EVIDENCE-BASED MEDICINE

Corticosteroid minimization in renal transplantation: Careful patient selection enables feasibility

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Abstract

AIM
To explore the benefits and harms of corticosteroid (CS) minimization following renal transplantation.

METHODS
CS minimization attempts to improve cardiovascular risk factors (hypertension, diabetes, dyslipidemia), to enhance growth in children, to ameliorate bone disease and to lead to better compliance with immunosuppressive agents. Nevertheless, any benefit must be carefully weighed against the reduction in net immunosuppression and the potential harm to renal allograft function and survival.

RESULTS
Complete CS avoidance or very early withdrawal (*i.e.*, no CS after post-transplant day 7) seems to be associated with better outcomes in comparison with later withdrawal. However, an increased incidence of CS-sensitive acute rejection has been observed with all CS minimization strategies. Among the prerequisites for the safe application of CS minimization protocols are the administration of induction immunosuppression and the inclusion of calcineurin inhibitors in maintenance immunosuppression regimens.

CONCLUSION
Transplant recipients at low immunological risk (primary transplant, low panel reactive antibodies) are

thought as optimal candidates for CS minimization. CS avoidance may also be undesirable in patients at risk for glomerulonephritis recurrence or with severe delayed graft function and prolonged cold ischemia time. Thus, CS minimization is not yet ready for implementation in the majority of transplant recipients.

Key words: Acute rejection; Corticosteroid withdrawal; Corticosteroid minimization; Corticosteroid avoidance; Immunosuppression; Renal transplantation

Core tip: Although corticosteroids have been traditional components of immunosuppressive regimens in renal transplantation, corticosteroid minimization strategies are developed in an attempt to mitigate their many side-effects. The benefit from this approach must be balanced against the risk of acute rejection due to insufficient immunosuppression and the potential harm to allograft survival. We present an overview of these strategies and their impact on clinical outcomes analyzing the key clinical trials performed. Furthermore, we focus on patient selection according to the immunological risk and the induction immunosuppression, the principal factors that determine the success of corticosteroid withdrawal and avoidance protocols.

INTRODUCTION

Corticosteroids (CS) have been ubiquitously included in immunosuppressive regimens since the early days of renal transplantation (Tx). They have significantly contributed to the successful transformation of a highly experimental intervention into a universally adopted clinical treatment. However, their use is associated with a plethora of adverse events due to their non-specific mode of action. The negative impact of CS on cardiovascular disease risk factors such as hypertension, diabetes mellitus, and dyslipidemia is well known. Non-cardiovascular adverse events such as growth retardation, impaired wound healing, subcapsular cataract, bone problems (osteoporosis, fractures, avascular necrosis) and cosmetic effects leading to patient non-compliance are equally established[1-4]. An increasing interest in minimizing the exposure to CS in transplant recipients with stable allograft function has been manifested by renal transplant clinicians to reduce the morbidity burden associated with their use. In the United States, CS avoidance regimens were administered to 23% of all first renal transplant recipients in 2004[5]. Among the remaining 77% who were discharged on CS, roughly 10% had CS withdrawn during the first post-transplant year. Nonetheless, this policy has to be carefully balanced against the risk of acute rejection due to insufficient immunosuppression and should not jeopardize renal allograft function and survival.

MATERIALS AND METHODS

Definitions

Strategies for CS minimization can be categorized as: (1) CS avoidance; and (2) CS withdrawal following a period after Tx. The latter can be further divided as early withdrawal (weeks or months after Tx, usually 3-6 mo after Tx) or late withdrawal (at least 6 mo after Tx). Overlapping between these categories has been reported in the literature leading to a degree of uncertainty over the exact terminology. For instance, very early withdrawal (< 2 wk) has been classified under both CS avoidance and CS withdrawal strategies. For the purpose of this manuscript, we will include very early withdrawal under the CS avoidance strategy. The overall efficacy of CS minimization regimens depends on the extent to which the rest of the immunosuppressive agents can suppress the alloimmune response and on the immunological risk stratification. In general, induction immunosuppression is required for the safe application of CS minimization as well as the inclusion of calcineurin inhibitors in maintenance immuno-suppression. Patients at low immunological risk (first transplant, non-sensitized) are considered as ideal candidates for the implementation of CS minimization[6].

