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

**Manuscript NO:** 61030

**Manuscript Type:** MINIREVIEWS

**Does steroid-free immunosuppression improve the outcome in kidney transplant recipients compared to conventional protocols?**

Aref A *et al*. Steroid free immune suppression

Ahmed Aref, Ajay Sharma, Ahmed Halawa

**Ahmed Aref,** Department of Nephrology, Sur hospital, Sur 411, Oman

**Ajay Sharma,** Department of Transplantation, Royal Liverpool University Hospitals, Liverpool 111, United Kingdom

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

**Author contributions:** Halawa A selected the topics for the work, providing expert advice on our work and the final editing of the manuscript; Sharma A contributed the supervision of the scientific presentation of the data collection together with the quality evaluation of the data presented; Aref A designed the work, collected the data and wrote the manuscript.

**Corresponding author: Ahmed Halawa, FRCS (Gen Surg), MSc, Surgeon,** Department of Transplantation, Sheffield Teaching Hospitals, Herries Road, Sheffield S5 7AU, United Kingdom. ahmed.halawa@sth.nhs.uk

**Received:** November 22, 2020

**Revised:** January 22, 2021

**Accepted:** March 19, 2021

**Published online:** April 18, 2021

**Abstract**

Steroids continue to be the cornerstone of immune suppression since the early days of organ transplantation. Steroids are key component of induction protocols, maintenance therapy and in the treatment of various forms of rejection. Prolonged steroid use resulted in significant side effects on almost all the body organs owing to the presence of steroid receptors in most of the mammalian cells. Kidney allograft recipients had to accept the short and long term complications of steroids because of lack of effective alternatives. This situation changed with the intro-duction of newer and more effective immune suppression agents with a relatively more acceptable side effect profile. As a result, the clinicians have been contemplating if it is the time to abandon the unquestionable reliance on maintenance steroids in modern transplantation practice. This review aims to evaluate the safety and efficacy of various steroid-minimization approaches (steroid avoidance, early steroid withdrawal, and late steroid withdrawal) in kidney transplant recipients. A meticulous electronic search was conducted through the available data resources like SCOPUS, MEDLINE, and Liverpool University library e-resources. Relevant articles obtained through our search were included. A total number of 90 articles were eligible to be included in this review [34 randomised controlled trials (RCT) and 56 articles of other research modalities]. All articles were evaluating the safety and efficacy of various steroid-free approaches in comparison to maintenance steroids. We will cover only the RCT articles in this review. If used in right clinical context, steroid-free protocols proved to be comparable to steroid-based maintenance therapy. The appropriate approach should be tailored individually according to each recipient immuno-logical challenges and clinical condition.

**Key Words:** Kidney transplantation; Steroid free; Immune suppression; Steroid avoidance; Steroid withdrawal; Outcome

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Aref A, Sharma A, Halawa A. Does steroid-free immunosuppression improve the outcome in kidney transplant recipients compared to conventional protocols? *World J Transplant* 2021; 11(4): 99-113

**URL:** https://www.wjgnet.com/2220-3230/full/v11/i4/99.htm

**DOI:** https://dx.doi.org/10.5500/wjt.v11.i4.99

**Core Tip:** Prolonged steroid therapy was associated with many complications that ranged from cosmetic changes to life-threatening increase in cardiovascular risk profile. The utilisation of antibody induction, together with calcineurin inhibitors maintenance immune suppression, had markedly reduced the incidence of acute rejection. The improved rate of acute rejection encouraged different transplant centres to adopt new steroid-free protocols, especially in fragile cases with multiple comorbidities. Variable steroid-free approaches were tried. We aim to explore the safety and efficacy of various steroid-free protocols by comparing each different modality with the conventional triple immune suppression.

**INTRODUCTION**

Kidney transplantation continues to prove itself as the best treatment modality for patients with end stage renal disease (ESRD). Kidney transplantation not only improves patient survival, but enhances the quality of life and psychological well-being for those patients[1-3]. The introduction of potent induction protocols utilizing antibodies targeting T-cell receptors together with the availability of effective maintenance immune-suppressive agents has dramatically improved the first-year allograft outcome. On the other hand, the long-term outcome did not show similar improvement, mostly secondary to long term side effects of prolonged immune suppressive medications[4,5]. Steroids have been used since the early days of organ transplantation to prevent the loss of transplanted organs by the recipient immune system[1,4]. The usage of steroids came with a high cost of complications that includes cosmetic changes, metabolic disturbances, skeletal complications, growth affection in pediatric patients and increase risk of cardiovascular morbidity and mortality[1,4]. Variable approaches were adopted by different transplant centers to decrease the burden of steroid side effects either by steroids withdrawal or total steroid avoidance[5]. Discontinuation of steroids after few days of transplantation is called early steroid withdrawal (ESW), while late steroid withdrawal (LSW) implies holding steroids after weeks or months after the transplantation. On the other hand, if steroids were not administered at all, this is called steroid avoidance[1]. Several studies were performed to evaluate the efficacy of various steroid minimization approaches which showed favorable short-term outcome. However, long term outcome is still not validated[5]. In the following sections we shall explore the safety and efficacy of various steroid-minimization approaches namely, steroid avoidance, ESW, and LSW in kidney transplant recipients.

**Epidemiology**

There has been a continuous rise in the number of patients suffering from ESRD, which was translated into a growing number of kidney transplant recipients. In the United States, the number of kidney transplant recipients increased by 106.6% during the period from 2000 to 2017. Furthermore, Kidney transplant recipients in the United States reached more than 222000 by the end of 2017, representing about 30% of all cases treated by renal replacement therapy[6].

A meta-analysis of randomized controlled studies proved the efficacy of induction protocols in lowering the risk of acute rejection (AR) among kidney allograft recipients in the first year allowing utilization of less aggressive maintenance immune-suppression[7]. Data from the United States published in Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report showed that more than 70% of the kidney transplant recipients received induction *via* a T-cell depleting agent (namely rATG or alemtuzumab), and less commonly the non-depleting agent basiliximab (chimeric anti-CD25) was used as the induction agent, while transplantation without induction became relatively uncommon for both adult[8] and pediatric recipients[9].

Early results from randomized controlled studies (RCS) showed a significant improvement in cardiovascular risk profiles in transplant recipients with steroid-free protocols[10,11]. On the other hand, there was an increased risk of AR, which did not significantly affect the first and five-years patient and graft outcome[11]. Nevertheless, long term benefits and consequences of steroid avoidance were not confirmed[10,11].

**Steroid-free protocols in special populations**

There is currently a generalized consensus that steroid-free protocols should be considered in kidney transplant candidates after careful evaluation of possible benefits and expected risks of each patient individually[1,10]. In 2009 Kidney Disease: Improving Global Outcomes Transplant Work Group have suggested using induction protocols utilising one of the lymphocytes depleting agents in case of high-risk of AR[12]. High-risk transplantation is considered in the presence of one or more of the following risk factors[12]: (1) Afro-American ethnicity; (2) Old aged donor; (3) Increased number of human leukocyte antigens (HLA) mismatch; (4) High panel reactive antibody (PRA); (5) Presence of donor-specific antibody (DSA); (6) Prolonged cold ischemia time; and (7) Blood group (ABO) incompatible transplantation.

Steroid free protocols have long been used for low immunological risk situations. However, the safety and efficacy of steroid minimization in high immunological risk transplantation was not adequately addressed in clinical trials[13].

