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The Risks and Benefits of Late Steroid Withdrawal

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Abstract

Steroid withdrawal after the first posttransplant months in patients receiving a kidney transplant has been recently discouraged in clinical guidelines. A systematic review of studies assessing late steroid withdrawal beyond the third month after kidney transplantation was undertaken.

A special meta-analysis of the nine randomized controlled trials of steroid withdrawal between three and six months after kidney transplantation, using the current most frequently used immunosuppressive regimen, a calcineurin inhibitor plus mycophenolic acid, was included in our review. Death and graft loss were similar in steroid withdrawal and control patients. Including all trials, acute rejection was not more frequent after steroid withdrawal, but stratifying by the drug used, cyclosporin A was associated with an increased incidence of overall acute rejection or biopsy proven acute rejection. Conversely, tacrolimus allowed steroid withdrawal without increased biopsy proven acute rejection. Serum cholesterol was lower after steroid withdrawal than in controls either using cyclosporin A or tacrolimus. Serum creatinine, blood pressure, serum triglycerides, new-onset diabetes mellitus, infections, or malignancies were similar in steroid withdrawal and control patients, so the benefits of late steroid withdrawal were not easily demonstrated.

A total of 30 reports from 26 observational or randomized controlled trials without an adequate conventional steroid control group were also analyzed. In general, an increase in acute rejection without increased graft loss was evident in these low-quality studies, with some benefits in cholesterol reduction, and less glucose metabolism and bone metabolism alterations.

Steroid withdrawal three to six months after kidney transplantation is associated with increased rates of acute rejection only if cyclosporin A is used, but not with tacrolimus. Graft function and survival remain stable up to three years after transplantation, the longest follow-up reported.

The interest in late steroid withdrawal has decreased over the last years in the literature. More trials with carefully designed outcome measures are needed in patients treated with low-exposure tacrolimus and mycophenolic acid derivatives. **(Trends in Transplant. 2011;5:69-82)**

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Key words

Immunosuppression withdrawal. Corticosteroid withdrawal. Randomized controlled trial. Observational study.

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Introduction

More than 95% of transplant recipients are treated with corticosteroids as a usual component of clinical immunosuppressive regimens. They are effective in reducing the incidence of acute rejection, but are an important cause of morbidity and probably mortality[1]. Moreover, they have adverse effects on cardiovascular risk factors such as hypertension, hyperglycemia or hyperlipidemia, deleterious effects on bone metabolism, and may contribute to an increased risk of infection[2]. Clinicians have attempted to reduce the steroid dosages used after kidney transplantation to prevent acute rejection, and complete steroid avoidance or withdrawal have been tested in a number of controlled studies. The first systematic review of prednisone withdrawal and avoidance published in 1993 showed an unacceptable rate of acute rejection after steroid withdrawal (SW)[3]. A second systematic review was published in 2000, and again showed a significant increase in acute rejection and graft failure rates after prednisone elimination[4]. During the last few years, use of the new immunosuppressants tacrolimus and mycophenolate mofetil (MMF) has led to important declines in the incidence of acute rejection and could provide a more potent substrate to attempt safe steroid-free immunosuppression or SW. In 2004 we undertook a systematic review that investigated SW in kidney allograft recipients receiving cyclosporine (CsA) or tacrolimus plus MMF[5]. Acute rejection rates were higher in patients withdrawing from steroids, but short-term graft failure rates were unaffected. Surprisingly, recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have discouraged late SW as a safe strategy for steroid-sparing maintenance treatment, supporting steroid avoidance or very early withdrawal as the safest way to manage steroid treatment after kidney transplantation[6]. We have updated our previous analyses and assessed the safety and efficacy of SW in patients receiving a kidney transplant.

A meta-analysis of randomized controlled trials

In a very recent systematic review[7], we included nine randomized controlled trials including 1,820 patients, assessing SW compared with steroid maintenance in patients with MMF or mycophenolate sodium (MPS) as a third drug[8-17]. None included mammalian target of rapamycin (mTOR) inhibitors. One additional study including 364 patients compared SW at three months with SW after the first days, without a steroid maintenance control group, and was finally excluded for analyses[18]. One randomized controlled trial in pediatric recipients was also excluded[19]. Most of the trials had two arms; one of them had three arms where patients were randomized to (i) continue with tacrolimus, MMF and steroids, or (ii) stop steroids, or (iii) stop MMF; in this meta-analysis only patients in subgroups (i) and (ii) were included[16].

