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REVIEW

Minimization of steroids in kidney transplantation

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Summary

The goal of steroid minimization trials has been to minimize or eliminate steroid-related side-effects while simultaneously not increasing the rate of acute rejection (AR) and chronic graft loss. Early trials of *late* steroid withdrawal (≥3 months post-transplant) were associated with significantly increased AR rates and late graft loss. More recent trials of rapid discontinuation of prednisone (RDP) (≤7 days post-transplant) have been associated with little or no increase in AR rates and no difference in graft survival (versus maintenance prednisone). Of note, induction therapy appears to be important for success; however, it is not clear if any single maintenance protocol is superior. Intermediate-term follow-up (5–7 years) is now available for some randomized and nonrandomized trials; graft survival and renal function remain excellent. Most of these trials have been done in low immunologic risk recipients, but there are reports of success of RDP in children, black recipients, sensitized recipients, recipients with potentially recurring disease, and kidney–pancreas recipients. Of critical importance, steroid-related side-effects have been minimized. Steroid minimization protocols can clearly be recommended for low-risk patients; additional trials are necessary for those at higher risk. Additional research is also necessary on integrating calcineurin inhibitor minimization with steroid minimization.

Introduction

The goal of steroid minimization protocols has been to eliminate or minimize steroid-related side-effects while not increasing the rates of acute rejection (AR) or chronic graft loss. Until recently, corticosteroids had been a mainstay of kidney transplant immunosuppressive protocols. However, though 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 al.* [2] recently showed that an 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 post-transplant noncompliance [4]; noncompliance is associated with an increased incidence of AR, 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 stated that the immunosuppressive drug they would most like *not* to take is prednisone [6].

Late (≥3 months) steroid withdrawal

Historically, numerous attempts have been made either to avoid steroids or, in selected recipients, to gradually withdraw steroids late (≥3 months) post-transplant. After cyclosporine (CsA) was introduced, CsA monotherapy was associated with a high incidence of AR [7,8]. Similarly, meta-analyses of studies of late steroid withdrawal in selected recipients on CsA and prednisone [with or without azathioprine (AZA)] showed an increased incidence of AR and graft loss [9,10].

Of particular concern has been a multicenter Canadian study in which recipients on CsA and prednisone were

randomized at 3 months to either switch to CsA monotherapy or continue the two drugs [11]. For the first 500–600 days after randomization, that study's authors found no significant differences between the two groups; but 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 AR on long-term graft outcome was recognized [12]; the authors did not determine whether or not the rate of AR increased after prednisone withdrawal.

After studies showing mycophenolate mofetil (MMF) was associated with a lower AR rate than AZA, randomized studies of late steroid withdrawal were done in selected recipients on CsA and MMF, and subsequently in selected recipients on tacrolimus (TAC) and MMF [13–18]. Recent meta-analyses of those studies (4 used CsA, 2 TAC) showed a significantly increased AR rate in the steroid withdrawal group, but no increased risk of early graft failure [19,20]. Longer-term follow-up has only been reported for one of those six studies [21], a TAC–MMF study in which 3-year follow-up showed no difference between the steroid withdrawal and the maintenance immunosuppression groups in patient and graft survival rates or in renal function; the steroid withdrawal group had less hypertension and significantly lower mean total cholesterol and LDL-cholesterol values ($P = 0.02$).

In contrast to the above studies, Opelz *et al.* [22] recently reported no increased AR rates for recipients on CsA-based immunosuppression who underwent steroid withdrawal >6 months post-transplant. Median time to steroid withdrawal was 1.1 years; after enrollment, steroids were tapered in a step-wise fashion. Using the Collaborative Transplant Study (CTS) database, Opelz *et al.* matched each enrolled recipient ($n = 1015$) with three controls. The actuarial 7-year patient, graft, and death-censored graft survival rates were significantly better for the withdrawal group ($P < 0.01$). Outcomes did not differ for those treated with AZA or MMF. The difference in outcomes between Opelz's versus the above studies may be a result of the later withdrawal of steroids in Opelz's study.