***Steroid withdrawal in African American transplant recipients***

Kidney transplantation in African American population was traditionally considered a procedure with high immunological risk due to the associated higher incidence of AR and chronic allograft nephropathy as well as the inferior graft outcome compared to other ethnic groups[14]. Several studies have shown that African American recipients have immune hyper-responsiveness, more HLA polymorphisms, in addition to several important cytokine polymorphisms[13].

The short and intermediate-term outcome after ESW were evaluated in a few studies that showed acceptable results in the term of patient and graft survival[14,15]. However, these studies were retrospective in nature and included a small number of patients and control.

Data from the United Network of Organ Sharing (UNOS) transplant registry was utilized to perform the most extensive comparative study comparing the outcome of 5565 black kidney transplant recipients who had their steroids withdrawn by the time of hospital discharge after the transplantation versus a matched 5565 black recipients who continued on steroid maintenance therapy[13]. Ten years patient and allograft outcomes were comparable in both groups[13].

***Steroid withdrawal in kidney re-transplantation***

There is a growing number of patients who are being relisted and re-transplanted after the failure of their kidney allograft[16]. Candidates for kidney re-transplantation are more likely to suffer from significant co-morbid conditions (secondary to prolonged immune suppression, pre-transplant comorbidities, the original renal disease, and ageing itself)[17].

Many of the existing co-morbidities are likely to benefit from ESW. On the other hand, re-transplantation candidates are likely to have antibodies to HLA that are expressed on the donor's kidney, and they will be progressively sensitised with each failed allograft experience. Therefore, they are more prone to poor graft outcome secondary to immunological causes unless potent immune suppression was imple-mented[16,17]. Few studies focused on the outcome of ESW in the setting of kidney retransplantation[18,19]. The available studies showed an acceptable short and intermediate-term patient and graft outcome provided that the recipient received induction therapy with a T-cell depleting agent[18,19].

***Steroid withdrawal in sensitised kidney transplant recipients***

Kidney transplant candidates are called sensitised if they have anti-HLA antibodies which increase the risk of rejection. Therefore, such patients used to be considered at high immunological risk and steroids were a cornerstone in their maintenance immune suppression[20]. Sensitised patients may have antibodies to HLA antigens secondary to previous blood transfusion, pregnancy, or prior failed transplants[20]. The analysis of data obtained from OPTN/UNOS showed that maintenance steroid therapy was associated with increased risk of death with functioning graft in kidney allograft recipients with peak PRA less than 30%. However, maintenance steroid usage was associated with improved death censored graft survival and without negative impact on patient survival for recipients with peak PRA more than 60%[20].

***Steroid withdrawal in ABO incompatible kidney transplantation:***

ABO incompatibility was once a contraindication for kidney transplantation as it was associated with hyperacute rejection and graft loss[1]. The introduction of desen-sitisation protocols has changed this concept over the past few decades making ABO incompatible (ABOi) kidney transplantation relatively a realistic option[21]. Nevertheless, potent maintenance immune suppression utilising triple agents was commonly used to achieve excellent patient and graft survival[22]. Several centres investigated the challenge of early withdrawal[23,24] and the late withdrawal of steroids[25,26]. All these studies showed an acceptable patient and graft outcome in addition to the avoidance of long-term complications of steroids. However, all these studies involved a small number of cases. Well organised studies still required to investigate the outcome of a large number of cases over prolonged time of follow up to consolidate the cost-effectiveness of steroid sparing in the setting of ABOi kidney transplantation[24-26].

***Steroid withdrawal in transplantation after glomerulonephritis***

Treatment of most of the primary glomerulonephritis includes the use of steroids to achieve and maintain remission[2]. Recurrence of glomerulonephritis post-transplantation is a feared situation as it indicates a worse allograft survival[27]. Large data registry showed that maintenance steroid therapy has no statistical significance on patient and allograft outcome in recipients with recurrent glomerulonephritis[28,29].

***Steroid withdrawal in older patients***

Kidney transplant recipients older than 60 years are commonly defined as elderly patients[30,31]. The prevalence of ESRD in older people is substantial[6]. There is growing evidence that kidney transplantation in elderly suffering from renal failure has a better outcome than other modalities of renal replacement therapy. However, the ideal immune suppression protocol in elderly recipients remains undefined[30]. The innate and adaptive immune responses are blunted in the elderly. Furthermore, elderly recipients are more vulnerable to infection, malignancy and metabolic diseases which makes the reduction of maintenance immune suppression a sensible option[30,31]. There are no RCT evaluating ESW in the elderly. Nevertheless, retrospective data from a small number of patients showed a similar outcome in elderly recipients when compared to younger recipients in the setting of ESW[31].

***Steroid withdrawal in paediatrics***

Despite that pediatric recipients are liable to the same adverse effects of immune-suppressive medications expressed in adults; they are also vulnerable to unique complications like the affection of growth[32,33]. Factors associated with catch up growth includes recipients less than six years old, well-functioning allograft and steroid-free immune suppression[32,33]. Several reports concluded that steroid-free protocols in pediatric patients would eliminate the long-term complications of steroids without a negative impact on patient or graft survival[34,35].

**Databases**

Aiming to explore the data evaluating the impact of steroid-free protocols on the outcome in the field of kidney transplantation, we performed an extensive search of the online database using MEDLINE, SCOPUS, as well as Liverpool University library e-resources. Relevant articles obtained through our search were included.

***Supplementary search approaches***

After completing the initial electronic database search, grey literature and hand search of the table of contents of the relevant scientific journals were started, aiming to identify additional relevant data. Any related citations were checked against the previously collected data obtained from the electronic search to avoid articles duplication.

***Selection of the articles included***

The final collection of articles obtained from the search of the electronic database, grey literature, as well as a hand search of the related journals were screened initially *via* the title of the article. The next step was evaluating the abstracts of the selected papers accepted by the initial search. Finally, the complete manuscripts of the approved articles were reviewed to decide the final studies included in this review.

***Assessment of articles quality***

While preparing this literature review, a wide range of variability in methodology and study design was encountered. Therefore, we decided to include only randomized controlled trials (RCT). RCT are one of the most reliable tools for evaluating the safety and effectiveness of medical intervention. However, not all RCT present a reliable result[36]. Low-quality RCT with poor methodology may carry a significant bias which will result in misleading conclusions[36]. Therefore, RCT articles included in our study will be subjected to a further evaluation process utilizing the modified Jadad scale[37].

The Jadad scale (which sometimes called the Oxford quality scoring system) is a scoring tool created in 1996 to estimate the methodological quality of RCT[38]. The original scale was composed of 5 questions which evaluate the randomisation, blinding and accountability of all cases, including the dropouts. The modified Jadad scale is composed of 8 questions which assess the points covered by the original scale in addition to inclusion and exclusion criteria evaluation, assessment of adverse effects, and statistical analysis evaluation as illustrated in Table 1[37].

The RCT are scored between 0 (which is the lowermost quality) and 8 (the uppermost quality). Scores between 4 and 8 mean the articles considered of good to excellent quality, while articles with score 0 to 3 are of poor quality[37]. A data extraction sheet was prepared for summarizing the essence of the included studies as well as the quality assessment of the study as presented in Table 2.

