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REVIEW ARTICLE

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Interleukin-2 receptor antagonists and aggressive steroid minimization strategies for kidney transplant patients

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Abstract Steroid withdrawal during the first week after transplantation surgery, or complete avoidance of steroids, offers potential benefits. The interleukin-2 (IL-2) receptor antibodies, basiliximab and daclizumab, can enable aggressive steroid minimization protocols that are efficacious while reducing toxicity. A multicenter, randomized trial of kidney transplant recipients has shown the incidence of biopsy-proven acute rejection with basiliximab, cyclosporine and mycophenolate mofetil with steroids withdrawn at day 5 to be similar to a conventional triple-therapy regimen. A single perioperative dose of corticosteroids with an IL-2 receptor antagonist also seems as efficacious as standard steroid therapy. Corticosteroid-minimization with IL-2 receptor antagonists has also been investigated with sirolimus-containing regimens and has shown excellent outcomes. Experience with complete steroid avoidance, using an IL-2 receptor antagonist, is limited, but initial results are promising, particularly in pediatric patients. Administration of an IL-2 receptor antagonist with aggressive steroid minimization in selected, well-monitored patients seems reasonable, but further trials are required to define optimal protocols.

Keywords IL-2 receptor antagonist · Basiliximab · Daclizumab · Corticosteroids · Renal

Introduction

Corticosteroids have played an integral part in preventing allograft rejection since the first successful kidney transplant took place in 1954. Despite the introduction of a range of more selective immunosuppressive agents, corticosteroid therapy remains a standard part of post-transplant management. However, the complications associated with corticosteroids are such that strategies to minimize corticosteroid load are high on the agenda of transplant practitioners. The long-term adverse effects of corticosteroids include susceptibility to infection, increased cardiovascular risk factors, weight gain, osteopenia, cataracts and body disfigurement [1], as well as growth retardation in children [2], all of which incur management costs [3] and risk non-compliance in addition to burdening patients with further morbidity.

Furthermore, sustained corticosteroid therapy predisposes to atherosclerotic cardiovascular disease through increased risk of hypertension, hyperlipidemia and insulin resistance [4], an issue of particular concern since cardiovascular disease is now the leading cause of death following renal transplantation [5, 6]. Withdrawal of corticosteroids in renal transplant patients has been shown to lead to an improvement in bone density and a reduction in the severity of diabetes mellitus, and a reduced requirement for antihypertensive medication and lipid-lowering agents [7, 8, 9].

Many of the adverse events associated with corticosteroids are, of course, common to other classes of

immunosuppressive drugs. Accordingly, attention is increasingly being focussed on strategies that could harness the efficacy of new immunosuppressants using combinations that allow minimizing corticosteroid exposure without the effect of a different set of adverse events.

Introduction of the monoclonal antibody antagonists basiliximab and daclizumab, which bind with high specificity and affinity to the interleukin-2 (IL-2) receptor, provides an important opportunity for more rigorous corticosteroid minimization than has been achieved so far, without loss of efficacy. 'Aggressive' corticosteroid-sparing strategies range from early withdrawal of corticosteroids (i.e. during the first week after transplantation) to the complete avoidance of corticosteroids in the immunosuppressive protocol.

This article reviews clinical evidence on the use of the IL-2 receptor antagonists, basiliximab and daclizumab for supporting aggressive corticosteroid minimization protocols, and we offer suggestions as to the type of patients most likely to benefit from this approach.

Conventional corticosteroid-sparing strategies

During the azathioprine era, attempts to withdraw corticosteroids were made relatively late, usually not earlier than 3 or 6 months after transplantation. Corticosteroid withdrawal during the first 3 months after transplantation, or complete avoidance of corticosteroids in patients receiving only cyclosporine and azathioprine, increased the risk of acute allograft rejection [10, 11]. In one prospective study, corticosteroids were successfully withdrawn at 6 months after transplantation in 54% of patients receiving cyclosporine and azathioprine [12], but generally, to avoid late rejection, corticosteroid doses were tapered over the first year after transplantation to a low maintenance dose without attempting outright withdrawal.

