Steroid Sparing after Kidney and Pancreas Transplantation

Arthur J. Matas

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ABBREVIATIONS

AZA	Azathioprine
BMD	Bone mineral density
CSA	Cyclosporine
MMF	Mycophenolate mofetil
P	Prednisone
PAK	Pancreas after kidney
SKP	Simultaneous kidney-pancreas
TAC	Tacrolimus

Arthur J. Matas, MD
Department of Surgery
University of Minnesota
MMC 328
420 Delaware St. SE
Minneapolis, Minnesota 55455
USA
Tel.: 612.625.6460
Fax: 612.624.7168
e-mail: matas001@umn.edu

Introduction

Steroids, part of the mainstay of posttransplant immunosuppression for decades, are associated with numerous side effects, including hypertension, osteoporosis (and fractures), avascular necrosis, cataracts, easy bruisability, puffy appearance, and skin changes. Some of these side effects are related to the cumulative steroid dose.[1] Others develop rapidly posttransplant; for example, by 3 weeks after a heart transplant, a significant loss of trochanter and cortical bone density occurs.[2] In addition, some side effects occur at low steroid doses. Two prospective, placebo-controlled studies in nontransplant patients demonstrated a significant loss of bone mineral density (BMD) within 3 months in those taking as little as 7.5 mg prednisone (P) daily versus no loss of BMD in the placebo-treated patients.[3,4] A large retrospective review of the United Kingdom General Practice Database (mean follow-up = 1.3 years/patient) showed a significant increase in fractures in patients taking as little as 2.5 to 7.5 mg P daily.[5]

Steroid-related side effects are costly to the health care system. Veenstra et al. estimated that, over 10 years, the average cost of treating steroid-related side effects posttransplant is $5,300 per recipient.[6] There is likely a hidden cost as well. Medication side effects have been shown to be a risk factor for posttransplant noncompliance.[7] And noncompliance has been associated with an increased incidence of acute rejection, chronic rejection, and graft loss.[8]

To avoid these steroid-related side effects, many transplant centers now have clinical study protocols in place to eliminate or minimize long-term steroid use.

Steroid-Sparing Terminology

The goal of steroid-sparing protocols is to avoid (minimize) steroid-related side effects while not increasing the rate of graft loss. Such protocols can be divided into 4 major categories:

1. low-dose steroids,
2. alternate-day steroids,
3. steroid withdrawal (subdivided into early [3 to 6 months] vs. late [> 6 months] posttransplant), and
4. steroid elimination (either never using steroids or giving a very short [< 7 days] course).

Both low-dose and alternate-day steroids are associated with the side effects discussed above, so these 2 approaches will not be discussed further. (Note, however, that tapering to alternate-day steroids has been shown to benefit posttransplant growth in children.)

Steroid Withdrawal

Kidney

Cyclosporine (CSA) and Azathioprine (AZA)

Before cyclosporine (CSA) was introduced, few attempts were made to completely withdraw steroids. However, once CSA was introduced, numerous studies looked at both early and late steroid withdrawal in recipients taking either CSA-P or CSA-AZA-P. Meta-analyses of these studies showed that steroid withdrawal was associated with an increased incidence of acute rejection[9,10] and graft loss.[10]

Table 1 | **Recent Steroid Elimination Protocols in Kidney Transplantation**

Reference	Protocol	*n*	Rejection Rate	Time Frame
24	Thymo, CSA, MMF	100	13%	1 y
25	Thymo, CSA, MMF, P (6 days)	51	13%	6 months
26	Thymo, MMF, delayed CSA	11	27%	6 months
27	Anti-CD25, MMF, CSA	59	25%	1 y
28	Anti-CD25, MMF, CSA, P (4 days)		20%	1 y
29	TAC, MMF, P (2 days)	52	25%	1 y
30	Anti-CD25, TAC, MMF, P (3 days)	54	13%	6 months
31	Anti-CD25, TAC, MMF	10	0%	6 months

83 randomized.
CSA = Cyclosporine; MMF = Mycophenolate mofetil; TAC = Tacrolimus; P = Prednisone; Thymo = Thymoglobulin.