**DISCUSSION**

Despite being one of the oldest available immune suppressants, steroids continue to play a central role in the modern immune suppression protocols. Steroids can be used as an induction agent, in maintenance immune suppression as well as in the treatment of rejection episodes[1,2]. Most mammalian cells have cytoplasmic receptors for steroids that explains the potent and diffuse anti-inflammatory and immunosuppressive actions on both innate and adaptive immune systems[1]. Common steroid-induced complications include osteoporosis, impaired glucose metabolism, hypertension, dyslipidemia, growth retardation in children, weight gain, cataract, poor wound healing, cosmetic changes, mood disturbance, and insomnia[1,3].

***Steroid-free protocols***

The use of steroids in the field of transplantation was considered indispensable for many decades. However, the better understanding of immune response, improved techniques of tissue typing and cross-matching, together with the introduction of potent and relatively safe immune suppressants have potentiated the trend of steroid-free immune suppression[1,2]. Various approaches for steroid-free do have comparable AR in the first-year post-transplantation in comparison to conventional protocols. However, the long-term patient and graft outcome remains controversial[1-3].

***RCT on steroid-free protocols***

The published RCT papers were involving adult and pediatric recipients, as mentioned in Table 2. Steroid-free protocols were associated with a better metabolic profile, an improved cardiovascular risk profile and lower total costs of medical care (owing to fewer expenses on the management of steroid-induced complications). Pediatric recipients have an additional advantage which is the improvement of growth parameters with a remarkable catch-up growth, especially in pre-pubertal recipients. On the other hand, some studies showed a mild but real risk of increased incidence of early AR which did not affect the patient and graft survival for up to 5 years of follow up[11].

In middle east, the patients carry the burden of significant co-morbidities (*e.g.* diabetes mellitus, hypertension, and ischaemic heart disease) the assumed risk of steroids outweigh the mildly increased risk of AR (which was documented by most of the listed RCT to be mild and responding to treatment with no long term effects on patient and graft survival).

***Other study modalities on steroid-free protocols***

Many studies of different modalities were evaluating the effect of steroid-free approaches not only in adults and pediatrics but also in other special population recipients like African American, elderly, ABOi recipients and after kidney re-transplantation. Retrospective analysis of long term follow up (up to 15 years post-transplant) showed significantly lower rates of steroid associated complications. Furthermore, there was a significant improvement in patient and allograft survival[39,40].

Recipients with special medical considerations like elderly, patients with high immunological risk and those with a history of glomerulonephritis in native kidneys were traditionally kept on oral steroids indefinitely assuming that steroid-free protocols carry a detrimental effect on the patient and allograft outcome. Surprisingly, most of the studies focused on these special population groups showed a favorable outcome with steroid-free protocols. Nevertheless, a well-designed RCT still awaited to confirm these observations.

***Essential considerations with steroid-free approaches***

Adopting any of the available steroid-free protocols should be carefully designed based on meticulous evaluation of the patient medical history, associated co-morbidities, clinical assessment, and immunological challenges. The recommendations obtained from all the listed studies include: (1) The patients should receive induction with a lymphocytic depleting agent; (2) Ensure adequate dosing of potent immune suppressants (*e.g.*, tacrolimus and mycophenolate mofetil) to compensate for the absence of steroids; (3) Regular evaluation of DSA, especially in highly sensitized recipients; (4) Repeated and timely protocol biopsy may provide a tool of early detection of AR before a clinically evident sequel; and (5) Keep a high index of suspicion for early symptoms and signs of AR.

***Continuing steroid-free regimen versus initiating maintenance steroids after recovery from AR***

One of the critical decisions after managing an AR episode is whether to start a low dose of maintenance steroid or to keep the recipient on his previous steroid-free protocol. The aim is to prevent a second attack of AR as it is undeniably associated with a poor allograft outcome[41,42]. The initiation of maintenance steroids seems to be associated with lower rates of AR and a slight improvement in allograft survival over the next three years of follow up, yet, it did not reach a statistical significance[41]. The most significant risk factor for developing a second AR episode was the histological pattern and severity of the first AR episode (RR = 5.6, *P* = 0.001)[41].

Based on the available data, we recommend individualizing the decision of prescribing maintenance steroids based on the histological description of AR, the clinician clinical judgement as well as the patient preference. Steroid use is highly recommended following the management of moderate to severe AR with positive C4d staining[41].

**CONCLUSION**

The use of lymphocyte depleting induction agents is recommended whenever steroid-free maintenance therapy is planned. There are accumulating clinical studies which showed steroid-free protocols to be valuable in reducing drug-induced complications while keeping patient and allograft survival comparable to maintenance steroids.

Steroid-free protocols are the preferred therapy in pre-pubertal recipients to allow adequate catch-up growth. Steroid-free protocols may also be a valid option for patients with special medical considerations (*e.g.*, elderly, African American and borderline diabetics). A reasonable approach is to weigh the risk-benefit for each transplant candidate individually. Strict monitoring of recipients on steroid-free protocols is a must for early detection and management of AR. If the patient developed AR, then consider initiating lifelong maintenance steroids based on its severity.

Our article attempted to summarize the enormous scientific material covering this debatable topic, keeping in mind that no agreed recommendations or guidelines are available to date regarding any of the steroid withdrawal approaches. We concluded that an ideal steroid-free regimen remains elusive. Nevertheless, after reviewing all the presented RCT articles, we developed a strong belief that steroid-free protocols should have different shapes and forms taking into account patient variables (age, ethnicity, medical background, HLA mismatches, immunological risk stratification, *etc.*). It can offer a comparable outcome with a lower burden of associated co-morbidities.

**ACKNOWLEDGEMENTS**

We acknowledge the effort and the valuable advice of Professor Richard Fuller, Consultant Geriatrician/Stroke Physician and Vice-Dean of the School of Medicine at the University of Liverpool during the preparation of this work.

**REFERENCES**

1 **Danovitch GM**. Handbook of Kidney Transplantation. Sixth Edition, Wolters Kluwer, 2017

2 **Steddon S**. Oxford Handbook of Nephrology and Hypertension. Second edition, Oxford University Press, 2014 [DOI: 10.1093/med/9780199651610.001.0001]

3 **Srinivas TR**, Shoskes DA. Kidney and Pancreas Transplantation: A Practical Guide. Springer, 2011 [DOI: 10.1007/978-1-60761-642-9]

4 **Jaber JJ**, Feustel PJ, Elbahloul O, Conti AD, Gallichio MH, Conti DJ. Early steroid withdrawal therapy in renal transplant recipients: a steroid-free sirolimus and CellCept-based calcineurin inhibitor-minimization protocol. *Clin Transplant* 2007; **21:** 101-109 [PMID: 17302598 DOI: 10.1111/j.1399-0012.2006.00613.x]

5 **Abramowicz D**, Oberbauer R, Heemann U, Viklicky O, Peruzzi L, Mariat C, Crespo M, Budde K, Oniscu GC. Recent advances in kidney transplantation: a viewpoint from the Descartes advisory board. *Nephrol Dial Transplant* 2018; **33**: 1699-1707 [PMID: 29342289 DOI: 10.1093/ndt/gfx365]

6 **Saran R**, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, Gu H, Hirth RA, Hutton D, Jin Y, Kapke A, Kurtz V, Li Y, McCullough K, Modi Z, Morgenstern H, Mukhopadhyay P, Pearson J, Pisoni R, Repeck K, Schaubel DE, Shamraj R, Steffick D, Turf M, Woodside KJ, Xiang J, Yin M, Zhang X, Shahinian V. US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2020; **75**: A6-A7 [PMID: 31704083 DOI: 10.1053/j.ajkd.2019.09.003]