Two randomized trials using calcineurin inhibitors (CNIs) recently published their results (not included in the above meta-analyses). Pelletier *et al.* [23] selected, on a randomized basis, CsA–MMF–prednisone recipients >6 months post-transplant, to either withdraw or continue prednisone; the long-term outcome of the two groups did not significantly differ. Wlodarczyk *et al.* [24] randomized recipients, at the time of their transplant, to take either TAC–MMF–prednisone or TAC–AZA–prednisone. At 3 months post-transplant, selected recipients (i.e., those who were then rejection-free and having had no more than one steroid-sensitive rejection episode in the first 2 months; whose serum creatinine level was <160 μmol/l between days 84 and 91 post-transplant; and who was receiving at least 0.5 g/day of MMF or 1 mg/kg/day of AZA) were randomized to either taper off or stay on steroids. For both the TAC–MMF and TAC–AZA groups, the rejection rate in the next 3 months was similar to the rate in each group randomized to stay on steroids.

Success with steroid withdrawal >3 months post-transplant has also been reported with mTOR inhibitors. Buchler *et al.* [25] reported a multicenter study in which recipients were randomized, at the time of their transplant, to take either sirolimus (SRL) or CsA. All were treated with antithymocyte globulin (ATG), MMF, and a 6-month course of corticosteroids. Within 48 h post-transplant, SRL recipients received a 15-mg loading dose for 2 days, followed by 10 mg/day (target, 10–15 ng/ml). At 12 months post-transplant (6 months after steroid withdrawal), the patient and graft survival rates, the incidence of biopsy-proven rejection, and the rate of steroid withdrawal did not significantly differ between the two groups. At 12 months, for recipients who remained on their protocol, the estimated glomerular filtration rate (GFR) was significantly higher with SRL (69 ± 19 ml/min) than with CsA (60 ± 14 ml/min) ($P = 0.01$). However, study drug discontinuation rates were higher with SRL (28.2%) than with CsA (14.9%). Adverse events were also much higher with SRL. Buchler *et al.* felt that avoiding a loading dose of SRL and delaying the introduction of SRL during antibody induction might have prevented many of the SRL-related complications. Both Mahalati and Kahan [26] and Citterio *et al.* [27] have reported successful late steroid withdrawal for recipients on CsA plus SRL.

In an interesting nonrandomized study, Hricik *et al.* [28] reported their results of late prednisone withdrawal in 30 African American kidney transplant recipients on TAC–SRL. With a mean follow-up of 14 months, the AR rate was only 6.7% [28]; but during longer follow-up (mean, 48.5 months), the cumulative incidence of rejection was 41%, and graft loss occurred in 25% of recipients. Of importance, nine out of the 13 rejection episodes were related to noncompliance [29].

Of note, most (but not all) studies reporting success of late steroid withdrawal have been done in Europe; most (but not all) reporting failure have been done in the United States. Differences in organ allocation systems, population demographics, or timing of withdrawal may explain these outcome differences.

Rapid discontinuation of prednisone

The recognition that late steroid withdrawal was associated with increased AR rates, combined with the intro-

duction of more potent induction and maintenance immunosuppressive agents, led many investigators to consider either rapid discontinuation of prednisone (RDP) (≤7 days post-transplant) or complete avoidance of steroids. Such protocols have the potential advantage of minimizing any early steroid-related side-effects. Both RDP and avoidance protocols have used a variety of induction agents (Thymoglobulin, alemtuzumab, interleukin-2 inhibitors), either of the two CNIs (CsA or TAC), and either MMF or SRL.

Birkeland [30,31] was the first to report success with steroid avoidance (Table 1). In his series, 100 recipients (67 deceased donor, 33 living donor) were on ATG, CsA, and MMF. Only 13% had an AR episode; the actuarial 4-year graft survival rate was 82%.

