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The Risks and Benefits of Early Steroid Withdrawal

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Abstract

Numerous studies (single- and multicenter trials, registry reports, and meta-analyses) have defined many of the benefits of early steroid withdrawal. Most trials stopped prednisone in the first posttransplant week (rapid discontinuation of prednisone). To date, the only identified risk has been an increased rate of "mild" rejection episodes. Rapid discontinuation of prednisone has not been associated with an increase in "moderate/severe rejection", and treated recipients have had equivalent patient and graft survival rates to those on maintenance prednisone.

Rejection risk with rapid discontinuation of prednisone may depend on which agents are used for induction and maintenance immunosuppression. Benefits of rapid discontinuation of prednisone include decreased rates of new onset diabetes and decreased cardiovascular risk. Most studies of rapid discontinuation of prednisone have been done in low-risk groups. Additional studies are necessary to determine if the same risk-benefit profile applies to groups at higher immunologic risk. **(Trends in Transplant. 2011;5:59-68)**

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Key words

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Introduction

Historically, transplant recipients have been started on high doses of daily prednisone (up to 2 mg/kg/day), and the dose was gradually tapered over the first year. Long-term, recipients were maintained on 5-10 mg (or more) of prednisone per day. Prolonged exposure to these high doses led to a number of well-characterized, steroid-related side effects including hypertension, posttransplant glucose intolerance and new onset diabetes mellitus (new onset diabetes after transplant; NODAT), hyperlipidemia, cataracts, loss of bone mineral density and increased rates of fractures, avascular necrosis, appearance changes, mood swings, and in children, growth retardation. Recipients, when surveyed, stated that the immunosuppressive drug that they would most like to eliminate from their regimen was prednisone[1].

Because of the significant steroid-related side effects, there have been numerous attempts to minimize or eliminate use of long-term steroids. Initial strategies utilized

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late (≥ 3 months) steroid withdrawal. When cyclosporine (CsA) was introduced, studies, both randomized and non-randomized, were done of late steroid withdrawal in clinically-well, rejection-free kidney transplant recipients taking CsA, azathioprine (AZA), and prednisone[2,3]. These were associated with increased acute rejection rates and worse long-term graft survival. After the introduction of mycophenolate mofetil (MMF), there were new trials of late steroid withdrawal in recipients taking CsA, MMF, and prednisone. These trials similarly reported a significantly increased rate of acute rejection episodes in the steroid-free arm[4-7].

In the late 1990s, consideration was given to early steroid withdrawal (< 14 days posttransplantation) and a number of centers developed clinical protocols for rapid discontinuation of prednisone (RDP), usually within the first posttransplant week (as reviewed[8-11]). There have now been reports of RDP in recipients taking various combinations of induction and maintenance drugs, including: (i) differing induction agents (thymoglobulin, alemtuzumab, IL-2R inhibitors, none); (ii) differing calcineurin inhibitors (CsA, tacrolimus [TAC]); (iii) differing anti-metabolites (mycophenolates [MMF, mycophenolate sodium enteric coated]; mammalian target of rapamycin [mTOR] inhibitors [sirolimus, everolimus]); and (iv) with belatacept[8-14]. Some of these studies have been single-center trials, randomized and nonrandomized, and others, multicenter trials. More recently, there have been a number of meta-analyses of these trials and registry reports comparing recipients on RDP protocols to recipients on long-term prednisone-maintenance therapy[11,15-17].

These trials and analyses have shown both benefits and risks to RDP protocols. However, because of the myriad of protocols used, it is difficult to determine whether or not benefits could be maximized and risks minimized with an optimized protocol. For the interested reader, there have been other recent detailed reviews of RDP trials[8-11]. Thus, herein, rather than reiterating each study observation, we will focus on an overview and discussion of the key findings while mentioning certain salient observations.