The main study characteristics are depicted in table 1. Cyclosporin A was used in seven randomized controlled trials comparing SW with maintenance[8-14]; tacrolimus was used in the other two[15-16]. All SW randomized controlled trials were performed without initial protocol antibody induction treatment. Consequently, it was not possible to compare SW with or without induction.

Risks of late steroid withdrawal

In our recent review, death and graft loss (both including or excluding death) were similar in SW and control patients (Table 2). Acute rejection was not more frequent after SW, including all trials and analyzing intent-to-treat (ITT) populations. However, stratifying by the drug used, SW in subjects receiving CsA appeared to be associated with a higher incidences of overall acute rejection (RR: 1.42 [1.08; 1.87]) or biopsy proven acute rejection (RR: 1.61 [1.20; 2.17])[7]. Steroid withdrawal in

Table 1. Characteristics of the randomized controlled trials on late steroid withdrawal after kidney transplantation

Trials	n	Multicentre trial	Treatment			Follow-up (months)
			CNI	Other	Timing of steroid withdrawal	
Pascual, et al.[17]	446	Yes	TAC	MMF + prednisone	In 2 weeks after 3 months	36
Del Castillo, et al.[8]	142	Yes	CsA	Myf + prednisone	In 3 months after 3 months	12
Sola, et al.[15]	92	No	TAC	MMF + prednisone	In 3 weeks after 3 months	24
Smak Gregoor, et al.[13]	139	Yes	CsA	MMF + prednisone	In 10 weeks after 6 months	> 6
Vanrenterghem, et al.[14]	500	Yes	CsA	MMF + prednisone	Low-dose prednisone and stopped at 3 months	12
Boletis, et al.[11]	66	No	CsA	MMF + prednisone	In 6 weeks after 6 months	12
Pelletier, et al.[12]	118	No	CsA	MMF + prednisone	Variable period	45
Francos, et al.[9]	51	No	CsA	MMF + prednisone	After 3 months	36
Ahsan, et al.[10]	266	Yes	CsA	MMF + prednisone	In 8 weeks after 3 months	12

CNI: calcineurin inhibitor; TAC: tacrolimus; CsA: cyclosporin A; MMF: mycophenolate mofetil; Myf: myfortic (enteric-coated mycophenolic acid).

tacrolimus trials was not associated with increased overall or biopsy proven acute rejection. However, this difference in overall acute rejection between using CsA and tacrolimus lost significance when interaction analysis was applied (p = 0.438)[20].

The analysis of ITT biopsy proven acute rejection, however, showed significant difference between CsA and tacrolimus, and confirmed that biopsy proven acute rejection after SW was significant only if CsA is used, not with tacrolimus (p for the interaction = 0.005)[7].

This review confirmed that SW in kidney transplantation is not associated with increased mortality or graft loss[7]. Only SW without MMF using CsA has been associated with higher rates of graft loss[21]. The increase in graft loss was previously reported in a meta-analysis including mainly studies without MMF[4], while the safety of steroid withdrawal had been previously reported in a meta-analysis including only studies with MMF[5]. All the SW studies were designed without any antibody induction treatment, so the safety of SW observed in this review was obtained without the need for antibody induction cover.

Overall, acute rejection was more frequent with SW after three to six months than with conventional steroid use. In the previously published meta-analyses, acute rejection rates were assessed from the moment of effective SW (i.e. on-treatment analysis), showing an increased acute rejection rate[3,4], without detecting a difference between both drugs. This kind of on-treatment analysis was not performed in the current study, and an ITT approach was preferred. An increase in acute rejection rates (including both biopsied and non-biopsied cases) with ITT analysis including all patients since the time of kidney transplantation was initially observed only in patients receiving CsA and not in those receiving tacrolimus. However, using the interaction analysis proposed by Altman and Bland[20], this difference in outcome between using CsA and tacrolimus lost significance. This illustrates that even when the two subgroup estimates, using CsA vs. using tacrolimus, and P values, seem very different, the test of interaction may not be significant. It is not sufficient for the relative risk to be significant in one subgroup and not in another[20]. The analysis of ITT biopsy proven acute rejection, however, showed significant differences between CsA and tacrolimus, and confirmed