One particular study serves as a caveat for interpretation of reports of all future studies.[11] In this Canadian multicenter study, recipients were randomized at 3 months to remain on P versus undergo withdrawal. Of importance, there was no significant difference in graft survival for the 1st 3 years. Thereafter, however, the steroid withdrawal group had worse graft survival.[11] Thus, long-term follow-up is necessary before we can be comfortably sure that outcome of future steroid-sparing protocols is acceptable.

Individual studies of steroid withdrawal demonstrated some benefits to recipients who can be successfully weaned off steroids. Specifically, serum lipids are lower,[12-14] hypertension is easier to control,[13,15] and many with posttransplant diabetes are able to discontinue insulin or oral hypoglycemic agents.[13,16] Of note, however, is that although total cholesterol falls after steroid withdrawal, HDL falls at the same rate, so the impact on cardiovascular risk remains unclear.

CSA and Mycophenolate Mofetil (MMF)

The introduction of MMF led to 2 large prospective randomized studies of steroid withdrawal in recipients taking CSA-MMF-P. The 1st trial was done in Europe.[17] Recipients were randomized to take either full-dose steroids tapered to 10 mg at 3 months posttransplant (full-dose group) or half-dose steroids tapered to 0 mg P at 3 months posttransplant (low/stop group). Significantly more acute rejection episodes occurred in the low/stop group. Some of this increase came during the 1st month when both groups were taking P. However, in an analysis of rejection only after the 3rd month, the incidence in the low/stop group was still significantly higher. This increased rejection risk was countered by several advantages in the low/stop group: lower systolic ($P < 0.01$) and diastolic ($P < 0.01$) blood pressure, lower total cholesterol ($P < 0.11$) and triglycerides ($P < 0.01$), and significantly higher BMD ($P < 0.01$) at 12 months posttransplant.

The 2nd trial of P withdrawal in recipients taking CSA-MMF-P was done in North America.[18] In that study, primary transplant recipients who were rejection-free at 3 months posttransplant (and who were taking full-dose MMF and 5 to 15 mg/kg/day CSA) were randomized to either stay on P or undergo P withdrawal (lowered by 2.5 mg/kg/week). The incidence of acute rejection in the steroid withdrawal group ($P = 0.0007$) was significantly higher. In the subgroup of African American recipients, the increase in acute rejection was striking.

Simultaneous Kidney-Pancreas (SKP)

No large multicenter studies of steroid withdrawal in pancreas recipients have been published. However, single-center reports suggest that late posttransplant withdrawal can be successful in selected recipients. Jordan et al. reported complete steroid withdrawal 4 to 40 months posttransplant (mean = 15 ± 8 months) in 47% of the center's pancreas recipients,[19] with no increased rejection risk. Gruessner et al. randomized simultaneous kidney-pancreas (SKP) and pancreas after kidney (PAK) recipients

Table 2 | **Rapid Discontinuation of Steroids Protocol at the University of Minnesota**

Thymo	1.25 to 1.5 mg/kg × 5 days, with the 1st dose given in the OR
P	Solu-Medrol 500 mg in the OR; P, 1 mg/kg on day 1, 0.5 mg/kg on days 2 and 3, 0.25 mg/kg on days 4 and 5
CSA*	4 mg/kg BID to maintain levels of 150 to 200 ng/ml by HPLC
MMF	1 Gm BID

*Currently, randomizing CSA-MMF versus TAC-RAPA.
CSA = Cyclosporine; MMF = Mycophenolate mofetil; TAC = Tacrolimus; P = Prednisone; Thymo = Thymoglobulin.

to steroid withdrawal versus P maintenance 6 to 36 months posttransplant.[20] Entrance criteria included no rejection in the previous 6 months, normal pancreas and kidney function, and tolerance of full doses of other immunosuppressives. There was no difference in subsequent acute rejection episodes between recipients who underwent steroid withdrawal versus those who underwent P maintenance.