Clinical data

The most recent and extensive reviews and meta-analyses of steroid withdrawal strategies concluded that studies to date had shown that RDP was associated with increased acute rejection rates, but had no impact on long-term patient or graft survival[11,15]. A benefit of RDP was a decreased rate of NODAT. In the analysis by Pascual, et al., the increased acute rejection rates were found only when CsA was the calcineurin inhibitor used (RR: 1.38; 95% CI: 1.21-1.56); RDP with TAC for maintenance immunosuppression was not associated with increased acute rejection rates. In contrast, Pascual, et al. noted that decreased rates of NODAT were only seen with RDP protocols incorporating CsA; there was no decrease in NODAT when TAC was used. One limitation of current data, as noted by Pascual, et al., was the relatively short follow-up of many of the studies. A second limitation was the relatively few studies of prednisone-specific side effects. Knight and Morris also concluded that steroid withdrawal had no impact on patient and graft survival, but significantly decreased cardiovascular risk (lower rates of hypertension, NODAT, and hypercholesterolemia)[15].

Two important analyses, based on U.S. registry data, have recently been reported by Luan, et al.[16,17]. In the first analysis, they studied the outcome of 95,555 kidney transplants done between January 01, 2000 and December 31, 2006[16]. Of these, 16,491 (17%) were discharged on a prednisone-free regimen. Patient and graft survival were compared between prednisone-free and maintenance prednisone regimens. Using a Cox model adjusting for multiple donor and recipient covariates, they

found that the prednisone-free patients had significantly better one- and four-year patient and graft survival rates. There are numerous limitations, as noted by the authors, to this study. First, it was not a randomized trial, and although the authors controlled for multiple covariates, selection bias may have played a role. Second, whether or not a recipient is taking prednisone at discharge is not necessarily an indication of their long-term immunosuppressive regimen. However, other studies have shown that over 80% of recipients remain prednisone free and so this study approximates an intention-to-treat analysis. Importantly, the data do not show decreased patient and graft survival, suggesting that at least a subset of recipients can do well on a prednisone-free regimen after kidney transplantation.

In a second registry analysis, Luan, et al. studied the impact of RDP on the rate of development of NODAT[17]. Between January 01, 2004 and December 31, 2006, 25,837 (non-diabetic) patients underwent kidney transplant; of these, 6,922 (26.8%) were discharged on a prednisone-free regimen. Prednisone-free recipients had a 42% decreased chance ($p < 0.001$) of developing NODAT versus those on maintenance prednisone immunosuppression. Luan, et al. also noted that TAC/MMF-treated recipients had higher rates of NODAT than CsA/MMF-treated recipients.

The randomized study with the longest follow-up is a placebo-controlled multicenter trial in which 386 recipients were treated with antibody induction, TAC, MMF, and prednisone and randomized to prednisone withdrawal at seven days versus a slow taper to 5 mg/day by six months[18]. At five years posttransplantation, there was no difference between groups in the primary endpoint (composite of death, graft loss, or moderate/severe acute rejection). There were also no differences between groups at five years in the individual endpoints of patient survival, death-censored graft survival, rates of moderate/severe acute rejection, or of acute rejection requiring antibody treatment; and there was no difference in renal function (mean serum creatinine level and Cockroft Gault calculated creatinine clearance). However, there was an increased rate of biopsy-proven acute rejection in the RDP group. A subgroup analysis showed a 5% increased incidence of "chronic allograft nephropathy" at five years for those in the RDP group undergoing a kidney biopsy for clinical indications. A potentially critical, but not statistically significant, observation in this study was that the choice of induction agent affected acute rejection rates after RDP. In the trial protocol, transplant centers used either interleukin-2R (IL-2R) inhibitors or thymoglobulin for induction. For recipients in the long-term steroid arm, there was little difference in rejection rates between those treated with thymoglobulin (10.3% acute rejection) versus IL-2R inhibitors (11.9%). However, for those recipients randomized to RDP, rejection rates were notably lower with thymoglobulin (14.4% acute rejection) versus IL-2R inhibitors (24.2%) (p = NS).