Table 2. Results obtained from the meta-analysis of randomized controlled trials of late steroid withdrawal after kidney transplantation stratified by calcineurin inhibitor

	No. of trials	No. of participants	Effect size		Tests for heterogeneity	
			Risk Ratio (95% CI)	P value	P value	I^2 (%)
Dichotomous outcomes, by calcineurin inhibitor						
Death						
All	8	1,779	0.96 (0.54; 1.70)	0.89	0.61	0
Cyclosporine	6	1,241	0.91 (0.41; 2.02)	0.81	0.47	0
Tacrolimus	2	538	1.02 (0.45; 2.30)	0.97	1.00	0
Graft loss including death						
All	8	1,779	1.05 (0.79; 1.41)	0.72	0.74	0
Cyclosporine	6	1,241	0.93 (0.58; 1.49)	0.76	0.68	0
Tacrolimus	2	538	1.13 (0.79; 1.63)	0.50	1.00	0
Graft loss excluding death						
All	8	1,779	1.07 (0.76; 1.52)	0.69	0.95	0
Cyclosporine	6	1,241	0.90 (0.50; 1.64)	0.74	0.96	0
Tacrolimus	2	538	1.17 (0.76; 1.80)	0.47	1.00	0
ITT acute rejection (since time of kidney transplant)						
All	4	1,180	1.20 (0.84; 1.71)	0.31	0.10	52
Cyclosporine	2	642	1.42 (1.08; 1.87)	0.013	0.85	0
Tacrolimus	2	538	1.05 (0.51; 2.13)	0.90	0.15	51
Intent to treat biopsy-proven acute rejection						
All	4	1,237	1.27 (0.84; 1.93)	0.26	0.04	64
Cyclosporine	3	791	1.61 (1.20; 2.17)	0.0018	0.83	0
Tacrolimus	1	446	0.82 (0.57; 1.18)	0.29	NA	NA
Patients on lipid-lowering therapy						
All	3	687	0.86 (0.49; 1.50)	0.60	0.15	48
Cyclosporine	1	149	1.49 (0.69; 3.24)	0.31	NA	NA
Tacrolimus	2	538	0.66 (0.46; 0.93)	0.017	0.66	0

that biopsy proven acute rejection after SW was significant only if CsA is used, not with tacrolimus. In any case, severe and recurrent rejections increase the risk of graft loss, but a single early rejection with complete functional recovery after treatment is not harmful for later graft outcome. Most of the rejections described in steroid-sparing protocols occurred early and were in most cases mild and easily controlled with steroids. Although the question remains whether the possible deleterious effects of reversible rejection in a very low percentage of patients outweigh the possible beneficial effects of steroid avoidance, the vast majority of patients do benefit from being without steroids early after transplantation without immediate risk of rejection. Despite a significant increase in acute rejection risk, the very low absolute

number of rejections might be enough of an argument for a positive recommendation.

Benefits of late steroid withdrawal

Our review showed that lipid-lowering therapy was less frequently needed when tacrolimus and MMF were used in the only trial with this combination addressing this outcome (Table 2). However, the interaction analysis showed that this was not significantly different to the need observed using CsA ($p = 0.06$; Table 2). Steroid withdrawal strategies were associated with a lower relative risk (RR) in new onset diabetes after transplantation (NODAT), but the difference did not reach statistical significance. Steroid withdrawal strategies were not associated with significantly lower RR of infections or malignancies.

Serum cholesterol was lower after SW than in controls either using CsA or tacrolimus (Table 2). Serum creatinine, mean blood pressure, and serum triglycerides were similar in SW and in controls. Creatinine clearance, worsening proteinuria, number of antihypertensive drugs, hemoglobin A1c, cardiovascular events, cataracts, Cushing syndrome, bone density, and weight gain were not assessed in more than one randomized controlled trial, so we could not undertake a meta-analysis[7].