Randomized studies of RDP

Short-term (≤1 year) results

Since Birkeland's report, a number of prospective randomized trials of RDP versus maintenance prednisone have been done (Table 2) [32–43]. 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 al.* [33] (n = 364) in which the only exclusion criteria were use of

Table 1. Nonrandomized studies of RDP.

N	Induction	Maintenance	1-year AR rate (%)	1-year GS rate (%)	Ref. no.
≤1 year follow-up					
57	Daclizumab	CsA–MMF	25	89	44
301	ATG	CsA–SRL	4.9	91	45
77	–	TAC–SRL	13	100	46
130	Basiliximab	CsA–MMF	19*	97	47

N	Antibody	Maintenance	1-year AR rate (%)	1-year GS rate (%)	Long-term GS rate	Ref. no.
>1 year follow-up						
100	ATG	CsA–MMF	–	97	82% at 4 years	31
84	ATG	TAC–MMF–SRL	11	96	93% at 2.5 years	48
775	ATG	CsA–MMF or TAC–SRL	13	95	80% at 4 years	50
116	Basiliximab	TAC–MMF	–	97	90% at 6 years	52

AR, acute rejection; GS, graft survival; ATG, antithymocyte globulin; CsA, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus.
*Higher in ABO-compatible (versus ABO-incompatible).

Table 2. Prospective randomized trials of RDP.

N	F/U	Antibody	Maintenance	AR rate versus controls	GS rate versus controls	Ref. no.
≤1 year follow-up						
83	1 year	Basiliximab	CsA–MMF	NS	NS	32
381	1 year	Daclizumab	TAC–MMF	NS	NS	33
538	6 months	Daclizumab	TAC–MMF	NS	NS	34
451	6 months	None	TAC–MMF	Significant ↑ (P = 0.001)	NS	35
		Basiliximab	TAC	Significant ↑ (P = 0.046)	NS	
151	1 year	ATG	TAC–MMF	NS	NS	36
337	1 year	Basiliximab	TAC–EC-MPS	Significant ↑ (P = 0.046)	NS	37
60	1 year	ATG	TAC–MMF	NS	NS	38
>1 year follow-up						
386	4 years	Basiliximab or ATG	TAC–MMF	↑ (P = 0.08)	NS	39
133	3 years	Basiliximab	Everolimus–CsA	↑ (P = 0.059)	NS	40
300	3 years	Basiliximab	TAC or CsA MMF or RAPA	NS	NS	41
62	2.7 years	None	TAC–MMF	NS	NS	43

AR, acute rejection; GS, graft survival; NS, no significant difference versus control group; ATG, antithymocyte globulin; CsA, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus; EC-MPS, enteric-coated mycophenolate sodium.

an HLA-identical living donor and treatment with prednisone at the time of the transplant. In general, short-term results of these studies have shown no difference between RDP and maintenance prednisone groups in patient survival, graft survival, or AR rates; in severity of AR; or in renal function (Table 2).

In contrast to others, Vincenti *et al.* [37] recently reported the 12-month outcome of a trial in which recipients ($n = 357$) on basiliximab–CsA and enteric-coated mycophenolate sodium were randomized to one of three groups: no prednisone, versus prednisone till day 7 post-transplant, versus maintenance prednisone. Biopsy-proven AR rates were significantly increased in the two prednisone minimization groups (versus the maintenance group). When recipients with graft loss or death were assigned a GFR of 0 ml/min, the mean 12-month GFR was lower in the two prednisone minimization groups (versus the prednisone maintenance group). Per a subset analysis of recipients with functioning grafts at 12 months, GFR did not differ among the groups.

In the above studies, RDP was done in the context of induction plus two maintenance drugs. In a different trial design, Vitko *et al.* [35] randomized 471 recipients to triple therapy (TAC–MMF–prednisone), versus TAC–MMF, versus basiliximab–TAC. The two prednisone-free groups had significantly increased AR rates (TAC–MMF, 30.5%; basiliximab–TAC, 26.1%) [versus the triple therapy group (8.2%)] ($P < 0.001$). But the groups did not significantly differ in patient or graft survival rates. Vitko's study suggests that both induction and dual-agent maintenance therapy may be important for successful RDP.