Data from studies on CS minimization have produced conflicting results regarding benefit *vs* harm. Clinical heterogeneity across these studies is moderate to high, especially regarding the spectrum of induction and maintenance immunosuppression agents used. Some studies have reported reductions in cardiovascular risk factors such as dyslipidemia[7], but there is no clearly proven reduction of the burden of cardiovascular disease. On the other hand, although CS avoidance or withdrawal studies resulted in increased rates of acute rejection, the impact on allograft survival appears to be neutral. Given the current dilemma over the efficacy *vs* safety profile of CS minimization strategies, our institution has continued on the traditional strategy of rapid CS tapering after Tx to the lowest possible dose. We reserve CS avoidance or withdrawal for highly selected cases at low immunological risk who present compelling contraindications to CS such as severe osteoporosis. We will try to elaborate on the potential advantages and disadvantages of our protocol focusing on the comparison with the CS minimization practices mentioned above. Our goal is to identify the optimal management strategy, which will allow for the maximum benefit of different patient subsets without compromising safety and will likely improve Tx outcomes.

Table 1 Characteristics of the multi-center, randomized Astellas Corticosteroid Withdrawal Study with a follow-up time of 5 years[8]

	CS withdrawal at day 7 arm (*n* = 191)	Standard CS arm (*n* = 195)	*P*-value
Baseline demographic, immunological risk and immunosuppressive therapy data			
Age (mean ± SD, yr)	46.6 ± 12.2	46.2 ± 12.7	NS
Female gender (%)	30.9	36.4	NS
African American (%)	17.8	21.5	NS
Deceased donor (%)	43.5	42.6	NS
Cold ischemic time (mean ± SD, h)	18.4 ± 5.7	17.2 ± 7.3	NS
HLA mismatch (mean)	3.5	3.5	NS
Current PRA (mean ± SD)	1.6 ± 5.3	1.8 ± 5.5	NS
Induction immunosuppression (%)			NS
Thymoglobulin	65.4	69.7	
Basiliximab	31.4	27.2	
Daclizumab	3.1	3.1	
Maintenance immunosuppression	TAC, MMF	TAC, MMF	
Main outcomes			
Biopsy-proven acute rejection (%)	17.8	10.8	0.04 (with Kaplan-Meier analysis)
Allograft survival (%)	94.2	93.3	NS
Patient survival (%)	94.2	96.4	NS
Creatinine clearance (Cockroft-Gault equation, mean ± SD, mL/min)	58.6 ± 19.7	59.8 ± 20.5	NS

CS: Corticosteroid; HLA: Human leukocyte antigens; MMF: Mycophenolate mofetil; NS: Not significant; PRA: Panel-reactive antibodies; SD: Standard deviation; TAC: Tacrolimus.

RESULTS

Low CS dose as maintenance therapy

We advocate the immunosuppressive protocol, which involves the administration of three daily intravenous pulses of 500, 250 and 250 mg methylprednisolone intraoperatively and on postoperative days 1 and 2 respectively. We attempt to rapidly taper CS dose to 20 mg oral methylprednisolone per day by 2-4 wk following Tx. Thereafter, we further reduce CS dose with the aim of 4 mg methylprednisolone per day at 3 mo in the absence of acute rejection. This dose is continued indefinitely. Data from randomized clinical trials (RCT) argue that maintenance CS treatment has still a dominant place in the management of renal transplant recipients. In the RCT with the longest follow-up to date (Astellas Corticosteroid Withdrawal Study), Woodle *et al*[8] assigned 386 renal transplant recipients with PRA (panel reactive antibodies) ≤ 25% to either very early CS withdrawal at one week post-transplant or CS continuation tapered to 5 mg prednisolone per day at 6 mo (Table 1). All patients received induction immunosuppression; 68% of them with the lymphocyte-depleting agent anti-thymocyte globulin (ATG) and 32% with anti-interleukin-2 receptor monoclonal antibodies. Maintenance immunosuppressive regimen consisted of tacrolimus and mycophenolate mofetil (MMF). After a follow-up of 5 years, no difference was found in the rate of patient death, death-censored allograft loss and moderate/severe acute rejection. Total biopsy-confirmed acute rejection was lower in the CS continuation arm (10.8% *vs* 17.8%, *P* = 0.04). This result was driven by the increased rates of mild, CS-sensitive acute rejection in the very early CS withdrawal