The benefits of steroid-sparing strategies were not easily determined in this review because of frequent under-reporting of relevant data in many studies. The kidney function comparison was very limited due to missing data in the majority of published studies. It might be more informative to compare the number of patients at risk of graft loss, with low creatinine clearance, rather than assessing mean data. However, these data were not provided by the studies. It is evident from this review that many adverse events classically related to steroid use were not significantly reduced with a well-defined steroid-sparing strategy, or at least, such benefits were not adequately reported. The effects on blood pressure were scarcely reported. The reduction in total cholesterol and antihyperlipidemic drug need was important in SW patients in comparison with steroid maintenance, and is of particular relevance as this parameter is one of the most important risk factors for cardiovascular morbidity and mortality. Although the reduction in serum cholesterol was observed after SW both in CsA and tacrolimus studies, the reduction in antihyperlipidemic drug need was more relevant with tacrolimus. It seems that for kidney transplant recipients, CsA partially outweighs SW regarding the benefits in lipid profile seen after stopping of steroids. The NODAT rate was lower in late SW than in control patients, but the difference did not reach statistical significance. This outcome was addressed only in three randomized controlled trials, and the trend to a lower incidence in NODAT (RR: 0.58) could have reached significance with a greater sample size. In addition, it is likely that the diabetes inducement of CsA and tacrolimus partially outweighed the benefits of SW strategies in NODAT incidence. Bone disease, cataracts, Cushing syndrome, weight gain, and cardiovascular events were not adequately assessed in SW trials. Finally, no relevant impact could be observed in the infection rate and cancer development, thus suggesting that the increased rates of such events in kidney transplant recipients are not strongly related to steroid use.

Evidence from observational or other randomized controlled trials

Limiting our assessment again to those studies including MMF or another mycophenolate derivative in addition to CsA or tacrolimus, we found 30 reports from 26 observational studies or randomized controlled trials designed to answer a question not directly related to steroid withdrawal efficacy and safety[1,22-50] (Table 3). The beneficial effects of late SW in

Table 3. Observational or randomized controlled studies of low quality for the specific question regarding safety and efficacy of steroid withdrawal late after kidney transplantation with the use of mycophenolate derivatives or mammalian target of rapamycin inhibitors. There are 30 reports from 26 studies done in 24 different institutions and published between 1999 and 2005

Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Smak Gregoor, et al.[22]	Prospective randomized (mycophenolic acid trough levels at 6 and 9 months after KT between the 3 randomized groups, including only the first 52 patients)	After Jan 1997	52/14	CsA-MMF-prednisone A: triple (n = 19) B: CsA stop (n = 19) C: SW (n = 14)	6 months post-KT	N/A	Significant increase in MPA levels found after CsA withdrawal, no change after SW	N/A	N/A
Kupin, et al.[23]	Prospective observational	2-years after SW	128/128 complete SW 95% N/MMF 89% N/AZA 94% San/AZA	Neoral/MMF: 19 Neoral/ AZA: 8 Sandimmune/ AZA: 101	Complete SW at 14 months post-KT	After SW 5%, 14%, 22% ($p < 0.05$)	No	Significant decrease in serum cholesterol (mean 13%) in all groups. NODAT improved in 90%	N/A
Hjelmesaeth, et al.[24]	Prospective	May 1995 to April 1996	91/91	CsA + prednisone (n = 91) and 87% with AZA	Daily prednisone dose reduced by mean of 6 mg/d at 1 year	N/A	1	The proportion of glucose intolerant (NODAT or impaired glucose tolerance) reduced from 55 to 34%	N/A
Mahalati, et al.[25]	Retrospective	3 years	156/156 117 off steroids after 3 year period	CsA + sirolimus	Mean 379 days post KT (1 week to > 2 years)	AR episodes in 6.4%	12 (7.7%)	N/A	N/A
Nowacka-Cieciura, et al.[26-28]	Prospective randomized (23 Polish patients from Ashan 1999)	2 years	23/12 10 at 1 year and 8 at 2 years remained off steroids	CsA + MMF	3 months post KT	5/12 (42%) vs. 2/11 (18%) in controls	No	Significant increase in bone mineral density, decrease in serum iPTH and bone turnover Lower serum cholesterol and higher serum IgG	N/A