Corticosteroid withdrawal received renewed attention with the introduction of mycophenolate mofetil (MMF) in the mid-1990s; results were mixed, however. A large prospective study was undertaken in which patients with no history of rejection were randomized at 3 months after renal transplantation to corticosteroid discontinuation or to a maintenance dose of 10 mg/day; all patients received cyclosporine and MMF [7]. The trial was stopped early due to excess rejection in the corticosteroid-withdrawal group (31% vs 9% in the group that continued to take corticosteroid at 1 year, $P=0.0007$). The greatest increase in risk of rejection was among black patients (40% vs 16%, $P<0.001$), and the majority of withdrawal patients did not experience rejection and benefited in terms of significantly lower cholesterol, improved renal function and lower requirements for antihypertensive agents. In another trial, 500 de novo renal transplant patients receiving cyclosporine and MMF were randomized to either standard corticosteroid dosing or to half the control dose of corticosteroids for 3 months followed by discontinuation, the incidence of acute rejection was again significantly higher in the corticosteroid-withdrawal group (24% vs 14% at 6 months, $P=0.008$), although most rejection episodes were mild and reversible. The corticosteroid-withdrawal patients had significantly lower serum cholesterol, triglycerides and systolic blood pressure, with greater bone density, than the corticosteroid-continuation group [13]. Similar findings have been reported in patients receiving tacrolimus and MMF [14], with a 6% increase in the incidence of rejection reported at 6 months in patients who stopped taking corticosteroids at 3 months compared to 1% in the control group that continued corticosteroid treatment. Currently, most transplant centers elect to taper the dosage of corticosteroid but continue to use a low dosage indefinitely.

Aggressive corticosteroid minimization strategies

More aggressive corticosteroid minimization (either withdrawal during the first week or avoidance) offers potential benefits compared to conventional corticosteroid-sparing strategies. Firstly, for patients undergoing early steroid withdrawal or steroid avoidance, acute rejection is most likely to occur during the first few days or weeks after transplantation surgery when the patient is being closely monitored and when anti-rejection treatment or immunosuppression modification can be implemented promptly. Moreover, rejection episodes that occur before hospital discharge, or within the first 60 days after transplantation, are associated with a reduced risk of chronic rejection [15] and improved long-term allograft survival [16] compared to rejection occurring after 6 months.

Secondly, early withdrawal or avoidance of corticosteroids leaves the immune system unmodified by prolonged corticosteroid therapy, such that corticosteroid dependence does not develop with the associated risk of a 'rebound' immunological response when corticosteroid is discontinued [17].

Finally, aggressive corticosteroid minimization allows the patient to avoid the adverse effects of corticosteroids on a host of metabolic functions, particularly during the early post-transplant period when the steroid dosage is conventionally high. The skeletal effects of corticosteroids, for example, are known to begin within the first month of administration [18].

The highly selective, short-term immunosuppressive effect of IL-2 receptor antagonists suggest that this class of drug could enable early corticosteroid withdrawal or avoidance, since their effect is concentrated on the highly

immunogenic period immediately after transplantation. Basiliximab has a half-life of 1 to 2 weeks and when administered in two doses of 20 mg at days 0 and 4 after transplantation, it saturates IL-2 receptors on peripheral lymphocytes for 4 to 6 weeks, the period of highest risk for acute rejection [19]. Daclizumab has a half-life of 20 days and depending on the regimen (two or five doses) can result in saturation of IL-2 receptors for 70 to 100 days. IL-2 receptor antagonists exert a complementary immunosuppressive effect to both calcineurin inhibitors and MMF, and significantly reduce the incidence of acute rejection when used in addition to standard therapy [20, 21].

Two single-center studies have already indicated that the use of an IL-2 receptor antagonist facilitates late withdrawal of corticosteroids (5 to 6 months after transplantation) without excessive acute rejection [22, 23]. Importantly, using IL-2 receptor antagonists does not increase the risk of cytomegalovirus infection or malignancies [21] and the side-effect profiles of basiliximab and daclizumab are similar to placebo.

