**Name of Journal: *World Journal of Transplantation***

**ESPS Manuscript NO:****28777**

**Manuscript Type:** **Evidence-Based Medicine**

**Corticosteroid minimization in renal transplantation: Careful patient selection enables feasibility**

Vlachopanos G *et al*. Corticosteroid minimization in renal transplantation

**Georgios Vlachopanos, Julie M Bridson, Ajay Sharma, Ahmed Halawa**

**Georgios Vlachopanos,** Department of Nephrology, Rethymnon General Hospital, 74100 Rethymnon, Greece

**Georgios Vlachopanos, Julie M Bridson, Ajay Sharma, Ahmed Halawa,**Faculty of Health and Life Sciences, Institute of Learning and Teaching, University of Liverpool, Liverpool L69 3BX, United Kingdom

**Ajay Sharma,** Department of Transplantation, Royal Liverpool University Hospital, Liverpool L7 8XP, United Kingdom

**Ahmed Halawa,** Department of Transplantation, Sheffield Teaching Hospitals, Sheffield S5 7AU, United Kingdom

**Author contributions:** All authors contributed to the conception and design of the review as well as giving final approval of the final version; Vlachopanos G performed the literature review as well as drafting of initial version and subsequent revisions up to final version; Bridson JM, Sharma A and Halawa A provided critical revision and editing of initial and all subsequent versions.

**Conflict-of-interest** **statement:** None declared.

**Data sharing statement:** The manuscript summarizes data as have been reported in published literature to date. There were no new patients studied, and no new data compiled. No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

# Manuscript source: Invited manuscript

**Correspondence to:** **Ahmed Halawa, Consultant Transplant Surgeon,** Department of Transplantation, Sheffield Teaching Hospitals, Herries Road, Sheffield S5 7AU, United Kingdom. ahmed.halawa@sth.nhs.uk

**Telephone:** +44-77-87542128

**Fax:** +44-11-42714604

**Received:**July 14, 2016

**Peer-review started:** July 25, 2016

**First decision:** September 2, 2016

**Revised:**October 23, 2016

**Accepted:**November 16, 2016

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To explore the benefits and harms of corticosteroid (CS) minimization following renal transplantation.

***METHODS***

CS minimization attempts to improve cardiovascular risk factors (hypertension, diabetes, dyslipidemia), to enhance growth in children, to ameliorate bone disease and to lead to better compliance with immunosuppressive agents. Nevertheless, any benefit must be carefully weighed against the reduction in net immunosuppression and the potential harm to renal allograft function and survival.

***RESULTS***

Complete CS avoidance or very early withdrawal (*i.e.*, no CS after post-transplant day 7) seems to be associated with better outcomes in comparison with later withdrawal. However, an increased incidence of CS-sensitive acute rejection has been observed with all CS minimization strategies. Among the prerequisites for the safe application of CS minimization protocols are the administration of induction immunosuppression and the inclusion of calcineurin inhibitors in maintenance immunosuppression regimens.

***CONCLUSION***

Transplant recipients at low immunological risk (primary transplant, low panel reactive antibodies) are thought as optimal candidates for CS minimization. CS avoidance may also be undesirable in patients at risk for glomerulonephritis recurrence or with severe delayed graft function and prolonged cold ischemia time. Thus, CS minimization is not yet ready for implementation in the majority of transplant recipients.

**Key words:** Renal transplantation; Corticosteroid minimization; Corticosteroid withdrawal; Corticosteroid avoidance; Acute rejection; Immunosuppression

© **The Author(s) 2016**. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Although corticosteroids have been traditional components of immunosuppressive regimens in renal transplantation, corticosteroid minimization strategies are developed in an attempt to mitigate their many side-effects. The benefit from this approach must be balanced against the risk of acute rejection due to insufficient immunosuppression and the potential harm to allograft survival. We present an overview of these strategies and their impact on clinical outcomes analyzing the key clinical trials performed. Furthermore, we focus on patient selection according to the immunological risk and the induction immunosuppression, the principal factors that determine the success of corticosteroid withdrawal and avoidance protocols.

Vlachopanos G,Bridson JM, Sharma A, Halawa A. Corticosteroid minimization in renal transplantation: Careful patient selection enables feasibility. *World J Transplant* 2016; In press

**INTRODUCTION**

Corticosteroids (CS) have been ubiquitously included in immunosuppressive regimens since the early days of renal transplantation (Tx). They have significantly contributed to the successful transformation of a highly experimental intervention into a universally adopted clinical treatment. However, their use is associated with a plethora of adverse events due to their non-specific mode of action. The negative impact of CS on cardiovascular disease risk factors such as hypertension, diabetes mellitus, and dyslipidemia is well known. Non-cardiovascular adverse events such as growth retardation, impaired wound healing, subcapsular cataract, bone problems (osteoporosis, fractures, avascular necrosis) and cosmetic effects leading to patient non-compliance are equally established[1-4]. An increasing interest in minimizing the exposure to CS in transplant recipients with stable allograft function has been manifested by renal transplant clinicians to reduce the morbidity burden associated with their use. In the United States, CS avoidance regimens were administered to 23% of all first renal transplant recipients in 2004[5]. Among the remaining 77% who were discharged on CS, roughly 10% had CS withdrawn during the first post-transplant year. Nonetheless, this policy has to be carefully balanced against the risk of acute rejection due to insufficient immunosuppression and should not jeopardize renal allograft function and survival.