7 **Lim MA**, Kohli J, Bloom RD. Immunosuppression for kidney transplantation: Where are we now and where are we going? *Transplant Rev (Orlando)* 2017; **31**: 10-17 [PMID: 28340885 DOI: 10.1016/j.trre.2016.10.006]

8 **Hart A**, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, Wainright JL, Haynes CR, Snyder JJ, Kasiske BL, Israni AK. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant* 2018; **18 Suppl 1**: 18-113 [PMID: 29292608 DOI: 10.1111/ajt.14557]

9 **Hart A**, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, Robinson A, Wainright JL, Snyder JJ, Kasiske BL, Israni AK. OPTN/SRTR 2017 Annual Data Report: Kidney. *Am J Transplant* 2019; **19 Suppl 2**: 19-123 [PMID: 30811893 DOI: 10.1111/ajt.15274]

10 **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]

11 **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]

12 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group.** KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9 Suppl 3**: S1-S155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

13 **Taber DJ,** Hunt KJ, Gebregziabher M, Srinivas T, Chavin KD, Baliga PK, Egede LE. A Comparative Effectiveness Analysis of Early Steroid Withdrawal in Black Kidney Transplant Recipients. *Clin J Am Soc Nephrol* 2017; **12:** 131-139 [PMID: 27979979 DOI: 10.2215/CJN.04880516]

14 **Haririan A**, Sillix DH, Morawski K, El-Amm JM, Garnick J, Doshi MD, West MS, Gruber SA. Short-term experience with early steroid withdrawal in African-American renal transplant recipients. *Am J Transplant* 2006; **6**: 2396-2402 [PMID: 16869806 DOI: 10.1111/j.1600-6143.2006.01477.x]

15 **Zeng X**, El-Amm JM, Doshi MD, Singh A, Morawski K, Cincotta E, Losanoff JE, West MS, Gruber SA. Intermediate-term outcomes with early steroid withdrawal in African-American renal transplant recipients undergoing surveillance biopsy. *Surgery* 2007; **142**: 538-44; discussion 544-5 [PMID: 17950346 DOI: 10.1016/j.surg.2007.07.006]

16 **Redfield RR,** Gupta M, Rodriguez E, Wood A, Abt PL, Levine MH. Graft and patient survival outcomes of a third kidney transplant. Transplantation 2015; 99: 416-423 [PMID: 25121473 DOI: 10.1097/TP.0000000000000332]

17 **Halawa A**. The third and fourth renal transplant; technically challenging, but still a valid option. *Ann Transplant* 2012; **17**: 125-132 [PMID: 23274333 DOI: 10.12659/aot.883703]

18 **Mujtaba MA**, Taber TE, Goggins WC, Yaqub MS, Mishler DP, Milgrom ML, Fridell JA, Lobashevsky A, Powelson JA, Sharfuddin AA. Early steroid withdrawal in repeat kidney transplantation. *Clin J Am Soc Nephrol* 2011; **6**: 404-411 [PMID: 21051751 DOI: 10.2215/CJN.05110610]

19 **Alloway RR**, Hanaway MJ, Trofe J, Boardman R, Rogers CC, Hanaway MJ, Buell JF, Munda R, Alexander JW, Thomas MJ, Roy-Chaudhury P, Cardi M, Woodle ES. A prospective, pilot study of early corticosteroid cessation in high-immunologic-risk patients: the Cincinnati experience. *Transplant Proc* 2005; **37**: 802-803 [PMID: 15848537 DOI: 10.1016/j.transproceed.2004.12.129]

20 **Sureshkumar KK**, Marcus RJ, Chopra B. Role of steroid maintenance in sensitized kidney transplant recipients. *World J Transplant* 2015; **5**: 102-109 [PMID: 26421263 DOI: 10.5500/wjt.v5.i3.102]

21 **Takahashi K**, Saito K, Takahara S, Okuyama A, Tanabe K, Toma H, Uchida K, Hasegawa A, Yoshimura N, Kamiryo Y; Japanese ABO-Incompatible Kidney Transplantation Committee. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am J Transplant* 2004; **4**: 1089-1096 [PMID: 15196066 DOI: 10.1111/j.1600-6143.2004.00464.x]

22 **Okumi M**, Kakuta Y, Unagami K, Takagi T, Iizuka J, Inui M, Ishida H, Tanabe K. Current protocols and outcomes of ABO-incompatible kidney transplantation based on a single-center experience. *Transl Androl Urol* 2019; **8**: 126-133 [PMID: 31080772 DOI: 10.21037/tau.2019.03.05]

23 **Ando T**, Tojimbara T, Sato S, Nakamura M, Kawase T, Kai K, Nakajima I, Fuchinoue S, Teraoka S. Efficacy of basiliximab induction therapy in ABO-incompatible kidney transplantation: a rapid steroid withdrawal protocol. *Transplant Proc* 2004; **36**: 2182-2183 [PMID: 15518793 DOI: 10.1016/j.transproceed.2004.07.051]

24 **Galliford J**, Charif R, Chan KK, Loucaidou M, Cairns T, Cook HT, Dorling A, Hakim N, McLean A, Papalois V, Malde R, Regan F, Redman M, Warrens AN, Taube D. ABO incompatible living renal transplantation with a steroid sparing protocol. *Transplantation* 2008; **86**: 901-906 [PMID: 18852653 DOI: 10.1097/TP.0b013e3181880c0f]

25 **Novosel MK**, Bistrup C. Discontinuation of steroids in ABO-incompatible renal transplantation. *Transpl Int* 2016; **29**: 464-470 [PMID: 26706618 DOI: 10.1111/tri.12735]

26 **Nanmoku K**, Shinzato T, Kubo T, Shimizu T, Kimura T, Yagisawa T. Steroid Withdrawal Using Everolimus in ABO-Incompatible Kidney Transplant Recipients With Post-Transplant Diabetes Mellitus. *Transplant Proc* 2018; **50**: 1050-1055 [PMID: 29631750 DOI: 10.1016/j.transproceed.2018.01.028]

27 **Allen PJ**, Chadban SJ, Craig JC, Lim WH, Allen RDM, Clayton PA, Teixeira-Pinto A, Wong G. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int* 2017; **92**: 461-469 [PMID: 28601198 DOI: 10.1016/j.kint.2017.03.015]

28 **Mulay AV**, van Walraven C, Knoll GA. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. *Am J Transplant* 2009; **9**: 804-811 [PMID: 19353768 DOI: 10.1111/j.1600-6143.2009.02554.x]

29 **Vock DM,** Matas AJ. Rapid discontinuation of prednisone in kidney transplant recipients from at-risk subgroups: an OPTN/SRTR analysis. *Transpl Int* 2020; **33:** 181-201 [PMID: 31557340 DOI: 10.1111/tri.13530]

30 **Iwamoto H**, Nakamura Y, Konno O, Tomita K, Ueno T, Yokoyama T, Kihara Y, Kawachi S. Immunosuppressive Therapy for Elderly Kidney Transplant Recipients. *Transplant Proc* 2016; **48**: 799-801 [PMID: 27234739 DOI: 10.1016/j.transproceed.2016.02.039]

31 **Alsheikh R**, Gabardi S. Post-Renal Transplantation Outcomes in Elderly Patients Compared to Younger Patients in the Setting of Early Steroid Withdrawal. *Prog Transplant* 2018; **28**: 322-329 [PMID: 30213228 DOI: 10.1177/1526924818800039]