Early corticosteroid withdrawal using an IL-2 receptor antagonist

The ability of IL-2 receptor antagonists to facilitate corticosteroid withdrawal during the first week after transplantation has been evaluated in several prospective studies that have used a variety of different immunosuppressive regimens (Table 1). A multicenter, randomized trial compared the incidence of biopsy-proven acute rejection among 83 primary renal transplant patients receiving basiliximab, cyclosporine and

Table 1 Design and outcome of aggressive steroid-minimization trials using an IL-2 receptor antagonist (*BPAR* biopsy-proven acute rejection, *CsA* cyclosporine, *i.v.* intravenous)

Design and duration	Number	Treatment group	Control group	Incidence of BPAR	*P*	Reference
Open label Randomized Multicenter 12 Months	83	Basiliximab CsA MMF Steroids to day 4	Basiliximab CsA MMF Standard steroid therapy	Treatment: 20% Control: 16%	n.s.	[24]
Open label Randomized Multicenter 6 Months	538	Daclizumab Tacrolimus MMF Single i.v. steroid dose (day 0)	Tacrolimus MMF Standard steroid therapy	Treatment: 16.5% Control: 16.5%	n.s.	[26]
Open label Randomized Multicenter 6 Months	450	Basiliximab Tacrolimus Single i.v. steroid dose (day 0) or tacrolimus MMF Single i.v. steroid dose (day 0)	Tacrolimus MMF Standard steroid therapy	Basiliximab/tacrolimus: 26% Tacrolimus/MMF: 31% Control: 8%	<0.001	[27]
Single group Multicenter 6 Months	77	Basiliximab Tacrolimus Sirolimus Steroids to day 4	None	23% (clinical & subclinical)	-	[28]
Open label 12 Months	91	Basiliximab Tacrolimus or CsA MMF Steroids days 0 and 1	None	14%	-	[29]
Single group Multicenter 12 Months	57	Daclizumab CsA MMF	None	25%[a]	-	[30
Single group Historical controls Pediatric Mean follow-up 20 Months	57	Daclizumab (6 months) Tacrolimus MMF	Daclizumab or ALG/ATG MMF (50% of patients) Standard steroid therapy	Treatment: 8%[b] Controls: 32%[b]	<0.001	[31]

[a]Three of 14 episodes of rejection were not biopsy proven
[b]Not biopsy proven

MMF who were randomized to corticosteroid withdrawal at day 4 after transplantation or to standard corticosteroid therapy [24]. At 12 months, there was no significant difference in the incidence of rejection in the basiliximab/corticosteroid-withdrawal group (20%) and the control group (16%), and 73% of the patients in the corticosteroid-withdrawal group remained corticosteroid-free at 6 months, compared to only 5% in the control group. The median time to rejection was shorter in the corticosteroid-withdrawal group (31 vs 65 days), but the majority of episodes were mild [25] and easily reversed with corticosteroid therapy. Early corticosteroid withdrawal was not associated with any detrimental effect on renal function, infection or adverse events compared to the control group. Use of basiliximab with cyclosporine and MMF thus seems to allow for early corticosteroid withdrawal.

A further prospective study compared the use of the IL-2 receptor antagonist daclizumab with a single perioperative intravenous dose of corticosteroids against a standard corticosteroid regimen, combined with tacrolimus and MMF [26]. In this cohort of 538 renal transplant patients, the incidence of biopsy-proven acute rejection and other efficacy parameters were similar between the two treatment groups (16.5% in each group), with a similar safety profile other than a higher incidence of pneumonia in the corticosteroid-withdrawal group and increased incidence of new-onset diabetes mellitus in the corticosteroid-maintenance group.

An aggressive corticosteroid-minimization regimen using only an IL-2 receptor antagonist and a calcineurin inhibitor, or a calcineurin inhibitor with MMF without anti-IL-2 induction, does not seem adequate to effectively protect against rejection. In a 6-month study, 450 renal transplant patients were randomized to three treatment groups: basiliximab and tacrolimus with a single intravenous dose of corticosteroids on the day of transplantation; tacrolimus and MMF with a single intravenous corticosteroid dose, or triple therapy with tacrolimus, MMF and corticosteroids [27]. Biopsy-proven acute rejection occurred significantly more often, and renal function was inferior, in both dual-therapy groups compared to the standard-therapy group (Table 2).

