In the case of functional deterioration or dysfunction, steroids should be re-administered (C) [15] (where B and C are degrees of evidence in the Evidence Based Medicine).

**Steroid-sparing regimens with new immunosuppressants**

Recently, however, the interest in steroid-sparing strategies has been rekindled by the introduction of new xenobiotic immunosuppressants, such as mycophenolate mofetil (MMF) and biological agents which may be able to reduce—in conjunction with CNIs—the incidence of acute rejection to very low rates. In our centre we performed an open pilot study in a small number of low-risk patients treated with CsA and steroids. Elimination of prednisone was not accompanied by rejection episodes, and renal function remained stable, suggesting that corticosteroids could be safely and successfully withdrawn after renal allograft recipients receiving CsA and MMF [16]. The feasibility of steroid-sparing strategies in patients treated with MMF has been extensively explored in the last few years. With the rationale that late steroid withdrawal was safer than early elimination, initially in prospective and controlled trials steroid withdrawal was attempted 3 months after transplantation in patients receiving MMF. More recently, however, steroids have been stopped a few days after transplantation or even completely avoided.

A European multicentre, randomized, double-blind, 6-month, controlled steroid dose-reduction study assessed 500 renal transplant recipients. The study had an open 6-month follow-up arm (low/stop) where corticosteroids were given at half the dosage of control for 3 months from the date of transplantation, and then withdrawn [17]. The comparator group received conventional doses of steroids. Both arms were given CsA and MMF. At 6 months the low/stop group had
significantly more biopsy-proven acute rejection episodes than the control (23 vs 14%) and at 12 months this increased to 25 vs 15%. However, most rejections were Banff grade I, and renal function remained similar in both groups. The frequency of graft loss at month 12 was 5% in the low/stop group vs 4% in the controls. The lipid profile, bone mineral density and blood pressure were better in patients off steroids. This first large study with MMF indicated that reduction and withdrawal of prophylactic corticosteroids is feasible without an unacceptable increase in serious rejection episodes. In contrast, a similar trial with a similar sample size conducted in the USA stopped recruitment after half the patients were enrolled, because an excessive frequency of rejection was observed in the steroid withdrawal group [18]. A careful review of this study showed that the high incidence of acute rejection was mainly restricted to African American patients. Caucasians had a similar rate of rejection to that observed in the previous European study. In a recently published uncontrolled study in which African American transplant patients were initially treated with sirolimus, tacrolimus and corticosteroids, prednisone was withdrawn from eligible patients free of acute rejection beginning as early as 3 months post-transplant [19]. Seven percent of these patients developed acute rejection and at last follow-up, 27 of 30 patients (90%) remained steroid-free. However, there was a trend toward an increased serum creatinine concentration before and after steroid withdrawal. Consequently, concerns persist with respect to steroid withdrawal in African American patients even when they are on potent immunosuppressive regimens, e.g. on two macrolides in this trial.

The use of MMF provides the opportunity to compare CNI withdrawal and cessation of steroids in the same trial. This innovative approach has been explored in a Dutch study [20]. At 6 months after transplantation, 212 patients were randomized to discontinuation of CsA, discontinuation of prednisone, or continued triple drug therapy comprising these two agents plus MMF. Interestingly, patients off steroids experienced a similar incidence of acute and chronic rejection than the triple therapy group and less than those without CsA 2 years after transplantation surgery.

Biological immunosuppressants, anti-IL2-R monoclonal antibodies or polyclonal preparations may also help to design steroid sparing strategies. A single centre study aimed to minimize the toxicity of steroids and CNIs at the same time. A regimen comprising daclizumab, low dose tacrolimus, MMF and steroid discontinuation was compared to a conventional regimen comprising tacrolimus, MMF and steroids [21]. In this trial, patients free of steroids experienced significantly fewer acute rejections. Gift function at 1 year was significantly better than in the group on triple therapy. In 51 patients receiving living related donor kidney grafts, polyclonal rabbit anti-thymocyte globulin was used in conjunction with MMF and CsA. The protocol comprised rapid discontinuation of steroids 5 days after transplantation. With this immunosuppressive protocol, 87% of the patients remained free of acute rejection at 12 months after transplantation. Renal function was acceptable and no differences were observed compared to historical controls treated with triple therapy without induction [22]. This group has recently also reported that with this immunosuppressive strategy, patients free of steroids had excellent 4-year actuarial patient survival (92%), graft survival (90%), acute rejection-free graft survival (86%) and chronic rejection-free graft survival (95%) [23]. In a similar approach, basiliximab added to a maintenance regimen consisting of CsA and MMF mofetil was studied for its effectiveness in allowing early corticosteroid withdrawal at 4 days after transplantation in de novo renal allograft recipients. The incidence of biopsy-proven acute rejection at 12 months was not significantly different between the steroid withdrawal group (20%) and the standard treatment group (16%), and renal function remained stable and similar in both groups at the end of the first year [24]. In the same direction [25], a prospective multicentre study investigated whether it is feasible to withdraw steroids early after transplantation with the use of anti-IL-2R α induction, tacrolimus and MMF. A total of 364 patients were randomized to receive either two doses of daclizumab and, for the first 3 days, high doses of prednisolone or steroids (tapered to 0 mg at week 16). All patients received tacrolimus and MMF. The incidence of biopsy-confirmed acute rejection at 12 months was not different between the daclizumab group (15%) and the controls (14%). Graft survival at 12 months was comparable in the two groups. These last studies suggest that in renal transplantation regimens without steroids are around the corner. Trials comparing a very short course of steroids with complete avoidance are in progress in adult transplant recipients. This therapeutic alternative has been investigated in a paediatric population because children will benefit most from steroid-free protocols. With a completely steroid-free immunosuppressive regimen remarkable results were achieved in 100 children: after an initial 10-day antithymocyte induction and on a maintenance therapy with CsA and MMF, the rate of acute rejection was low (13%), and 4-year graft survival was 82% [26]. In a small single centre study with 10 low risk paediatric transplant recipients, steroids were substituted by extended daclizumab use in combination with tacrolimus and MMF. The results were compared to steroid-based historical controls [27]. In this preliminary report, there were no clinical acute rejection episodes and protocol biopsies did not display signs of chronic rejection. Besides the benefits on metabolic profile and cosmetic appearance, patients in the steroid-free regime did not require anti-hypertensive drugs. Renal function and growth were optimal.

Steroid discontinuation may also affect the pharmacokinetics of MMF mofetil. Steroid withdrawal is followed by an increase of mycophenolic acid exposure due to a decrease in its clearance. Steroids increase the activity of uridine diphosphate-GT, which
Steroid-sparing regimens close long-term follow-up will graft and patient outcomes. To assess the real impact of entry into a new era of low toxicity regimens. Their aim is responsible for mycophenolic acid metabolism [28] and such increased activity is reversed by steroid withdrawal. The resulting increased exposure to mycophenolic acid may compensate for the effects of steroid discontinuation on immunosuppression.

In summary, the interest of the transplant community in avoiding steroid-related morbidity and the new therapeutic arsenal used in renal transplantation allow entry into a new era of low toxicity regimens. Their aim is to avoid drug-related adverse effects and to improve graft and patient outcomes. To assess the real impact of steroid-sparing regimens close long-term follow-up will be necessary.

Conflict of interest statement. None declared.

References