**MATERIALS AND METHODS**

***Definitions***

Strategies for CS minimization can be categorized as: (1) CS avoidance; (2) CS withdrawal following a period after Tx. The latter can be further divided as early withdrawal (weeks or months after Tx, usually 3-6 mo after Tx) or late withdrawal (at least 6 mo after Tx). Overlapping between these categories has been reported in the literature leading to a degree of uncertainty over the exact terminology. For instance, very early withdrawal (< 2 wk) has been classified under both CS avoidance and CS withdrawal strategies. For the purpose of this manuscript, we will include very early withdrawal under the CS avoidance strategy. The overall efficacy of CS minimization regimens depends on the extent to which the rest of the immunosuppressive agents can suppress the alloimmune response and on the immunological risk stratification. In general, induction immunosuppression is required for the safe application of CS minimization as well as the inclusion of calcineurin inhibitors in maintenance immunosuppression. Patients at low immunological risk (first transplant, non-sensitized) are considered as ideal candidates for the implementation of CS minimization[6].

Data from studies on CS minimization have produced conflicting results regarding benefit *vs* harm. Clinical heterogeneity across these studies is moderate to high, especially regarding the spectrum of induction and maintenance immunosuppression agents used. Some studies have reported reductions in cardiovascular risk factors such as dyslipidemia[7], but there is no clearly proven reduction of the burden of cardiovascular disease. On the other hand, although CS avoidance or withdrawal studies resulted in increased rates of acute rejection, the impact on allograft survival appears to be neutral. Given the current dilemma over the efficacy *vs* safety profile of CS minimization strategies, our institution has continued on the traditional strategy of rapid CS tapering after Tx to the lowest possible dose. We reserve CS avoidance or withdrawal for highly selected cases at low immunological risk who present compelling contraindications to CS such as severe osteoporosis. We will try to elaborate on the potential advantages and disadvantages of our protocol focusing on the comparison with the CS minimization practices mentioned above. Our goal is to identify the optimal management strategy, which will allow for the maximum benefit of different patient subsets without compromising safety and will likely improve Tx outcomes.

**RESULTS**

***Low CS dose as maintenance therapy***

We advocate the immunosuppressive protocol, which involves the administration of three daily intravenous pulses of 500 mg, 250 mg, and 250 mg methylprednisolone intraoperatively and on postoperative days 1 and 2 respectively. We attempt to rapidly taper CS dose to 20 mg oral methylprednisolone per day by 2-4 wk following Tx. Thereafter, we further reduce CS dose with the aim of 4 mg methylprednisolone per day at 3 mo in the absence of acute rejection. This dose is continued indefinitely. Data from randomized clinical trials (RCT) argue that maintenance CS treatment has still a dominant place in the management of renal transplant recipients. In the RCT with the longest follow-up to date (Astellas Corticosteroid Withdrawal Study), Woodle *et al*[8] assigned 386 renal transplant recipients with PRA (panel reactive antibodies) ≤ 25% to either very early CS withdrawal at one week post-transplant or CS continuation tapered to 5 mg prednisolone per day at 6 mo (Table 1). All patients received induction immunosuppression; 68% of them with the lymphocyte-depleting agent anti-thymocyte globulin (ATG) and 32% with anti-interleukin-2 receptor monoclonal antibodies. Maintenance immunosuppressive regimen consisted of tacrolimus and mycophenolate mofetil (MMF). After a follow-up of 5 years, no difference was found in the rate of patient death, death-censored allograft loss and moderate/severe acute rejection. Total biopsy-confirmed acute rejection was lower in the CS continuation arm (10.8% *vs* 17.8%, *P* = 0.04). This result was driven by the increased rates of mild, CS-sensitive acute rejection in the very early CS withdrawal arm. It is interesting that biopsy-proven acute rejection rates were numerically lower with ATG induction than with anti-interleukin-2 receptor monoclonal antibodies in very early CS withdrawal patients, but that did not reach statistical significance (14.4% *vs* 24.2%, *P* = 0.09). Serum creatinine and creatinine clearance estimated by the Cockroft-Gault equation were similar between the two arms at 5 years. However, chronic allograft nephropathy (CAN) incidence at 5 years was more than double (9.9% *vs* 4.1%, *P* = 0.028) with very early CS withdrawal compared to a continuation. This finding raises an important concern. Although very early CS withdrawal seems to be non-inferior to CS continuation at 5 years concerning patient and allograft survival, it is unknown if the increased incidence of CAN would negatively influence those outcomes beyond that time-point. Clinical trials with extended follow-up time to 10 years are needed to resolve this issue. The effect of very early CS withdrawal on cardiovascular risk factors was mixed. No significant difference was found in hypertension, new-onset diabetes mellitus, total cholesterol and low-density lipoprotein (LDL) levels; very early CS withdrawal led only to improvement in serum triglycerides. As far as it concerns non-cardiovascular adverse events, very early CS withdrawal reduced bone fractures and avascular necrosis but it was paradoxically associated with more frequent subcapsular cataract.