Intermediate-term (>1 year) results

Woodle *et al.* [39] randomized 386 recipients (stratified by donor source and recipient race) on antibody induction (center choice) and TAC–MMF to either RDP or long-term prednisone. At 3 years, the primary composite endpoint of death, graft loss, or severe AR did not differ between groups. Nor did renal function (mean creatinine; calculated creatinine clearance). The RDP group had a significantly lower rate of diabetes and fractures; their triglyceride values were lower and their hypertension was easier to control. Although the difference was not statistically significant, there was a 6.5% increased AR rate in the RDP group ($P = 0.07$); in addition, the rate of chronic allograft nephropathy (biopsy for cause) was 5% higher in that group (P = NS). Of note, in a subgroup analysis, RDP recipients on Thymoglobulin had a lower AR rate than those on IL-2r inhibitors.

Montagnino *et al.* [40] randomized 133 de novo kidney transplant recipients on basiliximab, everolimus, and CsA to either RDP or long-term low-dose steroids. During the follow-up, 46% in the RDP group resumed prednisone. Per the intention-to-treat analysis, the 3-year graft survival rate was 95% in the RDP arm versus 87% in the steroid arm (P = NS). The RDP group had more biopsy-proven rejection episodes (32%) than the steroid group (18%), but the difference was only of borderline significance ($P = 0.059$). After 3 years, the two groups did not differ in their mean creatinine clearance, mean serum cholesterol, and mean triglyceride values.

Kumar *et al.* [41] randomized 300 recipients treated with basiliximab, a CNI, and either MMF or SRL, to either RDP or maintenance prednisone. Their study began as a randomized study; however, after an interim analysis showed the benefit of RDP, it was then continued, with IRB approval, as a nonrandomized study (patients were informed of the results of the interim analysis). The two groups did not differ in 3-year patient and graft survival rates, in AR rates, in mean serum creatinine level and creatinine clearance, in the incidence of subclinical rejection, or in the progression of chronic allograft nephropathy. At 3 years, the RDP group had a significantly lower rate of new-onset diabetes mellitus ($P < 0.01$), less increase in body mass index (BMI) ($P < 0.04$), and fewer infections requiring hospitalization ($P = 0.05$). Outcome did not significantly differ between those receiving SRL versus MMF (see below) [42].

In a pilot study with a differing trial design, Boots *et al.* [43] randomized TAC–MMF recipients to either RDP or steroid tapering and withdrawal at 3–6 months (median follow-up, 2.7 years). No induction therapy was used. The groups did not differ significantly in patient or graft survival rates or in renal function. Of note, AR episodes occurred in 29% of the RDP group and 30% of the withdrawal group.

Nonrandomized studies

Short-term (≤1 year) results

Cole *et al.* [44] reported a pilot study of 57 recipients on daclizumab, CsA, and MMF who underwent RDP. At 1 year, the patient survival rate was 95%; graft survival, 89%. Of the 57 recipients, 14 (25%) had an AR episode.

Rajab *et al.* [45] compared outcome for 301 first transplant recipients on ATG induction, CsA, SRL, and RDP versus for historical controls (502 first transplant recipients in the 2 years before institution of RDP) on basiliximab induction, CsA, MMF, and prednisone. The 1-year patient survival and death-censored graft survival rates, the mean serum creatinine level, and the mean serum triglyceride and cholesterol values did not differ significantly between the groups. The biopsy-proven AR rate was 4.9% in the RDP group and 9.4% in the control group ($P < 0.01$); weight gain was also significantly lower in the RDP group. However, more recipients in the RDP group

required erythropoietin and iron therapy for anemia ($P < 0.001$).

Woodle *et al.* [46] reported the results of a pilot study in 77 recipients on basiliximab, SRL, TAC, and RDP. At 12 months post-transplant, the patient and graft survival rates were each 100%. The biopsy-proven AR rate was 13%; the clinically diagnosed AR rate, an additional 10.5%.