32 **Bonthuis M**, Groothoff JW, Ariceta G, Baiko S, Battelino N, Bjerre A, Cransberg K, Kolvek G, Maxwell H, Miteva P, Molchanova MS, Neuhaus TJ, Pape L, Reusz G, Rousset-Rouviere C, Sandes AR, Topaloglu R, Van Dyck M, Ylinen E, Zagozdzon I, Jager KJ, Harambat J. Growth Patterns After Kidney Transplantation in European Children Over the Past 25 Years: An ESPN/ERA-EDTA Registry Study. *Transplantation* 2020; **104**: 137-144 [PMID: 30946218 DOI: 10.1097/TP.0000000000002726]

33 **Zhang H**, Zheng Y, Liu L, Fu Q, Li J, Huang Q, Liu H, Deng R, Wang C. Steroid Avoidance or Withdrawal Regimens in Paediatric Kidney Transplantation: A Meta-Analysis of Randomised Controlled Trials. *PLoS One* 2016; **11**: e0146523 [PMID: 26991793 DOI: 10.1371/journal.pone.0146523]

34 **Tsampalieros A**, Knoll GA, Molnar AO, Fergusson N, Fergusson DA. Corticosteroid Use and Growth After Pediatric Solid Organ Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2017; **101**: 694-703 [PMID: 27736823 DOI: 10.1097/TP.0000000000001320]

35 **Pape L**. State-of-the-art immunosuppression protocols for pediatric renal transplant recipients. *Pediatr Nephrol* 2019; **34**: 187-194 [PMID: 29067527 DOI: 10.1007/s00467-017-3826-x]

36 **Cho HJ**, Chung JH, Jo JK, Kang DH, Cho JM, Yoo TK, Lee SW. Assessments of the quality of randomized controlled trials published in International Journal of Urology from 1994 to 2011. *Int J Urol* 2013; **20**: 1212-1219 [PMID: 23573913 DOI: 10.1111/iju.12150]

37 **Liu Y**, Li Z, Li H, Zhang Y, Wang P. Protective Effect of Surgery Against Early Subtalar Arthrodesis in Displaced Intra-articular Calcaneal Fractures: A Meta-Analysis. *Medicine (Baltimore)* 2015; **94**: e1984-e1980 [PMID: 26559281 DOI: 10.1097/MD.0000000000001984]

38 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]

39 **Serrano OK**, Kandaswamy R, Gillingham K, Chinnakotla S, Dunn TB, Finger E, Payne W, Ibrahim H, Kukla A, Spong R, Issa N, Pruett TL, Matas A. Rapid Discontinuation of Prednisone in Kidney Transplant Recipients: 15-Year Outcomes From the University of Minnesota. *Transplantation* 2017; **101**: 2590-2598 [PMID: 28376034 DOI: 10.1097/TP.0000000000001756]

40 **Lopez-Soler RI**, Chan R, Martinolich J, Park L, Ata A, Chandolias N, Conti DJ. Early steroid withdrawal results in improved patient and graft survival and lower risk of post-transplant cardiovascular risk profiles: A single-center 10-year experience. *Clin Transplant* 2017; **31** [PMID: 27888534 DOI: 10.1111/ctr.12878]

41 **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]

42 **Arora S,** Marcus RJ, Dikkala S, Sureshkumar KK. Impact of the addition of maintenance steroids to a rapid steroid discontinuation immunosuppressive protocol following acute renal transplant rejection. *Exp Clin Transplant* 2009; **7:** 233-236 [PMID: 20353373]

43 **van Sandwijk MS**, de Vries APJ, Bakker SJL, Ten Berge IJM, Berger SP, Bouatou YR, de Fijter JW, Florquin S, Homan van der Heide JJ, Idu MM, Krikke C, van der Pant KAMI, Reinders ME, Ringers J, van der Weerd NC, Bemelman FJ, Sanders JS. Early Steroid Withdrawal Compared With Standard Immunosuppression in Kidney Transplantation - Interim Analysis of the Amsterdam-Leiden-Groningen Randomized Controlled Trial. *Transplant Direct* 2018; **4**: e354 [PMID: 30123827 DOI: 10.1097/TXD.0000000000000794]

44 **Andrade-Sierra J**, Rojas-Campos E, Cardona-Muñoz E, Evangelista-Carrillo LA, Gómez-Navarro B, González-Espinoza E, Lugo-Lopez O, Cerrillos-Gutiérrez JI, Medina-Pérez M, Jalomo-Martínez B, Nieves-Hernández JJ, Sandoval M, Abundis-Jiménez JR, Ramírez-Robles JN, Villanueva-Pérez MA, Monteón-Ramos F, Cueto-Manzano AM. Early Steroid Withdrawal in Recipients of a Kidney Transplant From a Living Donor: Experience of a Single Mexican Center. *Transplant Proc* 2016; **48**: 42-49 [PMID: 26915841 DOI: 10.1016/j.transproceed.2015.12.013]

45 **Nagib AM**, Abbas MH, Abu-Elmagd MM, Denewar AA, Neamatalla AH, Refaie AF, Bakr MA. Long-term study of steroid avoidance in renal transplant patients: a single-center experience. *Transplant Proc* 2015; **47**: 1099-1104 [PMID: 26036529 DOI: 10.1016/j.transproceed.2014.11.063]

46 **Thierry A**, Mourad G, Büchler M, Choukroun G, Toupance O, Kamar N, Villemain F, Le Meur Y, Legendre C, Merville P, Kessler M, Heng AE, Moulin B, Queré S, Di Giambattista F, Lecuyer A, Touchard G. Three-year outcomes in kidney transplant patients randomized to steroid-free immunosuppression or steroid withdrawal, with enteric-coated mycophenolate sodium and cyclosporine: the infinity study. *J Transplant* 2014; **2014**: 171898 [PMID: 24829794 DOI: 10.1155/2014/171898]

47 **Ponticelli C,** Carmellini M, Tisone G, Sandrini S, Segoloni G, Rigotti P, Colussi G, Stefoni S. A randomized trial of everolimus and low-dose cyclosporine in renal transplantation: with or without steroids? *Transplant Proc* 2014; **46:** 3375-3382 [PMID: 25498055 DOI: 10.1016/j.transproceed.2014.05.087]

48 **Krämer BK**, Klinger M, Vítko Š, Glyda M, Midtvedt K, Stefoni S, Citterio F, Pietruck F, Squifflet JP, Segoloni G, Krüger B, Sperschneider H, Banas B, Bäckman L, Weber M, Carmellini M, Perner F, Claesson K, Marcinkowski W, Ostrowski M, Senatorski G, Nordström J, Salmela K. Tacrolimus-based, steroid-free regimens in renal transplantation: 3-year follow-up of the ATLAS trial. *Transplantation* 2012; **94**: 492-498 [PMID: 22858806 DOI: 10.1097/TP.0b013e31825c1d6c]

49 **Thierry A**, Mourad G, Büchler M, Kamar N, Villemain F, Heng AE, Le Meur Y, Choukroun G, Toupance O, Legendre C, Lepogamp P, Kessler M, Merville P, Moulin B, Quéré S, Terpereau A, Chaouche-Teyara K, Touchard G. Steroid avoidance with early intensified dosing of enteric-coated mycophenolate sodium: a randomized multicentre trial in kidney transplant recipients. *Nephrol Dial Transplant* 2012; **27**: 3651-3659 [PMID: 22645323 DOI: 10.1093/ndt/gfs146]