A meta-analysis of 34 studies, which included 5637 patients, produced broadly similar results[9]. It was found that acute rejection risk was significantly increased with CS avoidance or withdrawal regimens compared to maintenance CS (relative risk: 1.56, 95%CI 1.31-1.87, *P* = 0.0001). No statistically significant differences were found for patient or allograft survival, but allograft function was modestly better with maintenance CS (weighted mean difference in creatinine clearance: 3.05 mL/min, 95%CI, 1.45-4.66). In contrast to the abovementioned RCT, occurrence of hypertension, new onset diabetes mellitus and hypercholesterolemia was reduced with CS avoidance or withdrawal regimens. However, the effect on hard cardiovascular endpoints cannot be estimated because included studies underreported cardiovascular events. In conclusion, acute rejection rates are constantly lower when CS maintenance regimens are used. Patient and allograft survival seems not to be influenced by CS minimization, but it is unknown if this remains the same with longer follow-up. Although CS minimization may permit some improvement in cardiovascular risk factors, data are not consistent about it.

***CS avoidance***

The rationale behind CS avoidance or very early withdrawal is that acute rejection may be triggered more easily with CS withdrawal within weeks or months after Tx. However, it invariably requires the use of potent induction immunosuppression and the selection of low immunological risk recipients. Attempts to use CS avoidance regimens in the absence of induction immunosuppression resulted in unacceptably high acute rejection rates[10]. In a three-arm multicenter RCT, which included 336 renal transplant recipients with PRA ≤ 20%, Vincenti *et al*[11] used basiliximab as an induction agent and compared no CS at all *vs* CS withdrawal by day 7 *vs* standard CS. Maintenance immunosuppression consisted of cyclosporine and enteric-coated mycophenolate sodium. Biopsy-proven acute rejection rates were significantly higher with complete CS avoidance and very early CS withdrawal regimens (31.5% *vs* 26.1% *vs* 14.7%) at a follow-up of 12 mo. No difference was found for patient and allograft survival as well as for median 12-mo estimated glomerular filtration rate. A prospective RCT, which included 300 patients, compared very early CS withdrawal at day 2 with standard CS[12]. It also used basiliximab for induction, but maintenance was a calcineurin inhibitor and mycophenolate mofetil or sirolimus. It found absolutely no difference in patient and allograft survival, acute rejection, incidence of CAN and allograft function between the two arms at 3 years. A lower frequency of new-onset diabetes mellitus was noted in the very early CS withdrawal group.

Induction with a lymphocyte-depleting agent (rabbit anti-lymphocyte globulin, rALG) was explored in the clinical context of CS avoidance for the first time by Laftavi *et al*[13]. They randomized 60 renal transplant recipients to either very early CS withdrawal at day 7 or CS continuation. Maintenance immunosuppression involved tacrolimus and MMF. No difference in acute rejection and allograft function was demonstrated with very early CS withdrawal at a follow-up time of 12 mo. However, increased interstitial fibrosis was found in protocol biopsies at 12 mo in the group of very early CS withdrawal. In a case series of 1241 renal transplant recipients with an impressive follow-up time of 10 years, the results of CS withdrawal at day 5 were reported[14]. All patients received induction immunosuppression with Thymoglobulin while maintenance immunosuppression comprised of a calcineurin inhibitor (tacrolimus or cyclosporine) and a secondary agent (MMF or sirolimus). Despite acute rejection rates of 25% for cadaveric donor Tx and 31% for living donor Tx at 10 years, patient and allograft survival was comparable to that reported in national registry databases. A beneficial effect of very early CS withdrawal was shown for new-onset diabetes mellitus, subcapsular cataract, and avascular necrosis. Till now, induction with lymphocyte-depleting agents seems to be the optimal option for consolidating the benefits of CS avoidance strategies without putting renal allografts at risk of acute rejection. It is not surprising that approximately 90% of United States renal transplant recipients with a steroid-free regimen on discharge have received induction with a lymphocyte-depleting agent[15]. Anti-interleukin-2 receptor monoclonal antibodies have been used in the remaining 10% of the patients.

The monoclonal lymphocyte-depleting antibody alemtuzumab has lately emerged as a promising CS-sparing agent. In a comparative, multicenter RCT, 852 unselected (both low and high immunological risk) renal transplant recipients were administered either induction with alemtuzumab (followed by reduced-dose tacrolimus and MMF without CS) or with basiliximab (followed by standard-dose tacrolimus, MMF, and CS)[16]. According to the preliminary results, alemtuzumab halved biopsy-proven acute rejection at 6 mo. Patient and allograft survival were not different between the two groups. Long-term follow-up results of this study are eagerly awaited. In a direct comparison of alemtuzumab with basiliximab (both arms were subjected to CS withdrawal by day 5) in a cohort of 335 low-risk patients, the rate of biopsy-confirmed acute rejection was lower with alemtuzumab (10% *vs* 22%, *P* = 0.003) at 3 years[17]. The major studies on CS avoidance are summarized in Table 2. Lastly, an important question is whether patients on CS avoidance regimens should be put in CS maintenance after treatment of an acute rejection episode. A retrospective study found that allograft survival is not affected by the introduction of CS maintenance or not but the lack of CS maintenance is a risk factor for a subsequent second acute rejection[18].