arm. It is interesting that biopsy-proven acute rejection rates were numerically lower with ATG induction than with anti-interleukin-2 receptor monoclonal antibodies in very early CS withdrawal patients, but that did not reach statistical significance (14.4% *vs* 24.2%, *P* = 0.09). Serum creatinine and creatinine clearance estimated by the Cockroft-Gault equation were similar between the two arms at 5 years. However, chronic allograft nephropathy (CAN) incidence at 5 years was more than double (9.9% *vs* 4.1%, *P* = 0.028) with very early CS withdrawal compared to a continuation. This finding raises an important concern. Although very early CS withdrawal seems to be non-inferior to CS continuation at 5 years concerning patient and allograft survival, it is unknown if the increased incidence of CAN would negatively influence those outcomes beyond that time-point. Clinical trials with extended follow-up time to 10 years are needed to resolve this issue. The effect of very early CS withdrawal on cardiovascular risk factors was mixed. No significant difference was found in hypertension, new-onset diabetes mellitus, total cholesterol and low-density lipoprotein (LDL) levels; very early CS withdrawal led only to improvement in serum triglycerides. As far as it concerns non-cardio-vascular adverse events, very early CS withdrawal reduced bone fractures and avascular necrosis but it was paradoxically associated with more frequent subcapsular cataract.

A meta-analysis of 34 studies, which included 5637 patients, produced broadly similar results[9]. It was found that acute rejection risk was significantly increased with CS avoidance or withdrawal regimens compared to maintenance CS (relative risk: 1.56, 95%CI: 1.31-1.87, *P* = 0.0001). No statistically significant differences

were found for patient or allograft survival, but allograft function was modestly better with maintenance CS (weighted mean difference in creatinine clearance: 3.05 mL/min, 95%CI: 1.45-4.66). In contrast to the abovementioned RCT, occurrence of hypertension, new onset diabetes mellitus and hypercholesterolemia was reduced with CS avoidance or withdrawal regimens. However, the effect on hard cardiovascular endpoints cannot be estimated because included studies underreported cardiovascular events. In conclusion, acute rejection rates are constantly lower when CS maintenance regimens are used. Patient and allograft survival seems not to be influenced by CS minimization, but it is unknown if this remains the same with longer follow-up. Although CS minimization may permit some improvement in cardiovascular risk factors, data are not consistent about it.

CS avoidance

The rationale behind CS avoidance or very early withdrawal is that acute rejection may be triggered more easily with CS withdrawal within weeks or months after Tx. However, it invariably requires the use of potent induction immunosuppression and the selection of low immunological risk recipients. Attempts to use CS avoidance regimens in the absence of induction immunosuppression resulted in unacceptably high acute rejection rates[10]. In a three-arm multicenter RCT, which included 336 renal transplant recipients with PRA ⩽ 20%, Vincenti *et al*[11] used basiliximab as an induction agent and compared no CS at all *vs* CS withdrawal by day 7 *vs* standard CS. Maintenance immunosuppression consisted of cyclosporine and enteric-coated mycophenolate sodium. Biopsy-proven acute rejection rates were significantly higher with complete CS avoidance and very early CS withdrawal regimens (31.5% *vs* 26.1% *vs* 14.7%) at a follow-up of 12 mo. No difference was found for patient and allograft survival as well as for median 12-mo estimated glomerular filtration rate. A prospective RCT, which included 300 patients, compared very early CS withdrawal at day 2 with standard CS[12]. It also used basiliximab for induction, but maintenance was a calcineurin inhibitor and mycophenolate mofetil or sirolimus. It found absolutely no difference in patient and allograft survival, acute rejection, incidence of CAN and allograft function between the two arms at 3 years. A lower frequency of new-onset diabetes mellitus was noted in the very early CS withdrawal group.

