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Steroid Elimination—Who, When, How?

A.J. Matas

Department of Surgery, University of Minnesota, Minneapolis, Minnesota

Abstract

Steroids have numerous side effects, many occurring early posttransplantation with relatively low prednisone doses. Consequently, investigators have attempted steroid minimization or withdrawal. The first attempts at steroid minimization used early low-dose steroids and were associated with an increased rate of acute rejection episodes, late graft dysfunction, and graft loss. Subsequent studies, with cyclosporine-based immunosuppression, attempted steroid withdrawal late posttransplantation (>3 months) in highly selected, clinically well, and immunologically low-risk recipients. Again, steroid withdrawal was associated with an increased risk of acute rejection episodes and these episodes were associated with graft dysfunction and increased graft loss. The development of new powerful immunosuppressive agents has led to renewed attempts at late prednisone withdrawal. These also have been associated with increased late rejection risk. A more exciting innovation has been the attempts at rapid discontinuation (7 days posttransplantation) of prednisone with the following results: (1) Randomized studies have shown no significantly increased risk of acute rejection; (2) Randomized and nonrandomized studies have shown no increase in late graft loss; (3) Successful use in living and deceased donor recipients, primary and re-transplant recipients, adult and child recipients, white and black recipients, and low-risk and highly sensitized recipients; (4) About 80% of recipients remain prednisone-free long term. Recent nonrandomized data suggest that recipients who have an acute rejection episode while prednisone free are more likely to have a second rejection episode if they are returned to prednisone-free immunosuppression. In these cases the acute rejection episode should be treated and long-term prednisone continued at 5 mg/d.

The goal of steroid minimization protocols has been to eliminate or minimize steroid-related side effects while not increasing the rates of acute rejection episodes (ARE) or chronic graft loss. Until recently, corticosteroids had been a mainstay of immunosuppressive protocols in kidney transplantation. However, although inexpensive, steroids are associated with debilitating side effects, including hypertension, hyperlipidemia, cataracts, avascular necrosis, osteoporosis, mood and appearance changes, and, in children, growth retardation.¹ Vanrenterghem et al² recently showed that increased long-term total steroid dose is associated with increased cardiovascular morbidity. Treatment of these steroid-related side effects adds to the cost of transplants.³ In addition, such side effects increase posttransplant noncompliance⁴; noncompliance is associated with an increased incidence of ARE, chronic rejection, and graft loss.⁵ Thus, a hidden cost of steroid-related side effects may be increased graft loss. When surveyed, kidney transplant recipients state that the immunosuppressive drug they would most like not to take is prednisone.⁶

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Address reprint requests to Arthur Matas, Department of Surgery, University of Minnesota, 420 Delaware St SE, Minneapolis, MN 55455. matas001@umn.edu.

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LATE (≥ 3 MONTH) STEROID WITHDRAWAL

Historically, numerous attempts have been made either to avoid steroids or, in selected recipients, to gradually withdraw steroids late (> 3 months) posttransplantation. However, meta-analyses of studies of late steroid withdrawal in selected recipients on calcineurin inhibitors and either azathioprine (AZA) or mycophenolate mofetil (MMF) showed an increased incidence of ARE and graft loss.⁷⁻⁹

Of particular concern has been a multicenter Canadian study in which recipients on cyclosporine (CsA) and prednisone were randomized at 3 months to either switch to CsA monotherapy or to continue the 2 drugs.¹⁰ For the first 500–600 days after randomization, the study's authors found no significant differences between the 2 groups; however, thereafter the CsA monotherapy group had an increased rate of graft loss. The Canadian study has led to ongoing concerns that even if steroid minimization protocols have early success, late graft failure will significantly increase. Yet it is critical to realize that this study was done before the impact of ARE on long-term graft outcome was recognized^{11,12}; the authors did not determine whether the rate of ARE increased after prednisone withdrawal.

In contrast with these studies, Opelz et al¹³ recently reported no increased ARE rates for recipients on CsA-based immunosuppression who underwent steroid withdrawal >6 months posttransplantation. Median time to steroid withdrawal was 1.1 years; after enrollment, steroids were tapered in a stepwise fashion. Using the Collaborative Transplant Study (CTS) database, Opelz et al matched each enrolled recipient ($n = 1015$) with 3 controls. The actuarial 7-year patient, graft, and death-censored graft survival rates were significantly better for the withdrawal group ($P < .01$). Outcomes did not differ for those treated with AZA or MMF. The difference in outcomes between Opelz's and the above studies may be due to the later withdrawal of steroids in Opelz's study.