Kato *et al.* [47] compared outcome for recipients on basiliximab and CsA–MMF who underwent RDP with concurrent recipients on CsA–MMF and long-term prednisone. At 1 year post-transplant, the patient survival, graft survival, and AR rates did not differ between groups. Kato *et al.* noted that for those successfully prednisone-free at 1 year, there was no need to subsequently restart prednisone.

Intermediate-term (>1 year) results

Jaber *et al.* [48] reported their experience with 3-agent immunosuppression involving RDP and CNI minimization ($n = 84$). Immunologically high-risk recipients were included. ATG was given for 5 days, together with TAC–MMF. SRL was initiated on day 6 post-transplant, when prednisone was discontinued. As compared with historical controls, the study group's 2.5-year actuarial patient survival rate (97%) was significantly higher ($P = 0.048$); there was no difference in graft survival (93%), AR-free graft survival (89%), or renal function. In addition, post-transplant, the study group had a decreased prevalence of cardiovascular disease risk factors, as compared with controls.

We began RDP at our institution in 1999 [49], and have reported 6-year outcome ($n = 775$) [50]. Our first and second transplant recipients were treated with ATG, a CNI, either MMF or SRL, and RDP. Our only exclusions were recipients already on prednisone. The actuarial 6-year patient survival rate was 88%; graft survival, 80%. At 1 year, 13% of recipients had had an AR episode. Renal function was stable through 6 years. Of note, 8% of recipients developed cytomegalovirus (CMV) infection; 0.5%, polyomavirus. We found that over 80% of recipients remained prednisone-free long-term.

In another study, we compared outcome for recipients who underwent RDP versus historical controls on ATG, CNI, MMF, and long-term prednisone [51]. The actuarial patient survival, graft survival, AR, and biopsy-proven interstitial fibrosis and tubular atrophy (IF/TA) rates did not differ significantly between the two groups; nor did the MDRD GFR. The RDP group had significantly lower rates of cataracts ($P < 0.001$), new-onset post-transplant diabetes ($P < 0.001$), avascular necrosis ($P < 0.001$), CMV infection ($P < 0.001$), fractures ($P = 0.04$), and non-PTLD malignancy ($P = 0.02$).

Gallon *et al.* [52] reported outcome with a sequential study in which recipients on IL-2r induction were either maintained on chronic prednisone ($n = 96$) or underwent RDP ($n = 116$). The two groups did not differ in actuarial 7-year patient and graft survival rates, the incidence and severity of acute cellular rejection, and the slope of GFR decline per month at 5 years post-transplant. The RDP group had a significantly lower incidence of hyperlipidemia and post-transplant diabetes.

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. Certainly, withdrawal and RDP protocols have helped move the transplant field forward by helping demonstrate that high long-term steroid doses are not necessary. Today, even recipients maintained on long-term prednisone are taking far less prednisone than they would have taken a decade ago. For example, recipients at our institution who are not on our RDP protocol (e.g., those on prednisone at the time of their transplant) are discharged to home on only 5 mg/day of prednisone.

However, 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 not supported by any data. In addition, it has been suggested that most steroid-related side-effects are related to long-term high doses and that the risk-benefit ratio may be far different with long-term low doses. However, van den Ham *et al.* [53] showed a significant difference in weight gain between recipients on 5 mg/day of prednisone versus RDP. Matsunami *et al.* [54] noted that recipients on high-dose steroids had a 55% incidence of posterior subcapsular cataracts; low-dose steroids, 28%; and no steroids, 6.2%. Steroids have been associated with rapid loss of bone mineral density in transplant recipients [55]; cumulative steroid dose has been correlated with bone mineral density loss [56]. 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 [57–61].

Individual populations on RDP

Most of the above studies limited RDP to adult recipients with a relatively low immunologic risk. However, some randomized and some nonrandomized studies have enrolled both high- and low-risk recipients [33,41,47,51].