50 **Gheith OA**, Nematalla AH, Bakr MA, Refaie A, Shokeir AA, Ghoneim MA. Steroid avoidance reduce the cost of morbidities after live-donor renal allotransplants: a prospective, randomized, controlled study. *Exp Clin Transplant* 2011; **9**: 121-127 [PMID: 21453230]

51 **Sandrini S**, Setti G, Bossini N, Chiappini R, Valerio F, Mazzola G, Maffeis R, Nodari F, Cancarini G. Early (fifth day) vs. late (sixth month) steroid withdrawal in renal transplant recipients treated with Neoral(®) plus Rapamune(®): four-yr results of a randomized monocenter study. *Clin Transplant* 2010; **24**: 669-677 [PMID: 20030684 DOI: 10.1111/j.1399-0012.2009.01171.x]

52 **Delgado JC,** Fuller A, Ozawa M, Smith L, Terasaki PI, Shihab FS, Eckels DD. No occurrence of de novo HLA antibodies in patients with early corticosteroid withdrawal in a 5-year prospective randomized study. *Transplantation* 2009; **87:** 546-548 [PMID: 19307792 DOI: 10.1097/TP.0b013e3181949d2e]

53 **Sandrini S**, Setti G, Bossini N, Maffei C, Iovinella L, Tognazzi N, Maffeis R, Nodari F, Portolani N, Cancarini G. Steroid withdrawal five days after renal transplantation allows for the prevention of wound-healing complications associated with sirolimus therapy. *Clin Transplant* 2009; **23**: 16-22 [PMID: 18727661 DOI: 10.1111/j.1399-0012.2008.00890.x]

54 **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]

55 **Pelletier RP**, Akin B, Ferguson RM. Prospective, randomized trial of steroid withdrawal in kidney recipients treated with mycophenolate mofetil and cyclosporine. *Clin Transplant* 2006; **20**: 10-18 [PMID: 16556147 DOI: 10.1111/j.1399-0012.2005.00430.x]

56 **Rostaing L**, Cantarovich D, Mourad G, Budde K, Rigotti P, Mariat C, Margreiter R, Capdevilla L, Lang P, Vialtel P, Ortuño-Mirete J, Charpentier B, Legendre C, Sanchez-Plumed J, Oppenheimer F, Kessler M; CARMEN Study Group. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation* 2005; **79**: 807-814 [PMID: 15818323 DOI: 10.1097/01.tp.0000154915.20524.0a]

57 **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]

58 **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]

59 **Kumar MS**, Xiao SG, Fyfe B, Sierka D, Heifets M, Moritz MJ, Saeed MI, Kumar A. Steroid avoidance in renal transplantation using basiliximab induction, cyclosporine-based immunosuppression and protocol biopsies. *Clin Transplant* 2005; **19**: 61-69 [PMID: 15659136 DOI: 10.1111/j.1399-0012.2004.00298.x]

60 **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; European Tacrolimus/MMF Renal Transplantation Study Group. 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]

61 **Vincenti F**, Monaco A, Grinyo J, Kinkhabwala M, Roza A. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. *Am J Transplant* 2003; **3**: 306-311 [PMID: 12614286 DOI: 10.1034/j.1600-6143.2003.00005.x]

62 **Boots JM,** Christiaans MH, Van Duijnhoven EM, Van Suylen RJ, Van Hooff JP. Early steroid withdrawal in renal transplantation with tacrolimus dual therapy: a pilot study. *Transplantation* 2002; 74: 1703-1709 [PMID: 12499885 DOI: 10.1097/00007890-200212270-00011]

63 **Sola E**, Alférez MJ, Cabello M, Burgos D, González Molina M. Low-dose and rapid steroid withdrawal in renal transplant patients treated with tacrolimus and mycophenolate mofetil. *Transplant Proc* 2002; **34**: 1689-1690 [PMID: 12176537 DOI: 10.1016/s0041-1345(02)02983-4]

64 **Boletis JN**, Konstadinidou I, Chelioti H, Theodoropoulou H, Avdikou K, Kostakis A, Stathakis CP. Successful withdrawal of steroid after renal transplantation. *Transplant Proc* 2001; **33**: 1231-1233 [PMID: 11267272 DOI: 10.1016/s0041-1345(00)02400-3]

65 **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 DOI: 10.1097/00007890-200011150-00015]

66 **Matl I**, Lácha J, Lodererová A, Símová M, Teplan V, Lánská V, Vítko S. Withdrawal of steroids from triple-drug therapy in kidney transplant patients. *Nephrol Dial Transplant* 2000; **15**: 1041-1045 [PMID: 10862645 DOI: 10.1093/ndt/15.7.1041]

67 **Ahsan N**, Hricik D, Matas A, Rose S, Tomlanovich S, Wilkinson A, Ewell M, McIntosh M, Stablein D, Hodge E. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil--a prospective randomized study. Steroid Withdrawal Study Group. *Transplantation* 1999; **68**: 1865-1874 [PMID: 10628766 DOI: 10.1097/00007890-199912270-00009]

68 **Höcker B**, Weber LT, John U, Drube J, Fehrenbach H, Klaus G, Pohl M, Seeman T, Fichtner A, Wühl E, Tönshoff B. Steroid withdrawal improves blood pressure control and nocturnal dipping in pediatric renal transplant recipients: analysis of a prospective, randomized, controlled trial. *Pediatr Nephrol* 2019; **34**: 341-348 [PMID: 30178240 DOI: 10.1007/s00467-018-4069-1]

69 **Tönshoff B**, Ettenger R, Dello Strologo L, Marks SD, Pape L, Tedesco-Silva H Jr, Bjerre A, Christian M, Meier M, Martzloff ED, Rauer B, Ng J, Lopez P. Early conversion of pediatric kidney transplant patients to everolimus with reduced tacrolimus and steroid elimination: Results of a randomized trial. *Am J Transplant* 2019; **19**: 811-822 [PMID: 30125462 DOI: 10.1111/ajt.15081]

70 **Webb NJ**, Douglas SE, Rajai A, Roberts SA, Grenda R, Marks SD, Watson AR, Fitzpatrick M, Vondrak K, Maxwell H, Jaray J, Van Damme-Lombaerts R, Milford DV, Godefroid N, Cochat P, Ognjanovic M, Murer L, McCulloch M, Tönshoff B. Corticosteroid-free Kidney Transplantation Improves Growth: 2-Year Follow-up of the TWIST Randomized Controlled Trial. *Transplantation* 2015; **99**: 1178-1185 [PMID: 25539467 DOI: 10.1097/TP.0000000000000498]

71 **Mericq V**, Salas P, Pinto V, Cano F, Reyes L, Brown K, Gonzalez M, Michea L, Delgado I, Delucchi A. Steroid withdrawal in pediatric kidney transplant allows better growth, lipids and body composition: a randomized controlled trial. *Horm Res Paediatr* 2013; **79**: 88-96 [PMID: 23429258 DOI: 10.1159/000347024]

72 **Sarwal MM**, Ettenger RB, Dharnidharka V, Benfield M, Mathias R, Portale A, McDonald R, Harmon W, Kershaw D, Vehaskari VM, Kamil E, Baluarte HJ, Warady B, Tang L, Liu J, Li L, Naesens M, Sigdel T, Waskerwitz J, Salvatierra O. Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. *Am J Transplant* 2012; **12**: 2719-2729 [PMID: 22694755 DOI: 10.1111/j.1600-6143.2012.04145.x]