***CS withdrawal***

**Early CS withdrawal:** Initial attempts to apply early CS withdrawal under cyclosporine-based maintenance immunosuppressive regimens did not meet success[19,20]. The advent of more potent maintenance immunosuppressants like tacrolimus and MMF renewed researchers’ interest in assessing the feasibility of early CS withdrawal (Table 3). Vanrenterghem *et al*[21] studied CS withdrawal 3 mo after Tx in 556 low immunological risk patients enrolled in a multicenter RCT. Maintenance immunosuppression consisted of tacrolimus and MMF. In the follow-up time of only 6 mo, it was shown that acute rejection rates were higher in the CS withdrawal arm during months 3-6. Mean total cholesterol and LDL were reduced in the CS withdrawal arm at the same period. Pascual *et al*[22] summarized RCTs in CS withdrawal between 3 and 6 mo in a systematic review including 9 studies with 1820 patients. They concluded that patient and allograft survival is not affected by early Cs withdrawal up to 3 years after Tx. Total acute rejection rates were higher with early CS withdrawal in cyclosporine-treated patients. Although reduction of total cholesterol levels was observed with early CS withdrawal, no significant difference was found for any of the other cardiovascular or non-cardiovascular adverse events. It is worth mentioning that induction immunosuppression was not used in any of the included studies. Overall, evidence about the benefit-risk ratio of early CS withdrawal is weaker than that of CS avoidance and follow-up times are shorter. It is unknown if induction with lymphocyte depleting agents or anti-interleukin-2 receptor monoclonal antibodies were used in any of the studies, it would have any meaningful impact on the results.

**Late CS withdrawal:** It appears that late CS withdrawal (more than 6 mo and possibly years after Tx) represents the least favorable method of the CS minimization strategies. It is apparent that certain CS-related complications would already have been established by that time. For instance, it is well known that a rapid deterioration in osteoporosis occurs within the first post-transplant year[23]. Moreover, acute rejection risk is clearly increased upon late withdrawal of immunosuppressants as dictated by cases of non-compliant patients[3]. In a single-center RCT, Smak Gregoor *et al*[24] examined the effect of CS withdrawal at 6 mo after Tx in 212 renal transplant recipients. Biopsy-proven acute rejection was manifested in 4% of CS withdrawal patients *vs* 1.4% of controls (*P* > 0.05). Patient and allograft survival was not different after a follow-up of 2 years. Allograft function was also not different. CS withdrawal resulted in reduced mean blood pressure but had no effect on other metabolic risk factors. Interestingly enough, a prospective, observational study from the Collaborative Transplant Study group reported that in renal transplant recipients with CS withdrawal more than 6 mo from Tx, patient and allograft survival was better than retrospectively matched controls over a follow-up time of 7 years with no difference in acute rejection rates[25]. The reduction was also noted in the incidence of cardiovascular parameters. However, the lack of randomized design remains a significant limitation of this study.

**DISCUSSION**

***Challenges and opportunities of CS minimization strategies***

The beneficial effects of CS minimization in selected, low-risk patients have prompted researchers to attempt CS minimization in renal transplant recipients at higher immunological risk. However, available data are sparse (Table 4). In a small RCT, 21 patients with PRA > 20% or retransplantation were assigned to either alemtuzumab and tacrolimus monotherapy without CS or Thymoglobulin with standard tacrolimus, MMF and very early CS withdrawal at day 5[26]. Biopsy-proven acute rejection rates were quite high at one year; 18.2% with alemtuzumab *vs* 37.5% with Thymoglobulin. In a more recent, head to head comparison of alemtuzumab with ATG (both arms underwent CS withdrawal by day 5) in a cohort of 139 high-risk patients, there was no difference in biopsy-proven acute rejection at 3 years (18% *vs* 15%, *P* = 0.63)[17]. The inference is that CS minimization is not yet ready for prime time in immunologically high-risk patients. It has been hypothesized that CS minimization may increase post-transplant glomerulonephritis recurrence. In a major retrospective study, it was found that recurrence rate was indeed higher with rapid CS discontinuation compared to CS maintenance for all glomerulonephritis types (hazard ratio 4.86, 95%CI, 2.34-10.07, *P* < 0.0001)[27]. The analysis also showed no difference in patient, allograft, and death-censored allograft survival. Pediatric patients are a subgroup in which CS minimization may be of special interest due to growth retardation that is associated with chronic CS use (Table 4). In a multicenter RCT, Grenda *et al*[28] assessed the effect of CS withdrawal at day 4 (together with daclizumab induction and tacrolimus, MMF) *vs* standard tacrolimus, MMF, and CS in a cohort of 196 children. Growth was significantly enhanced at 6 mo by CS withdrawal. Patient survival, allograft survival and allograft function were not different. The effect of CS withdrawal on total cholesterol and triglycerides was positive. Similar results were obtained by Höcker *et al*[29] who evaluated CS withdrawal ≥ 1 year after Tx in 42 moderate- to high-risk children (maintenance immunosuppression was cyclosporine and MMF).