Only a few reports have described outcome of RDP in specific higher-risk populations.

Children

Successful steroid avoidance in children was first shown by Birkeland *et al.* [62] using ATG induction, MMF, and CsA ($n = 14$); the early AR rate was 15%. Subsequently, Sarwal *et al.* [63,64] described a novel steroid avoidance protocol, based on TAC–MMF, and daclizumab induction for 6 months post-transplant. In 57 consecutive (low sensitization risk) recipients, AR rates were low (8%); there was excellent graft function and dramatic catch-up growth trends. The RDP group had better values of estimated creatinine clearance, less hypertension, a lower increase in BMI, and, importantly, better compliance as compared with historical controls. In a retrospective case-controlled study, Oberholzer *et al.* [65] noted that their RDP group had significantly higher creatinine clearance at 6 and 12 months post-transplant ($P = 0.04$), significantly lower BMI, a significantly higher delta Z score, and significantly less hyperlipidemia, body disfigurement, and need for antihypertensive medications.

Chavers *et al.* [66] compared 21 children (14 ± 3 years) on an RDP protocol with 39 matched controls on maintenance prednisone and found no difference in patient or graft survival, AR rates, anemia, hypertension, creatinine level, or CMV or EBV infection. Of the RDP group, 82% remained prednisone-free.

Black recipients

Black recipients have had an increased rate of AR episodes on late steroid withdrawal protocols [12]. Thus, there has been concern that early prednisone minimization would also result in an increased AR rate. However, data to date suggest that early steroid minimization can be successful in black recipients [67–70].

Haririan *et al.* [67] compared black recipients treated with RDP versus black recipients on chronic steroid therapy: the 1-year patient survival, graft survival, and AR rates did not differ between groups. The RDP group had less weight gain, lower cholesterol levels at 3 months, and a lower risk of post-transplant diabetes mellitus. Others compared their 1-year results for black recipients versus nonblack recipients in their RDP trials and found no difference in patient and graft survival rates, in AR rates, or in renal function [68–70]. However, Kumar *et al.* [69] found that subclinical rejection at 1 month was significantly higher in black recipients ($P = 0.04$). Kumar *et al.* [71] recently reported their 5-year outcome. Of note, in their series, black recipients (versus nonblack recipients) had a higher percentage of deceased donor transplants and of diabetes, as well as a longer duration of pretransplant dialysis. There was no difference between the two groups in 5-year graft survival; however, black recipients had a significantly increased subclinical rejection rate at 3 and at 5 years, significantly more tubular atrophy and interstitial fibrosis, and a significantly lower GFR at 5 years.

Potentially recurrent disease

Ibrahim *et al.* [72] studied outcome for 105 adult recipients whose transplant was for glomerulonephritis (GN) and who underwent RDP. Two control groups consisted of (i) 439 concurrent recipients whose transplant was for causes other than GN and who underwent RDP and (ii) 260 recipients whose transplant was for GN (between 1994 and 1999) and who were on maintenance steroids In all three groups, the 4-year patient and graft survival rate, AR-free survival rate, serial annual serum creatinine level, and estimated GFR were similar. Although longer follow-up is needed, Ibrahim *et al.* concluded that RDP conferred no increased short-term risks for recipients with GN. Likewise, Boardman *et al.* [73] noted no difference in outcome for recipients with focal segmental glomerulosclerosis (FSGS) who underwent RDP versus chronic steroid therapy.

High immunologic risk

Khwaja *et al.* [74] studied outcome for 78 recipients with a high immunologic risk, and recipients on ATG, CsA–MMF, and RDP. The actuarial 3-year patient survival rate was 95%; graft survival, 94%. Mean serum creatinine level (±SE) was 1.7 ± 0.6 at 6 months, 1.5 ± 0.5 at 12 months, and 1.6 ± 0.7 at 24 months. At the time of the report, only two had had biopsy-proven AR and 79% remained prednisone-free. In a pilot study, Alloway *et al.* [75] treated 10 high-risk recipients with daclizumab induction, TAC–MMF, and RDP; because of a high AR rate (60%), induction was switched to ATG, and AR rates subsequently were 27%.