73 **Benfield MR**, Bartosh S, Ikle D, Warshaw B, Bridges N, Morrison Y, Harmon W. A randomized double-blind, placebo controlled trial of steroid withdrawal after pediatric renal transplantation. *Am J Transplant* 2010; **10**: 81-88 [PMID: 19663893 DOI: 10.1111/j.1600-6143.2009.02767.x]

74 **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]

75 **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]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest to be declared by any of the authors.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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

**Peer-review started:** November 22, 2020

**First decision:** January 11, 2021

**Article in press:** March 19, 2021

**Specialty type:** Transplantation

**Country/Territory of origin:** United Kingdom

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Gonzalez FM **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Yuan YY

**Table 1 The modified Jadad scale[37]**

|  |  |  |
| --- | --- | --- |
| Item evaluated | Finding | Score |
| Was the study described as randomized? | Yes | + 1 |
| No | 0 |
| Was the method of randomization appropriate? | Yes | + 1 |
| No | - 1 |
| Not described | 0 |
| Was the study described as blinded? (double-blind with score 1; single-blind with score 0.5) | Yes | + 1 |
| No | 0 |
| Was the method of blinding appropriate? | Yes | + 1 |
| No | - 1 |
| Not described | 0 |
| Was there a description of withdrawals and dropouts? | Yes | + 1 |
| No | 0 |
| Was there a clear description of the inclusion/exclusion criteria? | Yes | + 1 |
| No | 0 |
| Was the method used to assess adverse effects described? | Yes | + 1 |
| No | 0 |
| Were the methods of statistical analysis described? | Yes | + 1 |
| No | 0 |

The randomised controlled trials are scored between 0 (which is the lowermost quality) and 8 (the uppermost quality). Scores between 4 and 8 mean the articles considered of good to excellent quality, while articles with score 0 to 3 are of poor quality[37]. A data extraction sheet was prepared for summarizing the essence of the included studies as well as the quality assessment of the study as presented in table 2.