In contrast to the perceived benefits of CS minimization in younger transplant recipients, this strategy may not be suitable for elderly patients. Although acute rejection rates may be lower in the elderly, it has been suggested that acute rejection may be more severe and lead to a compromised death-censored allograft survival[30]. Furthermore, the potentially beneficial effect of CS minimization in cardiovascular disease risk factors in the elderly may not be relevant due to their limited lifespan. For these reasons, it seems that CS minimization in the elderly may result in poor outcomes and should not be exercised except with extreme caution. Finally, CS minimization may not also be suitable for transplant recipients with delayed graft function (DGF) and prolonged cold ischemia time. The ischemic injury in these allografts is strongly associated with the development of acute rejection[31]. Therefore, it is prudent to avoid CS minimization in this patient subgroup if possible.

Based on current evidence, we believe that the majority of renal transplant recipients should continue to receive indefinite CS maintenance immunosuppression. However, selected patients can be good candidates for CS minimization protocols. The optimal patient phenotype to undergo CS minimization is that of a young transplant recipient (including children) who has no prior transplants and is unsensitized to HLA alloantigens. A primary disease that caused end-stage renal disease should not be glomerulonephritis. Any severe perioperative ischemic insult to the allograft should discourage the application of CS minimization. As such, CS minimization may be contraindicated with DGF, prolonged cold ischemia time, and donation after cardiac death. Available data indicate that the preferred CS minimization strategy is probably either complete CS avoidance or very early CS withdrawal. ATG (or alemtuzumab) may be preferable to anti-interleukin-2 receptor monoclonal antibodies as induction agents in this clinical scenario whereas maintenance immunosuppression should better contain the calcineurin inhibitor tacrolimus instead of cyclosporine.

In conclusion, CS maintain their position as important components of the therapeutic armamentarium in renal transplantation. A movement towards CS elimination from induction and maintenance immunosuppression regimens has developed to reduce the myriad side effects associated with chronic CS use. CS minimization strategies have resulted in an increased incidence of acute rejection compared to CS continuation. However, these acute rejection episodes are considered mild and amenable to treatment. Moreover, they do not seem to have detrimental effects on patient survival, allograft survival or allograft function at a follow-up until 5 years. Nonetheless, an observed trend towards increased fibrosis is alarming and calls for the conduction of RCTs with longer follow-up to determine the true consequences of CS minimization. Although CS minimization protocols have been associated with a reduction of adverse effects (especially improvement of dyslipidemia), these results are not always reproducible, and it is unclear if they could clinically translate to less cardiovascular events. At present, the implementation of CS minimization cannot be universally recommended to renal transplant recipients.

**COMMENTS**

***Background***

Due to their immunosuppressive properties, corticosteroids (CSs) have been extensively used for the prevention and treatment of rejection in solid organ transplantation. However, myriad side-effects have been associated with CS. Recent research attempts to minimize CS use in renal transplantation in an effort to reduce the burden of their side-effects without compromising allograft and patient survival.

***Research frontiers***

The choice of the induction immunosuppression agent - and of maintenance immunosuppression to a lesser degree - is an extremely important aspect of CS minimization strategies and the focus of many studies. Studies with follow-up times of more than 5 years and with data on interstitial tissue fibrosis are needed.

***Innovations and breakthroughs***

Alemtuzumab appears to be a very promising induction agent potentially allowing the combination of CS avoidance with lower doses of tacrolimus and mycophenolate mofetil. Long term results of the 3C study may provide valuable insights on this topic.

***Applications***

In the United States, CS avoidance regimens were administered to 23% of all first renal transplant recipients in 2004[5]. Although they cannot yet be recommended to the majority of renal transplant recipients, selected patient groups such as primarily those with low immunological risk and low risk for glomerulonephritis recurrence may benefit more from CS minimization.

***Terminology***

CS avoidance: Either no CS use at all or CS use only until day 7 after transplantation (Tx). CS withdrawal: CS tapering following a period after Tx. It is divided as early withdrawal (weeks or months after Tx, usually 3-6 mo after Tx) or late withdrawal (at least 6 mo after Tx).

***Peer-review***

This review paper is a well written paper of the impact of corticosteroid minimisation on kidney transplant and has valuable information.

**REFERENCES**

1 **Veenstra DL**, Best JH, Hornberger J, Sullivan SD, Hricik DE. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis* 1999; **33**: 829-839 [PMID: 10213637 DOI: 10.1016/S0272-6386(99)70414-2]

2 **Citterio F**. Steroid side effects and their impact on transplantation outcome. *Transplantation* 2001; **72**: S75-S80 [PMID: 11833145]

3 **Schweizer RT**, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipients. *Transplantation* 1990; **49**: 374-377 [PMID: 2305467 DOI: 10.1097/00007890-199002000-00029]

4 **Prasad GV**, Nash MM, McFarlane PA, Zaltzman JS. Renal transplant recipient attitudes toward steroid use and steroid withdrawal. *Clin Transplant* 2003; **17**: 135-139 [PMID: 12709080 DOI: 10.1034/j.1399-0012.2003.00034.x]