Continue

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Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Alarcón-Zurita, et al.[29]	Prospective	Mean 6 months	42/42	Tac + MMF + steroid	3 months post KT	3 (7%)	No	Low rate of viral and bacterial infections other than urinary	N/A
Beaunoyer, et al.[30]	Retrospective	Dec 1999 to May 2001	50/50 Only 33 remained at 6 months, 25 at 1 year	Tac + MMF + steroid Induction with thymoglobulin (7) or anti-IL2 (5)	After 6 months	5, only 1 episode after SW	3 (2 primary non function and 1 venous thrombosis)	N/A	N/A
Budde, et al.[31]	Prospective randomized	Mean 52 months after initiation of SW	23/11	CsA-AZA-steroid randomized to CsA-MMF or continue CsA-AZA-steroid	More than 1 year post KT, steroids tapered down within an 8-week period	0	1 in SW vs. 2 in controls	Blood pressure decreased significantly Cholesterol decreased but without statistical significance	During year 1, more adverse events in SW, especially infectious (25 vs. 17) and gastrointestinal (18 vs. 3); MMF effect
Citterio, et al.[32]	Observational study in some patients previously included in a randomized controlled trial (Vanrenterghem 2005)	1999 1 year	48/48 Steroids reintroduced in 4 patients	Original trial: Tac + MMF + prednisone and randomized into stop steroid, stop MMF or continuing triple In this study, patients in stop MMF (Tac + prednisone) or triple underwent SW	SW in 1-2 months	No	No	Significant decrease in creatinine after SW, associated to a decrease in tacrolimus exposure	In four cases a progressive slow rise of SCr was noted after SW but returned to baseline after reintroduction of prednisone
Lauzurica, et al.[33]	Retrospective	7.6 ± 6.5 months (1-24) from SW	21	Tac + MMF: n = 9 Tac + AZA: n = 7 TAC: n = 5 Aza/MMF stopped at 3 months	Mean 15 ± 10 months	No	N/A	N/A	N/A

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Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Dresske, et al.[34,35]	Prospective, randomized, open-label	May 2003 to Mar 2003 follow-up for 2 years	40 WOFIE group: 20/18 Control group: 20/17 One in WOFIE and 4 controls restarted steroids due to recurrent rejection	Daclizumab + MMF + Tac + steroids In WOFIE group, immunosuppression was stopped for 72 hours post KT	SW in both groups 12-16 weeks after KT	10 vs. 30% (p = 0.1)	2 in WOFIE group and 1 in control group) caused by renal vein thrombosis (1 vs. 1) and CMV infection (1 vs. 0)	All steroid-related side effects improved (not specified)	N/A
Kuypers, et al.[36]	Prospective observational	Sept 1999 to Dec 1999 (Group I) and Jan-May 2000 (Group II)	82/42 SW in 34 (Group 2) and (after day 270) in 11 (Group 1)	Standard-dose Tac-MMF-prednisone: n = 41 Daclizumab + low-dose Tac-MMF-prednisone (SW): n = 41	Steroids stopped at 150 days after KT	17 (41%) in Group I: vs. 7 (17%) in group II (p = 0.03) Only 1 after SW	In group II, graft survival 97.5%; one graft lost (rejection)	Mean creatinine clearance at 12 months was higher (p < 0.05) in group II (59.6 vs. 49 ml/min)	N/A
Gotti, et al.[37]	Prospective randomized The patients were randomly assigned to biopsy (Group 1) or no-biopsy (Group 2)	3 years	59 Group 1: 30/5 Group 2: 29	CsA-AZA-prednisone Group 1 (biopsy), patients underwent SW, CsA stop or reduction, or no change if no lesions, chronic CsA toxicity, or chronic rejection, respectively Group 2 (no biopsy), continued on their three drugs	Between 12-24 months post KT	3 in the 5 SW	No	By serial biopsy analysis, severe lesions did not develop in patients with steroid discontinuation in contrast to patients on standard therapy over follow-up	N/A
Hricik, et al.[38]	Prospective observational	Feb 2000 to Feb 2002,3-26 months (14.3 ± 7.7) after SW	44/30 (27 remain off)	Tac-SRL-prednisone	After 3 months post KT	9% at 3 months post KT and 16% at last follow-up		Significant reductions in blood pressure	N/A