Induction with a lymphocyte-depleting agent (rabbit anti-lymphocyte globulin, rALG) was explored in the clinical context of CS avoidance for the first time by Laftavi *et al*[13]. They randomized 60 renal transplant recipients to either very early CS withdrawal at day 7 or CS continuation. Maintenance immunosuppression involved tacrolimus and MMF. No difference in acute rejection and allograft function was demonstrated with very early CS withdrawal at a follow-up time of 12 mo. However, increased interstitial fibrosis was found in protocol biopsies at 12 mo in the group of very early CS withdrawal. In a case series of 1241 renal transplant recipients with an impressive follow-up time of 10 years, the results of CS withdrawal at day 5 were reported[14]. All patients received induction immunosuppression with Thymoglobulin while maintenance immunosuppression comprised of a calcineurin inhibitor (tacrolimus or cyclosporine) and a secondary agent (MMF or sirolimus). Despite acute rejection rates of 25% for cadaveric donor Tx and 31% for living donor Tx at 10 years, patient and allograft survival was comparable to that reported in national registry databases. A beneficial effect of very early CS withdrawal was shown for new-onset diabetes mellitus, subcapsular cataract, and avascular necrosis. Till now, induction with lymphocyte-depleting agents seems to be the optimal option for consolidating the benefits of CS avoidance strategies without putting renal allografts at risk of acute rejection. It is not surprising that approximately 90% of United States renal transplant recipients with a steroid-free regimen on discharge have received induction with a lymphocyte-depleting agent[15]. Anti-interleukin-2 receptor monoclonal antibodies have been used in the remaining 10% of the patients.

The monoclonal lymphocyte-depleting antibody alemtuzumab has lately emerged as a promising CS-sparing agent. In a comparative, multicenter RCT, 852 unselected (both low and high immunological risk) renal transplant recipients were administered either induction with alemtuzumab (followed by reduced-dose tacrolimus and MMF without CS) or with basiliximab (followed by standard-dose tacrolimus, MMF, and CS)[16]. According to the preliminary results, alemtuzumab halved biopsy-proven acute rejection at 6 mo. Patient and allograft survival were not different between the two groups. Long-term follow-up results of this study are eagerly awaited. In a direct comparison of alemtuzumab with basiliximab (both arms were subjected to CS withdrawal by day 5) in a cohort of 335 low-risk patients, the rate of biopsy-confirmed acute rejection was lower with alemtuzumab (10% *vs* 22%, *P* = 0.003) at 3 years[17]. The major studies on CS avoidance are summarized in Table 2. Lastly, an important question is whether patients on CS avoidance regimens should be put in CS maintenance after treatment of an acute rejection episode. A retrospective study found that allograft survival is not affected by the introduction of CS maintenance or not but the lack of CS maintenance is a risk factor for a subsequent second acute rejection[18].

CS withdrawal

Early CS withdrawal: Initial attempts to apply early CS withdrawal under cyclosporine-based maintenance immunosuppressive regimens did not meet success[19,20]. The advent of more potent maintenance immunosuppressants like tacrolimus and MMF renewed researchers' interest in assessing the feasibility of early CS withdrawal (Table 3). Vanrenterghem *et al*[21] studied CS withdrawal 3 mo after Tx in 556 low immunological risk patients enrolled

Table 2 Characteristics of major randomized corticosteroid avoidance trials (the trial by Woodle *et al*[8] is described separately in table 1); *P* > 0.05 for all comparisons unless otherwise stated

Ref.	Patient number	Immunological risk	Timing of CS withdrawal	Induction immunosuppression	Maintenance immunosuppression	Biopsy-proven acute rejection (%)	Allograf/ patient survival (%)	Follow-up (mo)
Vítko *et al*[10]	151	Low/moderate (PRA < 50%, first transplant)	Day 1	No	TAC, MMF	30.5[f]	97/99	6
	147		Standard CS			8.2[f]	96/100	
Laftavi *et al*[13]	30	Low (PRA < 30%, first transplant)	Day 7	rALG	TAC, MMF	13	NR	12
	30		Standard CS			11		
Kumar *et al*[12]	150	Low (PRA < 10%)	Day 2	Basiliximab	TAC or CsA, MMF or sirolimus	16	78/91	36
	150		Standard CS			14	79/89	
Vincenti *et al*[11]	112	Low (PRA < 20%, first transplant)	No CS	Basiliximab	CsA, EC-MPS	31.5[a]	96/95	12
	115		Day 7			26.1[b]	98/98	
	109		Standard CS			14.7[b,a]	97/98	
Hanaway *et al*[17]	164	Low (PRA < 20%, first transplant)	Day 5	Alemtuzumab	TAC, MMF	10[d]	93/95	36
	171		Day 5	Basiliximab		22[d]	92/98	
Haynes *et al*[16]	426	Unselected patients	No CS	Alemtuzumab	Low-dose TAC-MMF/ Standard TAC-MMF	7[h]	96/97	6
	426		Standard CS	Basiliximab		16[h]	97/99	