5 **Meier-Kriesche HU**, Li S, Gruessner RW, Fung JJ, Bustami RT, Barr ML, Leichtman AB. Immunosuppression: evolution in practice and trends, 1994-2004. *Am J Transplant* 2006; **6**: 1111-1131 [PMID: 16613591 DOI: 10.1111/j.1600-6143.2006.01270.x]

6 **[Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kidney%20Disease%3A%20Improving%20Global%20Outcomes%20(KDIGO)%20Transplant%20Work%20Group%5BCorporate%20Author%5D)**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

7 **Woodle ES**, Peddi VR, Tomlanovich S, Mulgaonkar S, Kuo PC; TRIMS Study Investigators. A prospective, randomized, multicenter study evaluating early corticosteroid withdrawal with Thymoglobulin in living-donor kidney transplantation. *Clin Transplant* 2010; **24**: 73-83 [PMID: 19930408 DOI: 10.1111/j.1399-0012.2009.01127.x]

8 **Woodle ES**, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P; Astellas Corticosteroid Withdrawal Study Group. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg* 2008; **248**: 564-577 [PMID: 18936569 DOI: 10.1097/SLA.0b013e318187d1da]

9 **Knight SR**, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation* 2010; **89**: 1-14 [PMID: 20061913 DOI: 10.1097/TP.0b013e3181c518cc]

10 **Vítko S**, Klinger M, Salmela K, Wlodarczyk Z, Tydèn G, Senatorski G, Ostrowski M, Fauchald P, Kokot F, Stefoni S, Perner F, Claesson K, Castagneto M, Heemann U, Carmellini M, Squifflet JP, Weber M, Segoloni G, Bäckman L, Sperschneider H, Krämer BK. Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil-in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. *Transplantation* 2005; **80**: 1734-1741 [PMID: 16378069 DOI: 10.1097/01.tp.0000188300.26762.74]

11 **Vincenti F**, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J; FREEDOM Study Group. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transplant* 2008; **8**: 307-316 [PMID: 18211506 DOI: 10.1111/j.1600-6143.2007.02057.x]

12 **Kumar MS**, Heifets M, Moritz MJ, Saeed MI, Khan SM, Fyfe B, Sustento-Riodeca N, Daniel JN, Kumar A. Safety and efficacy of steroid withdrawal two days after kidney transplantation: analysis of results at three years. *Transplantation* 2006; **81**: 832-839 [PMID: 16570004 DOI: 10.1097/01.tp.0000203558.34739.c6]

13 **Laftavi MR**, Stephan R, Stefanick B, Kohli R, Dagher F, Applegate M, O'Keefe J, Pierce D, Rubino A, Guzowski H, Leca N, Dayton M, Pankewycz O. Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. *Surgery* 2005; **137**: 364-371 [PMID: 15746793 DOI: 10.1016/j.surg.2004.10.013]

14 **Rizzari MD**, Suszynski TM, Gillingham KJ, Dunn TB, Ibrahim HN, Payne WD, Chinnakotla S, Finger EB, Sutherland DE, Kandaswamy R, Najarian JS, Pruett TL, Kukla A, Spong R, Matas AJ. Ten-year outcome after rapid discontinuation of prednisone in adult primary kidney transplantation. *Clin J Am Soc Nephrol* 2012; **7**: 494-503 [PMID: 22282482 DOI: 10.2215/CJN.08630811]

15 **Sureshkumar KK**, Thai NL, Hussain SM, Ko TY, Marcus RJ. Influence of induction modality on the outcome of deceased donor kidney transplant recipients discharged on steroid-free maintenance immunosuppression. *Transplantation* 2012; **93**: 799-805 [PMID: 22290269 DOI: 10.1097/TP.0b013e3182472898]

16 **3C Study Collaborative Group**, Haynes R, Harden P, Judge P, Blackwell L, Emberson J, Landray MJ, Baigent C, Friend PJ. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. *Lancet* 2014; **384**: 1684-1690 [PMID: 25078310 DOI: 10.1016/S0140-6736(14)61095-3]

17 **Hanaway MJ**, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, Holman J; INTAC Study Group. Alemtuzumab induction in renal transplantation. *N Engl J Med* 2011; **364**: 1909-1919 [PMID: 21591943 DOI: 10.1056/NEJMoa1009546]

18 **Humar A**, Gillingham K, Kandaswamy R, Payne W, Matas A. Steroid avoidance regimens: a comparison of outcomes with maintenance steroids versus continued steroid avoidance in recipients having an acute rejection episode. *Am J Transplant* 2007; **7**: 1948-1953 [PMID: 17617858 DOI: 10.1111/j.1600-6143.2007.01883.x]

19 **Hricik DE**, O'Toole MA, Schulak JA, Herson J. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. *J Am Soc Nephrol* 1993; **4**: 1300-1305 [PMID: 8130356]

20 **Vanrenterghem Y**, Lebranchu Y, Hené R, Oppenheimer F, Ekberg H. Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. *Transplantation* 2000; **70**: 1352-1359 [PMID: 11087152]

21 **Vanrenterghem Y**, van Hooff JP, Squifflet JP, Salmela K, Rigotti P, Jindal RM, Pascual J, Ekberg H, Sicilia LS, Boletis JN, Grinyo JM, Rodriguez MA. Minimization of immunosuppressive therapy after renal transplantation: results of a randomized controlled trial. *Am J Transplant* 2005; **5**: 87-95 [PMID: 15636615 DOI: 10.1111/j.1600-6143.2004.00638.x]