An equally important observation was made by Vitco, et al. who randomized 471 kidney transplant recipients to three arms: (i) triple therapy (TAC/MMF/prednisone); (ii) TAC/MMF (no induction and prednisone-free); and (iii) IL-2R inhibitor/TAC monotherapy (prednisone- and MMF-free)[19]. Acute rejection rates were significantly different between groups: (i) triple therapy (8.2%); (ii) no induction and prednisone free (30.5%); and (iii) induction with long-term TAC monotherapy (26.1%) ($p < 0.001$). Although rejection rates were unusually low in the triple-therapy arm, this data suggests that both induction and dual-agent maintenance therapy may be important for successful RDP.

Long-term results

Almost all studies to date have reported ≤ 5-year results. We now have eight-year

Table 1. One- and seven-year actuarial outcome after rapid discontinuation of prednisone (University of Minnesota)

	Living donor		Deceased donor	
	1-year	7-year	1-year	7-year
Primary transplants				
Patient survival	98%	84%	96%	77%
Graft survival (GS)	96%	76%	94%	66%
Death censored GS	96%	77%	98%	84%
Re-transplants				
Patient survival	97%	91%	97%	81%
Graft survival (GS)	96%	77%	93%	66%
Death censored GS	98%	83%	95%	74%

actuarial data for 1,060 recipients, including 12% re-transplants and 34% deceased donors, on a RDP protocol (Table 1)[20-22]. All first and second transplants, except for those on prednisone at the time of transplant, are treated with RDP. Our protocol consists of five doses of thymoglobulin (extended in recipients with delayed graft function) and discontinuation of prednisone on the sixth postoperative day. Maintenance therapy consists of a calcineurin inhibitor and either a mycophenolate or an mTOR inhibitor. Results for first and second transplants are equivalent (Table 1). Although we have not done a randomized trial, these results (with reasonably large numbers) compare well to national averages. Similar to patients taking steroids, the major risk factors for graft loss, by multivariate analysis, were: acute rejection (AR) plus delayed graft function (DGF) (HR: 7.3; $p < 0.0001$; DGF (no AR) (HR: 3.7; $p = 0.0001$); AR (no DGF) (HR: 3.8; $p < 0.0001$); pretransplant diabetes (HR: 1.5; $p = 0.007$); and deceased donor (HR: 1.3; $p = 0.01$)[21]. At five years post-transplantation, over 80% of recipients remained prednisone-free. One advantage of our data is the long follow-up of recipient outcome. A second is that we have not excluded any high-risk subgroups so our experience can be generalized, with the limitation of the demographics of our recipient population. A limitation is that our data is not from a prospective randomized trial.

Maintenance immunosuppression for rapid discontinuation of prednisone protocols

Most RDP protocols have incorporated a calcineurin inhibitor and a mycophenolate, although some have used an mTOR inhibitor. However, there have been few randomized studies comparing individual protocols. Kandaswamy, et al. randomized 450 recipients treated with thymoglobulin and RDP to three arms: (i) CSA/MMF; (ii) low-level TAC/high-level sirolimus (SRL); and (iii) high-level TAC/low-level SRL[23]. For both TAC and SRL, high level was 8-12 ng/ml and low level was 3-7 ng/ml. At five years, there were no differences between groups in patient, graft, or death-censored graft survival rates, rejection rates, or in renal function. There was a higher rate of NODAT in the TAC/SRL groups[24]. However, there were no other differences between groups in complication rates.

In a RDP protocol using IL-2R inhibitors, Kumar, et al. randomized 150 non-sensitized recipients to TAC/MMF versus TAC/SRL and found no differences[25]. Gallon, et al., also using

an IL-2R inhibitor for induction, randomized recipients to TAC/MMF versus TAC/SRL. Three-year graft survival was significantly better for the TAC/MMF group[26]. The same group compared TAC/MMF versus TAC/SRL in kidney-pancreas recipients treated with thymoglobulin induction and a RDP protocol[27]. There was no difference between groups in patient or graft survival rates or in renal function.