Kidney–pancreas recipients

Canterovich *et al.* [76] (ATG, CsA–MMF) and Kaufman *et al.* [77] (ATG, TAC–MMF) have reported excellent graft survival rates and low AR rates in simultaneous kidney–pancreas (SKP) recipients on RDP. In a protocol using ATG and RDP, Gallon *et al.* [78] showed no difference in outcome for SPK recipients on TAC–MMF versus TAC–SRL. Kaufman *et al.* subsequently showed that alemtuzumab and ATG were associated with equivalent results in their RDP protocol with TAC–SRL maintenance

[79]. Recently, Rajab *et al.* compared outcome for 97 pancreas recipients (80%, SPK; 20%, pancreas after kidney transplants) (on ATG, CsA–SRL and RDP) versus historical controls (basiliximab, MMF, and maintenance prednisone [80]: the patient and graft survival rates did not differ between the two groups; however, the RDP group had significantly lower AR rates ($P < 0.01$). In a recent randomized study, Canterovich *et al.* compared RDP versus prednisone withdrawal for SPK recipients on ATG, and CsA–MMF [81]. The two groups did not differ in 1-year patient and graft survival or AR rates; however, the serum creatinine level was higher in the RDP group ($P = 0.02$).

ABO-incompatible transplant recipients

We know of only one report of RDP in ABO-incompatible recipients. Kato *et al.* [47] noted that the success of RDP (as defined by the need to reintroduce steroids) was significantly lower in ABO-incompatible (versus ABO-compatible) recipients.

Which immunosuppressive protocol for RDP?

Induction

Most RDP protocols have used induction therapy; when induction therapy was not used, the AR rates were high [8,35,43]. In a randomized controlled trial of CsA monotherapy versus basiliximab–CsA, Parrot *et al.* [8] found that significantly more basiliximab–CsA-treated recipients remained prednisone-free ($P = 0.046$). Vitko *et al.* [35] noted a high AR rate (26.1%) in their basiliximab–TAC group. Boots *et al.* [43] had a 29% AR rate in their TAC–MMF group. No prospective randomized trials have compared induction agents in RDP protocols. Success has been reported with IL-2r antagonists, alemtuzumab, and ATG. However, in a randomized study of RDP versus prednisone in which institutions could choose which antibody to use, Woodle *et al.* [39] noted less AR with ATG (versus IL-2r antagonists).

Maintenance

Kumar *et al.* [42] randomized 150 nonsensitized patients treated with basiliximab and RDP to either TAC–MMF or TAC–SRL. The mean reported follow-up was 429 ± 301 days, with a minimum of 6 months. There was no significant difference between the groups in 2-year patient survival, graft survival, or AR rates. Of note, however, surveillance biopsies performed during their study showed a lower incidence of subclinical AR (16% vs. 27%) and chronic allograft nephropathy (10% vs. 22%) in the TAC–SRL group as compared with the TAC–MMF group.

At our institution, Kandaswamy *et al.* randomized 450 first and second kidney recipients on 5 days of ATG and RDP to one of three groups: CsA–MMF; high-level TAC (8–12 ng/ml) and low-level SRL (3–7 ng/ml); or low-level TAC (3–7 ng/ml) and high-level SRL (8–12 ng/ml) [42,82]. At 4 years post-transplant, patient, graft, death-censored graft, and AR-free graft survival rates did not differ significantly. But the two TAC–SRL groups had a higher rate of new-onset diabetes.