22 **Pascual J**, Galeano C, Royuela A, Zamora J. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation* 2010; **90**: 343-349 [PMID: 20574419 DOI: 10.1097/TP.0b013e3181e58912]

23 **Kulak CA**, Cochenski Borba VZ, Kulak J, Ribeiro Custódio M. Osteoporosis after solid organ transplantation. *Minerva Endocrinol* 2012; **37**: 221-231 [PMID: 22766889]

24 **Smak Gregoor PJ**, de Sévaux RG, Ligtenberg G, Hoitsma AJ, Hené RJ, Weimar W, Hilbrands LB, van Gelder T. Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. *J Am Soc Nephrol* 2002; **13**: 1365-1373 [PMID: 11961025 DOI: 10.1097/01.ASN.0000013298.11876.BF]

25 **Opelz G**, Döhler B, Laux G; [Collaborative Transplant Study](https://www.ncbi.nlm.nih.gov/pubmed/?term=Collaborative%20Transplant%20Study%5BCorporate%20Author%5D). Long-term prospective study of steroid withdrawal in kidney and heart transplant recipients. *Am J Transplant* 2005; **5**: 720-728 [PMID: 15760395 DOI: 10.1111/j.1600-6143.2004.00765.x]

26 **Thomas PG**, Woodside KJ, Lappin JA, Vaidya S, Rajaraman S, Gugliuzza KK. Alemtuzumab (Campath 1H) induction with tacrolimus monotherapy is safe for high immunological risk renal transplantation. *Transplantation* 2007; **83**: 1509-1512 [PMID: 17565326 DOI: 10.1097/01.tp.0000263344.53000.a1]

27 **Kukla A**, Chen E, Spong R, Weber M, El-Shahawi Y, Gillingham K, Matas AJ, Ibrahim HN. Recurrent glomerulonephritis under rapid discontinuation of steroids. *Transplantation* 2011; **91**: 1386-1391 [PMID: 21508898 DOI: 10.1097/TP.0b013e31821bf157]

28 **Grenda R**, Watson A, Trompeter R, Tönshoff B, Jaray J, Fitzpatrick M, Murer L, Vondrak K, Maxwell H, van Damme-Lombaerts R, Loirat C, Mor E, Cochat P, Milford DV, Brown M, Webb NJ. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transplant* 2010; **10**: 828-836 [PMID: 20420639 DOI: 10.1111/j.1600-6143.2010.03047.x]

29 **Höcker B**, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, Pohl M, Zimmering M, Fründ S, Klaus G, Wühl E, Tönshoff B. Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation. *Nephrol Dial Transplant* 2010; **25**: 617-624 [PMID: 19793929 DOI: 10.1093/ndt/gfp506]

30 **Meier-Kriesche HU**, Srinivas TR, Kaplan B. Interaction between acute rejection and recipient age on long-term renal allograft survival. *Transplant Proc* 2001; **33**: 3425-3426 [PMID: 11750467 DOI: 10.1016/S0041-1345(01)02477-0]

31 **Yarlagadda SG**, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2009; **24**: 1039-1047 [PMID: 19103734 DOI: 10.1093/ndt/gfn667]

**P- Reviewer:** Bhimma R, Watanabe T **S- Editor:** Gong XM

**L- Editor:** **E- Editor:**

**Table 1 Characteristics of the multi-center, randomized Astellas Corticosteroid Withdrawal Study with a follow-up time of 5 years[8]**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CS withdrawal at day 7 arm**  **(*n* = 191)** | **Standard CS arm**  **(*n* = 195)** | ***P*-value** |
| Baseline demographic, immunological risk and immunosuppressive therapy data | | | |
| Age (mean ± SD, yr) | 46.6 ± 12.2 | 46.2 ± 12.7 | NS |
| Female gender (%) | 30.9 | 36.4 | NS |
| African American (%) | 17.8 | 21.5 | NS |
| Deceased donor (%) | 43.5 | 42.6 | NS |
| Cold ischemic time  (mean ± SD, h) | 18.4 ± 5.7 | 17.2 ± 7.3 | NS |
| HLA mismatch (mean) | 3.5 | 3.5 | NS |
| Current PRA (mean ± SD) | 1.6 ± 5.3 | 1.8 ± 5.5 | NS |
| Induction immunosuppression (%)  Thymoglobulin  Basiliximab  Daclizumab | 65.4  31.4  3.1 | 69.7  27.2  3.1 | NS |
| Maintenance immunosuppression | TAC, MMF | TAC, MMF |  |
| Main outcomes | | | |
| Biopsy-proven acute rejection (%) | 17.8 | 10.8 | 0.04  (with Kaplan-Meier analysis) |
| Allograft survival (%) | 94.2 | 93.3 | NS |
| Patient survival (%) | 94.2 | 96.4 | NS |
| Creatinine clearance (Cockroft-Gault equation, mean ± SD, mL/min) | 58.6 ± 19.7 | 59.8 ± 20.5 | NS |

CS: Corticosteroid; HLA: Human leukocyte antigens; MMF: Mycophenolate mofetil; NS: Not significant; PRA: Panel-reactive antibodies; SD: Standard deviation; TAC: Tacrolimus.