Although many of the early reports of late prednisone withdrawal included recipients treated with a calcineurin inhibitor plus AZA or MMF, success has also been recently reported with mammalian target of rapamycin (mTOR) inhibitors.¹⁴⁻¹⁸

RAPID DISCONTINUATION OF PREDNISONE

The recognition that late steroid withdrawal was associated with increased ARE rates, combined with the introduction of newer and more potent induction and maintenance immunosuppressive agents, led many investigators to consider either rapid discontinuation of prednisone (< 7 days posttransplantation; RDP) or complete avoidance of steroids. Such protocols have the potential advantage of minimizing any early steroid-related side effects. These protocols have used a variety of induction agents (thymoglobulin, alemtuzumab, interleukin-2 inhibitors), either of the 2 calcineurin inhibitors (CsA or tacrolimus), and either MMF or sirolimus.

Birkeland was the first to report success with steroid avoidance.^{19,20} In his series of 100 recipients (67 deceased donor), recipients were treated with antithymocyte globulin (ATG), CsA, and MMF. Only 13% experienced an ARE; the actuarial 4-year graft survival rate was 82%. Since Birkeland's report, there have been a number of prospective randomized trials of RDP versus maintenance prednisone.²¹⁻³⁰ Almost all have used antibody induction. Most have limited the protocol to recipients with a relatively low immunologic risk; an exception was the study by ter Meulen et al²³ ($n = 364$), in which the only exclusion criteria were use of an HLA-identical living donor and treatment with prednisone at the time of the transplant. In general, short- and intermediate-term results of these studies have shown no difference between RDP and maintenance prednisone groups in patient or graft survival or ARE rates, in severity of ARE, or in renal function.

Additional nonrandomized studies—some with longer follow-up—have also shown excellent outcome with RDP.^{31–41} We have reported outcome for >1000 recipients treated with RDP and shown that compared with historical controls, patient and graft survival rates are excellent.^{39,40} Our first and second transplant recipients are treated with ATG, a calcineurin inhibitor, either MMF or sirolimus, and RDP. Our only exclusions were recipients already on prednisone (so that high immunologic risk recipients are included). The actuarial 7-year patient survival rate was 82%; graft survival was 77%. At 1 year, 13% of recipients had had an ARE. Renal function (MDRD GFR) was stable through 7 years. We found that over 80% of recipients remained prednisone-free long-term. In addition, compared with historical controls, RDP-treated recipients had significantly lower rates of cataracts ($P < .001$), new onset posttransplant diabetes ($P < .001$), avascular necrosis ($P < .001$), cytomegalovirus infection ($P < .001$), fractures ($P = .04$), and non-posttransplant lymphoproliferative disorder (PTLD) malignancy ($P = .02$).⁴⁰

Control Groups—A Moving Target

Late steroid withdrawal and RDP protocols were developed in the context of what, today, would be considered relatively high long-term prednisone doses. Thus, the validity of comparing outcome with historical controls has been questioned. Given that prednisone has an anti-inflammatory effect, concern remains that the rate of chronic graft loss will significantly increase in recipients on RDP protocols. To date, this concern is supported by no data. In addition, it has been suggested long-term low-dose steroids may be associated with minimal side effects. However, van den Ham et al⁴² showed a significant difference in weight gain between recipients on 5 mg/d prednisone versus RDP. Matsunami et al⁴³ noted that recipients on high-dose steroids had a 55% incidence of posterior subcapsular cataracts: low-dose steroids 28%; no steroids 6.2%. Steroids have been associated with rapid loss of bone mineral density in transplant recipients,⁴⁴ and cumulative steroid dose has been correlated with bone mineral density loss.⁴⁵ In addition, considerable data from the nontransplant literature showed that even a short course of low-dose prednisone is associated with significant loss of bone mineral density and with a significant increased fracture rate.^{46–50}

Individual Populations on RDP

Most of the above studies limited RDP to adult recipients with relatively low immunologic risk. However, some randomized and nonrandomized studies have enrolled both high-and low-risk recipients.^{23,31,39,40} Only a few reports have described outcome of RDP in specific higher risk populations. For example, successful RDP has been reported for children,^{51–55} black patients,^{56–60} recipients with potentially recurrent disease,^{61,62} high immunologic risk recipients,^{63,64} and kidney–pancreas recipients^{65–70} (Table 1).