Continue

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Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Teplan, et al.[39]	Prospective	2 years	118/118 (obese with BMI ≥ 0 kg/m^2)	CsA + MMF	At 1 year	N/A	N/A	In addition to SW, a hypoenergetic-hypolipidemic diet and supplements of folic acid, orlistat, and vitamin B6 led to a decrease in BMI and total homocysteine level and increase in serum folate and vitamin B6	N/A
Van der Ham, et al.[40]	Retrospective, longitudinal study	Jan 1982 to Dec 1994	123/57	CsA-prednisone If first KT, no hyperimmunized and no rejection, SW (57)	At 7.3 ± 2.6 months after KT	N/A	N/A	After the first year, weight gain was significantly and positively related only to the cumulative steroid dose	N/A
Van der Ham, et al.[41]	Prospective randomized	N/A	27/10	Tac-MMF Randomized to continue steroids or SW	3 months after KT, within 2 weeks	N/A	N/A	BMD of the lumbar spine decreased significantly in the steroid group while no changes were observed in the SW group The increase in fat mass tended to be lower in SW	N/A

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Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Remuzzi, et al.[42]	Prospective randomized multicenter parallel-group trial The study was organized in two sequential phases: A, from KT to 6 months; and B, month 6 to 21.	N/A	Initially 336 177 (60%) of the 296 patients completing phase A entered phase B of SW	Phase A: 2 groups: CsA-MMF n = 163 CsA-AZA n = 163 Phase B: if < 3 rejections and no steroid-resistant rejection, stable SCr ≤ 177 µmol/l and proteinuria < 1 g/d at phase A (they were 88 MMF, 89 AZA)	During the first 3 months of Phase B steroids were tapered until SW	After SW 25/177 (14%) had one clinical diagnosis of AR In 12 (7%) biopsy proven No differences between MMF and AZA groups (14 vs. 11)	1 (4%) steroid-resistant AR (in the MMF group)	No control group of steroid maintenance, so no benefits were seen in SW	N/A
Kim, et al.[43]	Prospective randomized open label	Sept 2000 to May 2002	Tac 43/39 CsA 44/37	1: Tac + MMF 2: CsA + MMF	At 6 months post KT	After SW: 0% in 1 vs. 13.5% in 2	No	N/A	N/A
Midvedt, et al.[44]	Prospective observational	N/A	57/11	CsA-AZA-prednisone SW in 11, steroid tapering (mean 16 to 9 mg/d) in 34, steroid stable in 12	Group SW: median of 91 months (range, 26-201 months) after KT	N/A	N/A	In steroid tapering the insulin sensitivity index increased 24%, but in the SW group the index did not change	N/A
Miozzari, et al.[45]	Prospective	Oct 2001 to June 2003	63/63	CsA + MMF	At least 6 months after KT	N/A	N/A	N/A	31% altered cortisol profile 60% symptomatic of fatigue and arthralgia
Abramowicz, et al.[46]	Prospective, open-label, single arm	12 months	79/61 ITT 67/61 completers	Daclizumab + MMF + Tac + steroid	At day 150 post KT	BPAR: 8/76 (10.5%) Clinical + BPAR: 10/76 (13.2%)	2/76 (2.6%)	Lower total cholesterol and triglycerides	N/A