Corticosteroid-minimization with IL-2 receptor antagonists was also investigated using sirolimus-containing regimens. A multicenter, open-label pilot study in renal transplant patients evaluated a regimen of basiliximab, tacrolimus and sirolimus with corticosteroids tapered rapidly from day 1 to day 4 after transplantation, then discontinued [28]. Eighty per cent of patients continued to receive corticosteroid-free immunosuppression at 6 months, with a 100% patient and graft survival. At one year biopsy-proven rejection (clinical and subclinical) was reported in 23% of the patients. The majority of rejections were graded mild and mean serum creatinine was 124 μmol/l at 6 months. These promising results merit further clinical investigation.

An ongoing study of 91 non-sensitized renal transplant patients is assessing the effect of early corticosteroid discontinuation on the occurrence of chronic allograft nephropathy [29]. All patients received either basiliximab with tacrolimus or cyclosporine, and sirolimus or MMF, with an intravenous dose of methylprednisolone on day 0 and day 1. Results at 1 year have proved excellent, with >90% graft survival, 14% incidence of acute rejection, and approximately 60% of patients free of chronic allograft nephropathy. Outcomes were similarly favorable regardless of whether tacrolimus or cyclosporine was used.

Corticosteroid avoidance using an IL-2 receptor antagonist

Fewer studies have been carried out in which an IL-2 receptor antagonist is used within an entirely cortico-

Table 2 Efficacy and safety outcomes at 6 months among renal transplant recipients. Tacrolimus dose was identical in all groups; MMF dose was identical in groups 2 and 3. A single dose of intravenous steroids was administered on the day of transplantation in groups 1 and 2 [27]

Parameter	Group 1 Basiliximab + tacrolimus +single dose steroids ($n=152$)	Group 2 Tacrolimus + MMF +single dose steroids ($n=151$)	Group 3 Tacrolimus + MMF + standard steroids ($n=147$)	P^a
Biopsy-proven acute rejection (% patients)	26	31	8	<0.001
Steroid-resistant acute rejection (% patients)	5	4	2	n.s.
Median serum creatinine (μmol/l)	135	135	123	n.s.
Anemia (% patients)	14.5	12.6	24.5	<0.05
Leukopenia (% patients)	5.9	18.5	7.5	<0.05
Tremor (% patients)	4.6	7.3	0.7	<0.05

[a]Multiple test for comparison with control

steroid-free regimen. A pilot study was carried out in which corticosteroid-free immunosuppression was attempted in 57 renal transplant patients treated with daclizumab, MMF and cyclosporine [30]. There was no control group. At 1 year, patient and graft survival were 95% and 89%. Fourteen patients (25%) experienced an episode of acute rejection, all but one of which was readily reversed with corticosteroids; mean serum creatine in the rejection-free patients was 149 μmol/l. At 1 year, only two patients required three or more antihypertensive agents compared to 17 patients at baseline, and there was no significant deterioration in lumber or femoral bone density compared with pre-transplant values.

In pediatric patients, eliminating corticosteroids is a particularly appealing goal because growth retardation is associated with long-term corticosteroid therapy. Alternate-day corticosteroid dosing was attempted but it led to a higher incidence of acute rejection [2] and it has not been widely adopted. A corticosteroid-free protocol using tacrolimus and MMF with extended administration of daclizumab over the first 6 months after transplantation was used in 57 pediatric patients [31]. The cumulative dose of daclizumab was 10 mg/kg versus the standard dose of 5 mg/kg. Results were compared to a matched historical cohort of 50 patients receiving tacrolimus and corticosteroids with daclizumab or another induction therapy; 50% of the control patients also received MMF.

At a mean follow-up of 20 months, death-censored graft survival was 100%, with an 8% incidence of clinical rejection compared to 32% in the corticosteroid-treated control group ($P<0.001$). Growth was significantly greater in the corticosteroid-free group, particularly among patients younger than 5 years of age, and estimated creatinine clearance was significantly higher in the corticosteroid-free cohort 6 months after transplantation. Incidence of hypertension was lower in the corticosteroid-free patients but hypercholesterolemia and hypertriglyceridemia did not differ significantly. Infection rates were also similar between the two treatment groups. These excellent outcomes emphasize the potential benefits of using IL-2 receptor antagonists to promote either corticosteroid avoidance or early corticosteroid elimination in the pediatric population, and controlled studies should be undertaken to identify optimal protocols.