Steroid Elimination

Kidney

Once CSA was introduced, some centers started recipients on CSA monotherapy. Unfortunately, the incidence of rejection was high,[21,22] and recipients who underwent an acute rejection episode had decreased graft survival. (With CSA-AZA, even trials of low- vs. high-dose steroids showed an increased incidence of rejection in the low-dose group.[23]) Recently, the introduction of multiple new immunosuppressive agents has led to new trials of early posttransplant steroid elimination (Table 1).

Polyclonal Antibody, CSA, and MMF

Birkeland reported on 100 recipients treated with a polyclonal antibody (Thymoglobulin), CSA, and MMF.[24] Only 13% have had an acute rejection episode; all episodes were treated with OKT_3. Four-year actuarial graft survival was 82%. None of the recipients has developed lymphoma, diabetes, osteoporosis, or appearance and skin changes.

We used a similar protocol in our population, except that we gave 6 doses of steroids (Table 2). Our 6- and 12-month actuarial rejection-free graft survival rate (87%) and serum creatinine level (1.7 mg/dl) did not increase, as compared with historical controls taking CSA-MMF-P.[25] In a small series, Cantarovich treated 11 kidney recipients with polyclonal antibody and MMF at the time of the transplant with CSA started on postoperative day 11.[26] The incidence of fever (73%), serum sickness (27%), and early rejection (27%) was relatively high, suggesting that CSA or a short course of steroids should be started at the time of the transplant.

Monoclonal Antibody, CSA, and MMF

In a Canadian multicenter study, Cole et al. treated 59 kidney recipients with a monoclonal anti-CD25 antibody, MMF, and CSA.[27] In the 1st year, 14 patients (25%) had an acute rejection episode. Vincenti et al. used a similar regimen (anti-CD25 antibody, MMF, and CSA) in a trial in which recipients were randomized to either long-term P or only 4 days of P.[28] The incidence of rejection did not significantly differ: about 20% at 1 year in both groups.

Tacrolimus (TAC) and MMF

Buell et al. treated 52 patients with TAC, MMF, and 7 days of steroids; 25% had an acute rejection episode in the 1st year posttransplant.[29] Kaufman et al. used an anti-CD25 monoclonal antibody, TAC, MMF, and a 3-day course of steroids;[30] only 13% had an acute rejection episode in the 1st 6 months (median time to rejection about 11 days posttransplant). Similarly, Sarwal et al. reported no rejection episodes in 10 pediatric kidney recipients treated with an anti-CD25 monoclonal antibody, tacrolimus, and MMF.[31]

SKP

Cantarovich et al. reported on 28 SKP recipients treated with Thymoglobulin, CSA, and MMF. Only 2 (7%) had an acute rejection episode.[32] Kaufman et al. saw a similar low incidence of rejection

(3%) in patients treated with Thymoglobulin, TAC, either MMF or sirolimus, and 6 days of steroids.[33]

Why Should Withdrawal or Elimination Work Now When Previous Trials of Steroid Avoidance Have Failed?

Current steroid withdrawal or elimination trials are succeeding, whereas past trials have failed. A number of reasons are possible. First, most current trials reporting low rejection rates are using antibody induction. Second, maintenance immunosuppression has improved, although this does not explain why steroid avoidance with CSA-MMF[24,25] has been successful whereas steroid withdrawal (with the same background immunosuppression) led to increased acute rejection.[17,18] Third, some in vitro data suggest that rapid elimination might be better than withdrawal.[34,35] Fourth, except for the study by Vincenti et al.,[28] the protocols for steroid elimination have not been subjected to a prospective randomized trial. Finally, follow-up in most of these series has been relatively short; long-term follow-up is necessary.

Conclusions

A number of studies have now shown that steroid avoidance or rapid withdrawal (<7 days) can be done in kidney or SKP recipients, without increasing the risk of an acute rejection episode. In general, these protocols have been used in low-risk recipients; follow-up has been relatively short. It remains to be seen whether similar protocols can be successful in high-risk recipients and whether long-term results will be as good as with steroid maintenance. Further studies are necessary to determine the best maintenance immunosuppression for recipients on a steroid-free protocol.

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