**Table 2 Characteristics of major randomized corticosteroid avoidance trials (the trial by Woodle *et al*[8] is described separately in table 1); *P* > 0.05 for all comparisons unless otherwise stated**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patient number** | **Immunological risk** | **Timing of CS withdrawal** | **Induction immunosuppression** | **Maintenance immunosuppression** | **Biopsy-proven acute rejection (%)** | **Allograf/patient survival (%)** | **Follow-up (mo)** |
| Vítko *et al*[10] | 151  147 | Low/moderate  (PRA < 50%, first transplant) | Day 1  Standard CS | No | TAC, MMF | 30.5f  8.2f | 97/99  96/100 | 6 |
| Laftavi *et al*[13] | 30  30 | Low (PRA < 30%, first transplant) | Day 7  Standard CS | rALG | TAC, MMF | 13  11 | NR | 12 |
| Kumar *et al*[12] | 150  150 | Low  (PRA < 10%) | Day 2  Standard CS | Basiliximab | TAC or CsA, MMF or sirolimus | 16  14 | 78/91  79/89 | 36 |
| Vincenti *et al*[11] | 112  115  109 | Low (PRA < 20%, first transplant) | No CS  Day 7  Standard CS | Basiliximab | CsA, EC-MPS | 31.5a  26.1b  14.7b,a | 96/95  98/98  97/98 | 12 |
| Hanaway *et al*[17] | 164  171 | Low  (PRA < 20%, first transplant) | Day 5  Day 5 | Alemtuzumab  Basiliximab | TAC, MMF | 10d  22d | 93/95  92/98 | 36 |
| Haynes *et al*[16] | 426  426 | Unselected  patients | No CS  Standard CS | Alemtuzumab  Basiliximab | Low-dose TAC-MMF Standard TAC-MMF | 7h  16h | 96/97  97/99 | 6 |

a*P* = 0.046, b*P* = 0.004, d*P* = 0.003, f*P* < 0.001, h*P* = 0.0001. CS: Corticosteroids; CsA: Cyclosporine; EC-MPS: Enteric-coated mycophenolate sodium; MMF: Mycophenolate mofetil; NR: Not reported; PRA: Panel-reactive antibodies; rALG: Rabbit antilymphocyte globulin; TAC: Tacrolimus.

**Table 3 Characteristics of major randomized corticosteroid withdrawal trials**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patient number** | **Immunological risk** | **Timing of CS withdrawal** | **Induction immunosuppression** | **Maintenance immunosuppression** | **Biopsy-proven acute rejection (%)** | **Allograft/patient survival (%)** | **Follow-up (mo)** |
| Vanrenterghem *et al*[20] | 252  248 | Low | At month 3  Standard CS | No | CsA, MMF | 23b  14b | 95/99  96/98 | 12 |
| Smak Gregoor *et al*[24] | 76  73 | Low | After month 6  Standard CS | No | CsA, MMF | 4.0a  1.4 | 98/97  97/97 | 24 |
| Vanrenterghem *et al*[21] | 279  277 | Low | After month 3  Standard CS | No | TAC, MMF | 5.9a,d  0.9d | 93/99  94/98 | 6 |

*P* > 0.05 for all comparisons unless otherwise stated. aAfter CS discontinuation, b*P* = 0.008, d*P* = 0.004. CS: Corticosteroids; CsA: Cyclosporine; MMF: Mycophenolate mofetil; TAC: Tacrolimus.

**Table4 Characteristics of corticosteroid avoidance/withdrawal trials in immunologically high-risk and in pediatric patients**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patient number** | **Immunological risk** | **Timing of CS withdrawal** | **Induction immunosuppression** | **Maintenance immunosuppression** | **Acute rejection (%)** | **Allograft/patient survival (%)** | **Follow-up (mo)** |
| Immunologically high-risk patients | | | | | | | | |
| Thomas *et al*[26] | 11  10 | PRA > 20%, or  repeat transplant | No CS  Day 5 | Alemtuzumab  ATG | TAC  TAC, MMF | 18.2  37.5 | 86/100  88/88 | 12 |
| Hanaway *et al*[17] | 164  171 | PRA > 20%, or  black race, or repeat transplant | Day 5  Day 5 | Alemtuzumab  ATG | TAC, MMF | 18  15 | 91/99  84/91 | 36 |
| Pediatric patients | | | | | | | | |
| Grenda *et al*[28] | 98  98 | Low/moderate  (PRA < 50%) | Day 4  Standard CS | Daclizumab  No induction | TAC, MMF | 10.2  7.1 | 97/99  97/100 | 6 |
| Höcker *et al*[29] | 23  19 | Moderate/high (PRA<80%) | After year 1  Standard CS | No | CsA, MMF | 4  10 | 100/100  100/100 | 24 |

ATG: Antithymocyte globulin; CS: Corticosteroids; CsA: Cyclosporine; MMF: Mycophenolate mofetil; PRA: Panel-reactive antibodies; TAC: Tacrolimus.