Which Immunosuppressive Protocol for RDP?

Most RDP protocols have used induction therapy; when induction therapy was not used, the AR rates were high.^{25,33} In a randomized study of RDP versus prednisone in which institutions could choose which antibody to use, Woodle et al²⁹ noted less AR with ATG than with interleukin (IL)-2R antagonists.²⁹

Similarly, a variety of maintenance protocols have been successful with RDP.^{71–73} There have been 2 randomized prospective trials of maintenance therapy: Kumar et al⁷¹ compared tacrolimus–MMF versus tacrolimus–sirolimus; Kandaswamy et al⁷² compared CsA–MMF versus tacrolimus–sirolimus. In both studies, there was no difference between groups in recipient or graft survival.

ARE After RDP: The Question of Long-Term Prednisone

One clinically important question is whether long-term maintenance steroids should be introduced in recipients who have an ARE after RDP. Humar et al⁷⁴ reported on 149 recipients who had 1 ARE while on our RDP protocol. ARE were treated with a steroid taper (with or without antibody).⁷⁴ Of the 149 recipients, 51 (34%) switched to maintenance prednisone (5 mg/d) after treatment of their first ARE; 98 (66%) were returned to a steroid-free protocol. Return to maintenance prednisone was not randomized but was based, in part, on physician and patient choice. Patient characteristics for the 2 groups were similar. At a mean follow-up of 26 months, there was no significant difference between groups in graft survival or renal function. However, multivariate analysis of risk factors for a second ARE suggested that whether or not steroids had been added to the maintenance protocol might have an impact (relative risk, 2.1; $P = .07$). Of concern, in the subgroup supposedly most likely to not have a second ARE—that is, recipients with minimal-to-mild AR—the rate of second ARE significantly increased if the recipient had returned to steroid-free immunosuppression ($P = .02$). Clearly, a randomized trial with longer follow-up and more recipients is necessary to definitively answer this question.

In conclusion, the potential benefit of eliminating steroid-related side effects for transplant recipients is obvious. Yet concerns remain that steroid-free maintenance immunosuppression protocols will have some long-term detrimental effects. It will be difficult to design studies to address such concerns. In the past decade, partly as a result of trials focused on late steroid withdrawal and RDP, recipients maintained on prednisone are taking far less prednisone than they would have been taking 10 years ago. The ideal study would be to compare RDP with a protocol involving rapid tapering to 5 mg/d, and with a protocol involving rapid tapering plus late withdrawal. Currently, early transplant results are so good that the number of patients required to power such a study would be enormous.

An interesting question is why RDP is not, in most studies, associated with an increased ARE rate, whereas steroid withdrawal at 3 months posttransplantation—using the same maintenance immunosuppression—is. Part of the answer might be that steroids lower cytokine production but upregulate cytokine receptor expression⁷⁵; when the steroids are slowly withdrawn, cytokine release returns to normal in an environment of upregulated receptors.

Of interest, steroids decrease the bioavailability of MMF by increasing hepatic UDP-glucuronyl transferase activity. One study showed that when steroids were tapered or withdrawn, the MMF AUC increased⁷⁶; thus there was more MMF exposure, possibly resulting in less AR. Another study showed that tacrolimus exposure also increased after steroid withdrawal.⁷⁷

A final question is how to balance steroid-free and calcineurin inhibitor-free approaches. Steroid-free immunosuppression has the obvious advantages of eliminating steroid-related side effects. But numerous studies have now demonstrated better long-term kidney allograft function when the use of calcineurin inhibitors is either minimized or eliminated. The ideal would be to develop protocols that are both steroid and calcineurin inhibitor free; to date, however, such protocols have been associated with significant side effects. Hopefully, development of newer immunosuppressive drugs will permit long-term effective immunosuppression without these side effects.

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Table 1**Populations of Kidney Recipients for Whom Rapid Discontinuation of Prednisone Has Been Successful**

Primary and retransplant recipients
Adults and children
Living and deceased donor transplants
Low and high panel reactive antibody recipients
Low- and high-risk recipients
Black and white recipients
Recipients with potentially recurring disease
Kidney and simultaneous kidney pancreas transplant recipients *

* Although not discussed in this manuscript, rapid discontinuation of prednisone has also been successful in liver recipients.