[a]*P* = 0.046, [b]*P* = 0.004, [d]*P* = 0.003, [f]*P* < 0.001, [h]*P* = 0.0001. CS: Corticosteroids; CsA: Cyclosporine; EC-MPS: Enteric-coated mycophenolate sodium; MMF: Mycophenolate mofetil; NR: Not reported; PRA: Panel-reactive antibodies; rALG: Rabbit antilymphocyte globulin; TAC: Tacrolimus.

in a multicenter RCT. Maintenance immunosuppression consisted of tacrolimus and MMF. In the follow-up time of only 6 mo, it was shown that acute rejection rates were higher in the CS withdrawal arm during months 3-6. Mean total cholesterol and LDL were reduced in the CS withdrawal arm at the same period. Pascual *et al*[22] summarized RCTs in CS withdrawal between 3 and 6 mo in a systematic review including 9 studies with 1820 patients. They concluded that patient and allograft survival is not affected by early Cs withdrawal up to 3 years after Tx. Total acute rejection rates were higher with early CS withdrawal in cyclosporine-treated patients. Although reduction of total cholesterol levels was observed with early CS withdrawal, no significant difference was found for any of the other cardiovascular or non-cardiovascular adverse events. It is worth mentioning that induction immunosuppression was not used in any of the included studies. Overall, evidence about the benefit-risk ratio of early CS withdrawal is weaker than that of CS avoidance and follow-up times are shorter. It is unknown if induction with lymphocyte depleting agents or anti-interleukin-2 receptor monoclonal antibodies were used in any of the studies, it would have any meaningful impact on the results.

Late CS withdrawal: It appears that late CS withdrawal (more than 6 mo and possibly years after Tx) represents the least favorable method of the CS minimization strategies. It is apparent that certain CS-related complications would already have been established by that time. For instance, it is well known that a rapid deterioration in osteoporosis occurs within the first post-transplant year[23]. Moreover, acute rejection risk is clearly increased upon late withdrawal of immunosuppressants as dictated by cases of non-compliant patients[3]. In a single-center RCT, Smak Gregoor *et al*[24] examined the

effect of CS withdrawal at 6 mo after Tx in 212 renal transplant recipients. Biopsy-proven acute rejection was manifested in 4% of CS withdrawal patients *vs* 1.4% of controls (*P* > 0.05). Patient and allograft survival was not different after a follow-up of 2 years. Allograft function was also not different. CS withdrawal resulted in reduced mean blood pressure but had no effect on other metabolic risk factors. Interestingly enough, a prospective, observational study from the Collaborative Transplant Study group reported that in renal transplant recipients with CS withdrawal more than 6 mo from Tx, patient and allograft survival was better than retrospectively matched controls over a follow-up time of 7 years with no difference in acute rejection rates[25]. The reduction was also noted in the incidence of cardiovascular parameters. However, the lack of randomized design remains a significant limitation of this study.