Recently, Ferguson, et al. reported on a RDP trial (n = 93) in which recipients were treated with thymoglobulin induction and were randomized to receive either belatacept/MMF, belatacept/SRL, or TAC/MMF[14]. Rejection rates were low in all three arms. At 12 months, more than two thirds of the belatacept arms remained both prednisone- and calcineurin inhibitor-free.

Acute rejection episodes in recipients on rapid discontinuation of prednisone

Risk factors for acute rejection in recipients treated with RDP appear to be the same as those associated with acute rejection in recipients maintained on long-term prednisone. Woodle, et al. reported factors associated with increased risk of rejection for recipients on RDP to be re-transplants, current panel reactive antibody (PRA) > 25%, African Americans, DGF, HLA donor/recipient mismatches, type 1 diabetes, and female gender[28]. Decreased rejection rates were seen with thymoglobulin induction, type 2 diabetes, living donor transplant, Caucasian recipient, and male gender. We found the risk factors for increased rejection rates in our series to be re-transplant , PRA ≥ 50, and African American race; decreased rejection rates were seen in those with age ≥ 50[21].

After treatment of a rejection episode, should RDP-treated recipients be maintained prednisone-free or on maintenance prednisone? Only one study has reported on immunosuppressive management after a rejection episode[29]. In that nonrandomized study, 40% continued on maintenance prednisone (5 mg/day) after rejection treatment; 60% returned to long-term, prednisone-free maintenance therapy (patient and physician choice). At 24 months after the first acute rejection episode, graft survival was 69% in those that remained prednisone-free versus 82% in those that started on maintenance steroids (p = 0.03). At 24 months after the first acute rejection episode, 42% of those remaining prednisone-free had had a second acute rejection episode versus 30% in those that started on maintenance prednisone (p = 0.13). Importantly, of those whose first rejection episode was classified as “mild to moderate”, there was a significantly higher rate of second rejection episodes if the recipient remained prednisone-free (p = 0.02). The recommendation from this study was that until a prospective randomized study is done, recipients having an acute rejection episode while on a RDP protocol should be maintained on prednisone 5 mg/day after treatment of the episode.

Subgroups at potentially increased risk

There have been a number of studies reporting success of RDP in subgroups at potentially increased long-term risk such as high PRA recipients, African Americans, children, or those with potentially recurrent disease (as reviewed[8-11]). However, none of these subgroups have been studied in a prospective randomized trial.

Of note, most large single- or multicenter trials have excluded high-risk recipients. For example, in the placebo-controlled, randomized trial discussed above, high PRA (≥ 50% peak, ≥ 25% current) was an exclusion criterion for study entry[17]. In the few large series that included subgroups of high-risk

recipients, the "n" in each subgroup have not been sufficient for analysis.

Importantly, an appropriate control group is required for these studies. Khwaja, et al. reported that, when compared to low PRA recipients, high PRA recipients on an RDP protocol had increased acute rejection rates[30]. However, when high PRA recipients (on RDP) were compared to high PRA historical controls taking prednisone, there were no differences.

Benefits of rapid discontinuation of prednisone

Individual studies have reported on benefits of RDP. These have included decreased NODAT, decreased cardiovascular events, decreased metabolic syndrome, improved lipid profile, less weight gain after transplant, and decreased rates of bone disease and of cataracts[11,15,17,19,31,32]. Meta-analyses have shown decreased NODAT[11,15] and cardiovascular risk[15]. In our retrospective analysis of RDP versus historical controls on prednisone, we noted that the RDP recipients had significantly less cytomegalovirus infection, avascular necrosis, cataracts, NODAT, fractures, and non-posttransplant lymphoproliferative disease malignancies[19]. The five-year follow-up of the placebo-controlled randomized study found that RDP provided improvements in cardiovascular risk factors (triglycerides, NODAT requiring insulin, and weight gain)[17]. Of note, Rogers, et al. reported that the lack of weight gain advantage occurred only in recipients who did not have acute rejection after RDP[33].