Patient selection for early corticosteroid withdrawal or avoidance

Aggressive corticosteroid minimization is not appropriate for all patients, and clinical experience to date is generally limited to primary transplants and to patients considered to be at low risk of rejection. In addition corticosteroid avoidance in patients with delayed graft function may result in slower recovery of renal function [32].

Currently, it would seem prudent to limit early corticosteroid withdrawal, and certainly complete corticosteroid avoidance, to patients at relatively low immunologic risk. This would include primary transplants, living-related or well-matched living or cadaveric graft recipients, and those with low PRA status (e.g. $<20\%$). Patients with delayed graft function are not suitable for early corticosteroid withdrawal because of their heightened risk of rejection, and evidence to date indicates that aggressive corticosteroid-minimization strategies carry higher risk of rejection among African-American patients [7], although a recent study has indicated that corticosteroid-free immunosuppression may not in fact affect the rejection rate or graft survival in the African-American population [33].

Certain patient types are at high risk of corticosteroid-related complications and are likely to particularly benefit from early corticosteroid withdrawal and minimization of corticosteroid exposure: pediatric patients; those who have pre-existing skeletal disease or who are at risk of developing it; patients with atherosclerotic cardiovascular disease; patients with known susceptibility for metabolic disease such as diabetes mellitus; or obese patients. The relative benefits of early corticosteroid withdrawal or complete avoidance in these populations has yet to be determined, but in the interim it would seem reasonable to select patients with these characteristics preferentially for aggressive corticosteroid minimization protocols unless precluded by the individual's immunologic risk status. Careful selection of patients, with close monitoring, is essential for successful minimization of corticosteroid exposure.

Conclusion

The role of the IL-2 receptor antagonists, basiliximab and daclizumab, within the immunosuppression armamentarium is well established due to their proven effect in reducing acute rejection and almost complete absence of side effects. More recently, the evidence base for the benefits of IL-2 receptor antagonists in supporting early and safe withdrawal of corticosteroids, or indeed complete elimination of corticosteroids, has grown, with a number of trials using a variety of different protocols showing excellent outcomes. A well-designed randomized trial compared early steroid withdrawal in patients receiving basiliximab-cyclosporine-MMF against a standard triple therapy regimen showing no increase in the risk of rejection [24], and initial results from a study that used daclizumab, tacrolimus and MMF indicate similar results [26].

Other trials have used less rigorous methodology, often not including a control group, or have used less

successful drug combinations. Thus, while results to date are highly promising, randomized trials are necessary to refine IL-2 receptor antagonist-based protocols that maximize the opportunity for aggressive corticosteroid minimization while maintaining efficacy. Key questions yet to be answered include the relative efficacy and safety of early corticosteroid withdrawal compared to corticosteroid avoidance; the use of a single dose of intravenous corticosteroids at the time of transplantation versus administration for several days after transplantation; and the optimal maintenance-drug combination to support corticosteroid withdrawal or avoidance with an IL-2 receptor antagonist.

The issue of steroid avoidance versus early withdrawal will be addressed by the ongoing FREEDOM trial, in which 330 patients are being randomized to corticosteroid avoidance, early corticosteroid withdrawal (at 7 days after transplantation) or standard corticosteroid maintenance therapy, in combination with basiliximab, cyclosporine and enteric-coated mycophenolic sodium, and incidence of biopsy-proven acute rejection and adverse events are being compared. First results are expected in late 2004.

Based on current evidence, it seems that the IL-2 receptor antagonists supports early steroid withdrawal, maintaining efficacy without conferring additional toxicity. Although the results of further trials are awaited, it would seem reasonable to harness the potential benefits for patients by attempting early withdrawal of corticosteroids in selected, well-monitored patients using a regimen containing an IL-2 receptor antagonist, a calcineurin inhibitor and mycophenolic acid or a proliferation signal inhibitor.

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