DISCUSSION

Challenges and opportunities of CS minimization strategies

The beneficial effects of CS minimization in selected, low-risk patients have prompted researchers to attempt CS minimization in renal transplant recipients at higher immunological risk. However, available data are sparse (Table 4). In a small RCT, 21 patients with PRA > 20% or retransplantation were assigned to either alemtuzumab and tacrolimus monotherapy without CS or Thymoglobulin with standard tacrolimus, MMF and very early CS withdrawal at day 5[26]. Biopsy-proven acute rejection rates were quite high at one year; 18.2% with alemtuzumab *vs* 37.5% with Thymoglobulin. In a more recent, head to head comparison of alemtuzumab with ATG (both

Table 3 Characteristics of major randomized corticosteroid withdrawal trials

Ref.	Patient number	Immunological risk	Timing of CS withdrawal	Induction immunosuppression	Maintenance immunosuppression	Biopsy-proven acute rejection (%)	Allograft/ patient survival (%)	Follow-up (mo)
Vanrenterghem *et al*[20]	252	Low	At month 3	No	CsA, MMF	23[b]	95/99	12
	248		Standard CS			14[b]	96/98	
Smak Gregoor *et al*[24]	76	Low	After month 6	No	CsA, MMF	4.0[a]	98/97	24
	73		Standard CS			1.4	97/97	
Vanrenterghem *et al*[21]	279	Low	After month 3	No	TAC, MMF	5.9[a,d]	93/99	6
	277		Standard CS			0.9[d]	94/98	

P > 0.05 for all comparisons unless otherwise stated. [a]After CS discontinuation, [b]*P* = 0.008, [d]*P* = 0.004. CS: Corticosteroids; CsA: Cyclosporine; MMF: Mycophenolate mofetil; TAC: Tacrolimus.

Table 4 Characteristics of corticosteroid avoidance/withdrawal trials in immunologically high-risk and in pediatric patients

Ref.	Patient number	Immunological risk	Timing of CS withdrawal	Induction immunosuppression	Maintenance immunosuppression	Acute rejection (%)	Allograft/ patient survival (%)	Follow-up (mo)
Immunologically high-risk patients								
Thomas *et al*[26]	11	PRA > 20%, or	No CS	Alemtuzumab	TAC	18.2	86/100	12
	10	repeat transplant	Day 5	ATG	TAC, MMF	37.5	88/88	
Hanaway *et al*[17]	164	PRA > 20%, or	Day 5	Alemtuzumab	TAC, MMF	18	91/99	36
	171	black race, or repeat transplant	Day 5	ATG		15	84/91	
Pediatric patients								
Grenda *et al*[28]	98	Low/ moderate	Day 4	Daclizumab	TAC, MMF	10.2	97/99	6
	98	(PRA < 50%)	Standard CS	No induction		7.1	97/100	
Höcker *et al*[29]	23	Moderate/	After year 1	No	CsA, MMF	4	100/100	24
	19	high (PRA < 80%)	Standard CS			10	100/100	

ATG: Antithymocyte globulin; CS: Corticosteroids; CsA: Cyclosporine; MMF: Mycophenolate mofetil; PRA: Panel-reactive antibodies; TAC: Tacrolimus.

arms underwent CS withdrawal by day 5) in a cohort of 139 high-risk patients, there was no difference in biopsy-proven acute rejection at 3 years (18% *vs* 15%, *P* = 0.63)[17]. The inference is that CS minimization is not yet ready for prime time in immunologically high-risk patients. It has been hypothesized that CS minimization may increase post-transplant glomerulonephritis recurrence. In a major retrospective study, it was found that recurrence rate was indeed higher with rapid CS discontinuation compared to CS maintenance for all glomerulonephritis types (hazard ratio 4.86, 95%CI: 2.34-10.07, *P* < 0.0001)[27]. The analysis also showed no difference in patient, allograft, and death-censored allograft survival. Pediatric patients are a subgroup in which CS minimization may be of special interest due to growth retardation that is associated with chronic CS use (Table 4). In a multicenter RCT, Grenda *et al*[28] assessed the effect of CS withdrawal at day 4 (together with daclizumab induction and tacrolimus, MMF) *vs* standard tacrolimus, MMF, and CS in a cohort of 196 children. Growth was significantly enhanced at 6 mo by CS withdrawal. Patient survival, allograft survival and allograft function were not different.

The effect of CS withdrawal on total cholesterol and triglycerides was positive. Similar results were obtained by Höcker *et al*[29] who evaluated CS withdrawal ≥ 1 year after Tx in 42 moderate- to high-risk children (maintenance immunosuppression was cyclosporine and MMF).