Problems with risk-benefit analyses of rapid discontinuation of prednisone

Most studies of RDP have only looked at a limited number of endpoints. Almost all studies have reported on patient and graft survival and on acute rejection rates. But few have specifically studied the benefits of RDP. It may have simply been assumed that steroid-free maintenance immunosuppression would not be associated with steroid-related side effects. It may be that most investigators assumed that an unreasonable number of patients would be required to show a statistically significant difference. Some may have not wanted to do the long-term follow-up required. Some, including our group, did not have the funding for routine posttransplant monitoring of side effects such as bone mineral density changes, appearance changes, and quality of life. But the paucity of reports of a beneficial side effect profile may under represent the true benefits. This is critical because steroid-related side effects, such as NODAT, hyperlipidemia, hypertension, and weight gain, have the potential to increase cardiovascular risk, cardiovascular events, and to shorten lifespan. Long-term recipient follow-up will be required to determine whether RDP protocols improve longevity.

Discussion

Is RDP a good choice for our recipients, a poor choice, or perhaps somewhere in between? The goal of our posttransplant immunosuppressive protocols is to provide 100% long-term patient and graft survival, without immunosuppression-related side effects. Within that framework, the goal of prednisone minimization protocols after kidney transplantation has been to minimize prednisone-related side effects without increasing the rates of acute rejection and of late graft loss. Are small, but statistically significant, increases in acute rejection rates or in interstitial fibrosis and tubular atrophy on biopsy justified by a decrease in cardiovascular risk factors and other prednisone-related side effects? To date, there is no data to suggest that RDP lowers long-term patient and graft survival; in

fact, Luan, et al. reported improved survival with RDP[16]. It stands to reason that if there is no impact on patient and graft survival, then eliminating prednisone-related side effects is clearly worthwhile. But what if patient and graft survival are slightly worse (versus patients on maintenance prednisone), but prednisone-related side effects are minimized? Or, what if graft survival is slightly worse with RDP, but patient survival is better?

It is difficult to determine the relative "value" of individual or a combination of side effects. We studied the relative impact of having one or more acute rejection episodes versus developing NODAT[34]. Recipients having both rejection and NODAT had the worst long-term outcome (15-year actuarial graft survival). But having a rejection episode was associated with significantly worse long-term graft survival than NODAT. In a similar but much larger analysis using the data from the US Renal Data System (first transplants, 1995-2002), Cole, et al. found that acute rejection and NODAT had an equivalent impact on long-term transplant survival[35]. However, the mechanisms of graft loss differed. Acute rejection was associated with death-censored graft loss, whereas NODAT was associated with increased risk for death with a functioning graft. These types of observations are critical in determining which side effect profile we are most worried about for our recipients.

How do we put a relative "value" on the development of appearance changes, mood swings, cataracts, osteoporosis, or vascular necrosis? Veenstra, et al. reported that treatment of prednisone-related side effects was expensive for the healthcare system[36]. But so is treatment of acute rejection episodes. And how do we determine what the "trade-off" is between one side effect profile and another? An individual recipient may prefer slightly increased rejection rates to a Cushingoid appearance.

If we accept that the benefits of RDP far outweigh the risks, should RDP be considered for all recipients? To date, many studies have limited RDP to low immunologic risk recipients. But any patient would potentially benefit from being spared prednisone-related side effects. Single-center studies have reported successful RDP in a variety of subgroups including African Americans, children, those with high PRA, and those with potentially recurring diseases[8-11]. No published prospective randomized study has yet compared maintenance prednisone to RDP in these high-risk populations.