Gallon *et al.* [83] randomized recipients on IL-2r antibody and RDP post-transplant to TAC–MMF ($n = 45$) versus TAC–SRL ($n = 37$). At 3 years post-transplant, the graft survival rate was significantly better in the TAC–MMF group (one graft lost) versus TAC–SRL (six grafts lost) ($P = 0.04$). But the AR rate did not differ. Of note, 70% of the AR episodes occurred early (<30 days post-transplant) in both groups, suggesting induction therapy using IL-2r antibody in RDP protocols may be ineffective. The slope of GFR decline per month was flatter in the TAC–MMF than in the TAC–SRL group. As described above, the same authors compared outcome for SPK recipients treated with ATG, RDP, and either TAC–MMF or TAC–SRL [78]. At 6 years, they found no difference between groups in patient survival, graft survival, or AR rates. Importantly, the slope of GFR decline per month at 5 years did not differ between the two groups.

Thus, studies to date suggest that excellent patient and graft survival rates and low AR rates can be obtained using a variety of maintenance drugs in RDP protocols.

AR after RDP: long-term prednisone?

One clinically important question is whether long-term maintenance steroids should be introduced in recipients who have an AR episode after RDP. Humar *et al.* reported on 149 recipients who had ≥1 AR episode while on our RDP protocol. AR episodes were treated with a steroid taper (with or without antibody) [84]. Of the 149 recipients, 51 (34%) switched to maintenance prednisone (5 mg/day) after treatment of their first AR episode; 98 (66%) returned to a steroid-free protocol. Return to maintenance prednisone was not randomized but was based, in part, on the physician's and patient's choice. Patient characteristics for the two groups were similar. At a mean follow-up of 26 months, 32% of the recipients had a second AR episode: 29.4% of those on maintenance steroids versus 33.7% of those remaining steroid-free ($P = 0.12$). Graft survival was not significantly different between the two groups. Multivariate analysis of risk factors for a second episode suggested that whether or not steroids had been added to the maintenance protocol might have an impact (RR = 2.1, $P = 0.07$). Of concern,

in the subgroup supposedly most likely to *not* have a second AR episode – i.e., recipients with minimal to mild AR – the rate of second AR episodes significantly increased if the recipient had returned to steroid-free immunosuppression ($P = 0.02$). Clearly, a randomized trial with longer follow-up and more recipients is necessary to definitively answer this question.

Conclusions

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 last 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 versus a protocol involving rapid tapering to 5 mg/day, and versus a protocol involving rapid tapering plus late withdrawal. Currently, early transplant results are so good that the n required to power such a study would be enormous.

Clearly, some steroid-related side-effects can occur early and with relatively low doses of steroids; the major benefit of a new randomized study would be to determine whether long-term low-dose prednisone has any salutary effects. And it might be important to do such a study with the 'correct' antibody or maintenance therapy. The randomized study of Woodle *et al.* [39] suggested – but the differences were not statistically significant – that ATG was associated with fewer early AR episodes than an IL-2r receptor antagonist.

The popularity of RDP protocols nowadays has other implications. The long-term, low-dose study contemplated above would likely be difficult to do at institutions already using RDP, as their recipients would want to be on an RDP protocol (rather than on a study of RDP). In the United States, use of RDP protocols is growing [85]. Yet steroid-free immunosuppression is not approved by the FDA. Therefore, any new drug trials must use prednisone in a comparison group. As a consequence, many recipients at institutions using RDP have no interest in participating in studies that might randomize them to long-term prednisone.

An interesting question is why RDP is not, in most studies, associated with an increased AR rate, whereas steroid withdrawal at 3 months post-transplant – using the same maintenance immunosuppression – is. Part of the answer might be that cytokine receptor expression is increased by glucocorticoid-pretreated T cells [86]; however, cytokine release is impaired. When steroids are reduced, there may be increased cytokine release in the context of increased cytokine receptors, and the result is a higher AR rate. 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 increased [87]; thus there was more MMF exposure, possibly resulting in less AR. Another study showed that TAC exposure also increased after steroid withdrawal [88].

A final question is how to balance steroid-free and CNI-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 CNIs is either minimized or eliminated. The ideal would be to develop protocols that are both steroid- and CNI-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 side-effects.

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