In contrast to the perceived benefits of CS minimization in younger transplant recipients, this strategy may not be suitable for elderly patients. Although acute rejection rates may be lower in the elderly, it has been suggested that acute rejection may be more severe and lead to a compromised death-censored allograft survival[30]. Furthermore, the potentially beneficial effect of CS minimization in cardiovascular disease risk factors in the elderly may not be relevant due to their limited lifespan. For these reasons, it seems that CS minimization in the elderly may result in poor outcomes and should not be exercised except with extreme caution. Finally, CS minimization may not also be suitable for transplant recipients with delayed graft function (DGF) and prolonged cold ischemia time. The ischemic injury in these allografts is strongly associated with the development of acute rejection[31]. Therefore, it is

prudent to avoid CS minimization in this patient subgroup if possible.

Based on current evidence, we believe that the majority of renal transplant recipients should continue to receive indefinite CS maintenance immunosuppression. However, selected patients can be good candidates for CS minimization protocols. The optimal patient phenotype to undergo CS minimization is that of a young transplant recipient (including children) who has no prior transplants and is unsensitized to HLA alloantigens. A primary disease that caused end-stage renal disease should not be glomerulonephritis. Any severe perioperative ischemic insult to the allograft should discourage the application of CS minimization. As such, CS minimization may be contraindicated with DGF, prolonged cold ischemia time, and donation after cardiac death. Available data indicate that the preferred CS minimization strategy is probably either complete CS avoidance or very early CS withdrawal. ATG (or alemtuzumab) may be preferable to anti-interleukin-2 receptor monoclonal antibodies as induction agents in this clinical scenario whereas maintenance immunosuppression should better contain the calcineurin inhibitor tacrolimus instead of cyclosporine.

In conclusion, CS maintain their position as important components of the therapeutic armamentarium in renal transplantation. A movement towards CS elimination from induction and maintenance immunosuppression regimens has developed to reduce the myriad side effects associated with chronic CS use. CS minimization strategies have resulted in an increased incidence of acute rejection compared to CS continuation. However, these acute rejection episodes are considered mild and amenable to treatment. Moreover, they do not seem to have detrimental effects on patient survival, allograft survival or allograft function at a follow-up until 5 years. Nonetheless, an observed trend towards increased fibrosis is alarming and calls for the conduction of RCTs with longer follow-up to determine the true consequences of CS minimization. Although CS minimization protocols have been associated with a reduction of adverse effects (especially improvement of dyslipidemia), these results are not always reproducible, and it is unclear if they could clinically translate to less cardiovascular events. At present, the implementation of CS minimization cannot be universally recommended to renal transplant recipients.

COMMENTS

Background
Due to their immunosuppressive properties, corticosteroids (CSs) have been extensively used for the prevention and treatment of rejection in solid organ transplantation. However, myriad side-effects have been associated with CS. Recent research attempts to minimize CS use in renal transplantation in an effort to reduce the burden of their side-effects without compromising allograft and patient survival.

Research frontiers
The choice of the induction immunosuppression agent - and of maintenance immunosuppression to a lesser degree - is an extremely important aspect of

CS minimization strategies and the focus of many studies. Studies with follow-up times of more than 5 years and with data on interstitial tissue fibrosis are needed.

Innovations and breakthroughs
Alemtuzumab appears to be a very promising induction agent potentially allowing the combination of CS avoidance with lower doses of tacrolimus and mycophenolate mofetil. Long term results of the 3C study may provide valuable insights on this topic.

Applications
In the United States, CS avoidance regimens were administered to 23% of all first renal transplant recipients in 2004. Although they cannot yet be recommended to the majority of renal transplant recipients, selected patient groups such as primarily those with low immunological risk and low risk for glomerulonephritis recurrence may benefit more from CS minimization.

Terminology
CS avoidance: Either no CS use at all or CS use only until day 7 after transplantation (Tx). CS withdrawal: CS tapering following a period after Tx. It is divided as early withdrawal (weeks or months after Tx, usually 3-6 mo after Tx) or late withdrawal (at least 6 mo after Tx).

Peer-review
This review paper is a well written paper of the impact of corticosteroid minimisation on kidney transplant and has valuable information.

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