It has been demonstrated that when using a RDP protocol, the other elements of the immunosuppressive protocol are important. It does matter which induction agent is used and it may matter which maintenance agents are used[17,18]. It will be important to do long-term studies of individual protocols. At the same time, there is a need for more data on how to adjust immunosuppression for a recipient having an acute rejection episode while on a RDP protocol.

Almost all data on the benefits of RDP come from studies comparing the benefits of RDP to the historically high maintenance prednisone dose protocols. One of the real benefits of the clinical research into RDP is that all centers, whether using RDP protocols or not, have dramatically reduced their prednisone dosing. New studies need to be done to compare RDP to these new low-dose (5 mg/day after the first 7-14 days) prednisone protocols. However, data from both the transplant and non-transplant literature suggests that patients taking these "low" prednisone doses still are at increased risk of some prednisone-related complications (e.g. weight gain, loss of bone mineral density, and increased risk of cataracts and fractures)[37-45].

It is unclear why there has been a difference in results between late versus early steroid withdrawal. Initial trials of both late and early (RDP) withdrawal were done on a similar

maintenance immunosuppression background (CsA, MMF); yet, rejection rates were higher with late withdrawal. This suggests that being on long-term prednisone altered physiology, making withdrawal more difficult[46]. At the same time, a recent meta-analysis by Pascual, et al. suggested that late steroid withdrawal was associated with increased acute rejection rates only when CsA was used as the maintenance calcineurin inhibitor; when the maintenance calcineurin inhibitor was TAC, rejection rates were not increased[47]. One potential explanation for this observation is that TAC exposure is increased after steroid withdrawal[48].

Given what we have learned about RDP to date, how should early prednisone withdrawal be viewed in the overall spectrum of our immunosuppressive protocols? Many of the randomized trials of RDP used induction therapy in the RDP arm and no induction in the maintenance prednisone control arm. These trials tended to show no difference between the arms in terms of rejection rates or in patient and graft survival. The prednisone-free arm benefited from having fewer steroid-related side effects[10]. Thus, one possibility is to consider the trade-off (costs, risks) of early antibody induction versus long-term prednisone. Alternatively, randomized trials that included antibody induction therapy in both arms tended to show slightly increased rejection rates in the RDP arm, although the difference in rejection rates between the two arms was related to which antibody was used. These trials also showed benefits to being prednisone-free. From the perspective of these studies, the trade-off would be slightly increased rejection rates (with, to date, no impact on long-term graft survival) versus increased prednisone-related side effects.

It is interesting that four recent reviews/editorials of RDP in kidney transplantation reached conflicting conclusions. Desai, et al., commenting on the placebo-controlled randomized trial described above[17], stated, “Before the transplantation community accepts steroid withdrawal as a new standard of care for kidney transplant recipients, we believe that more conclusive data are necessary. Until then chronic low-dose steroids… should remain the maintenance regimen of choice for kidney transplant recipients”[49]. Luan, et al., while supporting RDP, stated, “The major challenge remains the identification of individual patients who may not benefit from a steroid-free immunosuppressive regimen. Until then, steroid-free immunosuppression should be considered standard of care only for a carefully selected group of patients”[9]. Augustine and Hricik conclude, “Collectively, these studies make it clear that steroid withdrawal can be accomplished safely in a large majority of kidney transplant recipients. Rather than propose another trial, we suggest that research in this area focus on more pointed questions”[50]. And, Knight and Burrows write, “Therefore, on the basis of our data, we believe that withdrawal of steroids within the first week after transplantation is safe in low-risk recipients”[51].

If prednisone were newly introduced today, would it be widely accepted for maintenance therapy? If randomized studies were done, we would learn that the cost of the drug was low, which is important in today’s environment of reducing healthcare costs, and, perhaps, that rejection rates were slightly reduced. However, we would also learn that maintenance prednisone provided no increase in long-term graft survival, and was associated with a significant side effect profile. It is quite possible that these randomized trials would not lead to approval of prednisone for its use in a maintenance immunosuppressive regimen.

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