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Series	Design	Observation time	Total/steroid stop (n)	Concomitant immunosuppression	Moment of steroid stop	Acute rejection	Graft loss	Benefits of steroid stop	Adverse effects of steroid stop
Citterio, et al.[47]	Prospective multicenter, pilot study	N/A	81/81 Initially 42 (high CsA exposure), then 39 more after an amendment (reduced CsA)	CsA + steroids in long-term KT Phase A (1 month): SRL introduction Phase B (3 months): SW Phase C: steroid-free maintenance	Long-term "stable" KT patients	5/81 (6%) biopsy proven	N/A	N/A	In phases A + B, 18/42 adverse effects due to CsA + SRL combination After amendment (decrease CsA), less adverse events
Laouad, et al.[48]	Retrospective	Oct 1987 to May 2001	484/223	Thymoglobulin-AZA (MMF since 1997)-CsA/Tac (added when SCr < 250 µmol/l)	First year post KT	1- and 2-year incidences 7.2 and 12.1%, respectively	16% (chronic rejection and CI toxicity)	N/A	N/A
Opelz, et al.[1]	Observational multicenter prospective in cases but retrospective in controls	Between 1994 and 2002 Median 5 years	1110/1110 but 41% had needed steroids again at final follow-up	CsA in 94%, not said if AZA or MMF, but we assume that most were on MMF beyond 1997	> 6 months after KT; median 1.1 years	6.4% of those with rejection pre-SW and 4.4% of those without	N/A	Better 7-year patient and graft survival	N/A
Rama, et al.[49]	Retrospective observational	Jan 1993 to Dec 1997 10 years	379/91 Early SW (n = 35) Late SW (n = 56)	CsA + MMF	Early (< 6 months): 4 ± 2 months Late (> 6 months): 24 ± 10	No	9	N/A	Increase in proteinuria in late SW group
Wlodarczyk, et al.[50]	Prospective randomized control trial	Nov 1999 to Aug 2001	489/267 120 Tac-AZA-steroids 147 Tac-MMF-steroids	Tac + MMF + steroids (n = 243) Tac + AZA + steroids (n = 246)	At 3 months, patients assigned to steroid taper if they met criteria	Biopsy proven 44 (18.1%) MMF vs. 64 (26%) AZA 3 months after KT Similar in SW than in steroid maintenance	20 in MMF group and 16 in AZA group	N/A	N/A

N/A: not available; CsA: cyclosporin A; SW: steroid withdrawal; MMF: mycophenolate mofetil; KT: kidney transplantation; MPA: mycophenolic acid; AZA: azathioprine; NODAT: new-onset diabetes mellitus after transplantation; AR: acute rejection; Tac: tacrolimus; SRL: sirolimus; BMI: body mass index.

these studies are summarized in table 3. Overall, mild reductions in serum cholesterol, blood pressure, and glucose disturbances are seen. By contrast, no relevant adverse effects are noted in these observations.

Conclusions

Regarding the safety of steroid-sparing strategies in kidney transplantation, we did not find enough evidence demonstrating an increased high risk of early graft failure after SW in patients receiving CsA or tacrolimus and MMF, despite that an increased acute rejection rate could be observed in CsA-treated patients. Our results may support that this potent immunosuppression allows safe steroid elimination after three to six months in the absence of antibody induction treatment. The strength of the evidence was less when reviewing the potential benefits of late SW. A reduction in NODAT incidence could not be clearly observed, but decreased serum cholesterol levels were particularly significant. Steroid withdrawal after three to six months is a strategy that could well be advised for low to medium risk kidney transplant recipients. More long-term randomized controlled trials are clearly needed to clarify the benefits of late SW in low-exposure minimized tacrolimus in association with MMF/MPS. The main strength of our recent review is that it has identified all randomized controlled trials assessing SW beyond the first weeks after kidney transplantation. It also analyses different profiles in patients receiving CsA versus tacrolimus, and excludes more outdated trials including azathioprine. Our methodology was robust, including all possible studies published, even in abstract form, in any language, and with assessment of data quality. Consequently, this review provided information to guide treatment decisions on SW in adult kidney transplantation, particularly the absence of harmful consequences, rather than the existence of clear benefits.

Future directions

The available studies including the immunosuppressive protocol most widely used at present, tacrolimus plus MMF or MPS, was only represented by two trials, one of them a small single-center study. Consequently, late SW under tacrolimus-MMF/MPS treatment has not been adequately studied, and many important outcomes have not been properly assessed. No studies including mTOR inhibitors are available, and consequently, we cannot extrapolate the safety of SW to protocols including mTOR inhibitors instead of MMF as a third drug. Another limitation is that despite some studies having extended their follow-up periods to three years, the extension periods beyond the first year were frequently retrospective in nature and not prospectively designed.

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