**Table 2 Summary of randomised controlled trials articles**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Cases included** | **Aim of the study** | **Results and conclusions** | **Modified Jadad score** |
| van Sandwijk *et al*[43], 2018 | 186 patients with follow up for about 2 yr | To compare ESW (day 3 post-transplant), triple therapy with low dose tacrolimus and standard tacrolimus dose triple therapy | All groups showed no statistically significant differences in patient survival, allograft survival, incidence of acute rejection and eGFR | 6 |
| Steroid withdrawal group has better cardiovascular risk profile and lower rates of infection |
| Andrade-Sierra *et al*[44], 2016  | 71 patients with follow up for 12 mo | To compare the impact of ESW (day 5 post-operative) with maintenance steroid use.  | One-year graft survival was comparable (87% versus 94% in controls) | 4 |
| Steroid free group has higher eGFR and better blood pressure control with fewer anti-hypertensive drugs (8% versus 50%; *P* < 0.001). |
| Nagib *et al*[45], 2015  | 428 patients with follow up for 66 ± 41 mo | To investigate long term outcome of ESW (steroids used for three days only) in living donor kidney allograft recipients | Steroid avoidance in low immunological risk recipients was both safe and effective using basiliximab induction | 4 |
| Long term follow-up showed decreased total cost with steroid-free protocol despite comparable immune suppressant cost, mostly secondary to lowering the burden of chronic comorbidities related to steroid use |
| Thierry *et al*[46], 2014  | 131 patients were followed for 30 mo | To evaluate the impact of SA in comparison to LSW | At the end of the study period, 32.4% of steroid avoidance patients and 51.7% of steroid withdrawal group were receiving oral steroids | 6 |
| There were no significant differences in kidney functions, proteinuria, or documented rejection between both groups |
| Ponticelli *et al*[47], 2014  | 139 patients with follow up for 12 mo | Evaluating the short-term impact of LSW (3 mo post-transplantation)  | Treatment failure was noted in 14.7% of steroid withdrawal group compared to 2.8% in the control group | 6 |
| NODAT was reported in 13.2% of steroid withdrawal group compared to 1.9% in the control group |
| Krämer *et al*[48], 2012  | 421 patients with follow up for three years | The outcome of two different steroid-free regimens in comparison to the conventional triple immunosuppressive therapy | Despite the increased risk of early acute rejection with steroid-free protocols, the long-term patient and graft survival were comparable | 6 |
| Steroid free regimens were associated with a better cardiovascular risk profile |
| Thierry *et al*[49], 2012  | 222 low risk, de novo kidney transplant recipients with follow up for 6 mo | Evaluation of the short-term outcome of SA after 500 mg methylprednisolone + IL-2 receptor antibody induction in comparison to conventional maintenance steroids | The short-term outcome in the form of patient survival, graft survival, the incidence of BPAR and GFR were similar in both groups. However, SA was associated with a lower incidence of CMV infection (12.5% versus 22.7%, *P* = 0.045) | 6 |
| Gheith *et al*[50], 2011  | 100 patients with a median follow up of twelve months | Assessing the cost-benefit of ESW (3 d post-transplant) in living donor kidney allograft recipients | Despite the comparable immunosuppressant costs, steroid avoidance was associated with significantly lower total costs by the end of the first year after transplantation | 4 |
| The higher costs associated with steroid use was attributed to the cost of management of steroid-related comorbidities |
| Sandrini *et al*[51], 2010  | 96 patients were followed for up to 4 yr | To compare the efficacy of ESW (day 5) versus later withdrawal after 6 mo of transplantation | Both strategies had comparable patient survival, graft survival, allograft function and percentage of successful withdrawal | 5 |
| ESW was associated with less wound healing complications (4% *vs* 21%, *P* = 0.02). On the other hand, LSW was associated with a lower incidence of acute rejection at 12 mo (30% *vs* 48%, *P* < 0.04), and at 48 mo (33% *vs* 53%, *P* < 0.03) |
| Delgado *et al*[52], 2009  | 37 patients with follow up for five years | Evaluating ESW (7 d post-transplant) effect on the development of de novo donor-specific anti HLA antibodies (DSA) | ESW was not associated with increased risk of development of de novo DSA compared with conventional steroid maintenance protocol | 5 |
| Sandrini *et al*[53], 2009  | 148 patients were followed for the first 15 d | To measure the impact of ESW on wound healing in comparison to maintenance steroids in patients receiving sirolimus therapy | ESW was associated with a significantly lower rate of wound healing complications (18.8% *vs* 45.6%, *P* < 0.0004) | 3 |
| Woodle *et al*[11], 2008  | 386 patients with follow up for five years | To compare the outcome of ESW (7 d post-transplant) with low dose chronic corticosteroid therapy | ESW was associated with increased risk of BPAR mostly corticosteroid-sensitive Banff class 1A rejections. However, the five-year allograft survival and function were similar in both groups | 8 |
| Steroid withdrawal was associated with better metabolic and cardiovascular risk profiles |
| Vincenti *et al*[54], 2008  | 337 patients with follow up for 12 mo | Comparing the safety and efficacy of total SA (*n* = 112), ESW (*n* = 115) and standard maintenance steroid regimen (*n* = 109) in first kidney allograft recipients | The median eGFR by the end of the first year was comparable between all groups | 6 |
| The incidence of BPAR was significantly higher with both steroid-free and early withdrawal groups compared to patients maintained on steroids |
| Lipid profile, weight gain, and glycaemic control were better in steroid-free groups |
| Pelletier *et al*[55], 2006  | 120 recipients with follow up of minimum 1 yr after randomisation | To assess the impact of LSW compared to maintenance steroids | Patient and allograft survival, acute rejection rates and allograft function were similar in both groups | 5 |
| Steroid withdrawal was associated with a significant improvement in bone density and total cholesterol levels |
| Rostaing *et al*[56], 2005  | 538 patients with follow up for six months | Short term outcome with a steroid-free protocol using Dac, Tac and MMF versus Tac, MMF, and corticosteroids regimen | Steroid free protocol was associated with a significant reduction in the incidence of NODAT (5.4% *vs* 0.4%, *P* = 0.003), in addition to improvement of serum total cholesterol levels | 6 |
| No clinically significant difference detected between the two groups in the term of acute rejection or serum creatinine levels at the end of the study |
| Laftavi *et al*[57], 2005  | 60 patients were followed up by protocol biopsies at 1, 6, and 12 mo | Short term outcome of ESW (7 d after transplantation)  | ESW was associated with significant and accelerated allograft fibrosis as proved by protocol biopsy findings. However, this did not affect the renal functions measured by eGFR | 6 |
| Vítko *et al*[58], 2005  | 451 low-risk recipients of first kidney allograft were followed up for 6 mo | Short term outcome of a steroid-free protocol using tacrolimus monotherapy after basiliximab induction (Bas/Tac) (*n* = 153), tacrolimus + MMF (Tac/MMF) (*n* = 151) or triple therapy of tacrolimus + MMF + steroids (*n* = 147) | Short term patient and graft survival at 6 mo post-transplantation were similar in all groups. However, the incidence of BPAR was higher in steroid-free groups [26.1% in (Bas/Tac) group, 30.5% in (Tac/MMF) group, and 8.2% in triple therapy group (*P* < 0.001)] | 6 |
| The average creatinine clearance was higher in triple therapy group (65.3 ml/min), compared to Bas/Tac group (55.1 ml/min) and Tac/MMF group (59.4 ml/min) (*P* = 0.007) |
| Kumar *et al*[59], 2005  | 77 patients with follow up for 2 yr | Evaluating the impact of ESW (days 2-7) in comparison to low dose maintenance steroids | There were no statistically significant differences between both groups in all aspects (patient and allograft survival, acute rejection, metabolic profiles, and protocol biopsy findings) | 5 |
| Vanrenterghem *et al*[60], 2005  | 833 recipients with follow up for 6 mo | Estimating the short-term outcome of either steroid or MMF withdrawal after 3 mo of transplantation in comparison to standard triple therapy | The next 3 mo after randomisation showed a similar incidence of BPAR | 5 |
| Steroid withdrawal group had a better lipid profile (*P* < 0.001) |
| MMF withdrawal group had lower frequency of serious CMV infection (*P* = 0.024) and leukopenia (*P* = 0.0082) |
| Vincenti *et al*[61], 2003  | 83 recipients with follow up for 12 mo | Evaluating the impact of ESW (day 4 post-transplantation) in comparison to standard steroid therapy | Patient and allograft survival, the incidence of BPAR, graft function and rate of infections were similar in both groups | 5 |
| Boots *et al*[62], 2002  | 62 patients with a median follow up for 2.7 yr | To compare the outcome of ESW (7 d post-transplant) versus LSW (3-6 mo post-transplant) | Both groups had a similar patient and graft survival with similar acute rejection episodes. However, the incidence of NODAT was significantly lower in early withdrawal group | 6 |
| Sola *et al*[63], 2002 | 92 patients with follow up for 2 yr | Comparing the effect of LSW and maintenance steroids | There were no statistically significant differences between both groups in all aspects (patient and allograft survival, acute rejection, and metabolic profiles) | 2 |
| Boletis *et al*[64], 2001  | 66 patients with follow up for 12 mo | Short term outcome of LSW (6 mo post-transplant) | Serum creatinine levels were comparable in both groups, and none of them has rejection episode during the follow-up period | 4 |
| Serum triglycerides, cholesterol and mean arterial blood pressure levels were also similar in both groups |
| Vanrenterghem *et al*[65], 2000  | 248 patients with follow up for 12 mo | Evaluating the short-term outcome of steroid withdrawal (3 mo post-transplant) in comparison to maintenance steroids. | Despite the increased incidence of BPAR in steroid withdrawal group (23% versus 14%; *P* = 0.008), yet the mean serum creatinine levels were comparable in both groups by the end of 12 mo follow up | 6 |
| Steroid withdrawal was associated with a better lipid profile, blood pressure measurements and bone densitometry measurements at 12 mo |
| Matl *et al*[66], 2000 | 88 patients with follow up for 12 months. | To estimate the safety of LSW compared to continuation on triple therapy. | The allograft function, acute rejection rate and biopsy findings were similar in both groups | 2 |
| LSW was associated with a significantly lower serum cholesterol level. However, no significant changes were observed in serum triglycerides or blood pressure measurements |
| Ahsan *et al*[67], 1999  | 266 patients were followed up for one year | The effect of LSW *vs* continuation on low dose steroid (all patients were receiving cyclosporine and MMF) | LSW was associated with better control of hypertension and lower serum cholesterol level | 7 |
| There is an increased risk of Acute rejection among steroid withdrawal group 30.8% *vs* 9.8% only within maintenance steroid group |
| The risk of rejection or treatment failure within the first-year post-transplantation was 39.6% in blacks versus 16% in nonblack (*P* < 0.001) |
| **Steroid free immune suppression in paediatrics** |
| Höcker *et al*[68], 2019 | 42 paediatric patients (aged 11.2 ± 3.8 yr) were followed for 15 mo | The effect of steroid withdrawal on the recipient’s blood pressure measured *via* ABPM | After 15 mo of follow up, there were no significant differences between both study groups in terms of allograft functions | 6 |
| Steroid withdrawal was associated with better blood pressure readings as well as restoration of circadian blood pressure rhythm in 71.4% of cases versus 14.3% at baseline (*P* = 0.002) |  |
| Tönshoff *et al*[69], 2019  | 106 paediatric recipients with follow up for 12 mo | To estimate the short-term outcome of initiating everolimus with steroid elimination 5 mo post transplantation in comparison to conventional triple therapy | Patient and graft survival were 100% in both groups | 6 |
| No statistically significant differences in the incidence of BPAR, proteinuria, and longitudinal growth |
| Webb *et al*[70], 2015 | 196 subjects with follow up for up to 2 yr | Evaluating the impact of ESW (at day 4 post-transplant) on the longitudinal growth | There was a significant and sustained growth improvement with ESW documented through the two years of follow up, especially in prepubertal children | 5 |
| Patient and graft survival, the incidence of rejection and eGFR were comparable in both groups |
| Mericq *et al*[71], 2013 | 30 paediatric recipients were followed for 12 mo post-transplantation | Evaluating the effect of ESW on the longitudinal growth, body composition, and insulin sensitivity | Steroid withdrawal group showed better longitudinal growth, had lower trunk fat and improved lipid profile parameters compared to the control group | 6 |
| Sarwal *et al*[72], 2012  | 130 paediatric cases with follow up for 3 yr | Evaluating the safety and efficacy of total SA in comparison to low dose maintenance steroids | Complete SA was associated with improved cholesterol levels (*P* = 0.034) and lower systolic blood pressure readings (*P* = 0.017) | 5 |
| Recipients below the age of 5 years showed a significant linear growth catch up with the steroid-free protocol, while other age groups did not show a significant growth difference over the 3 years of follow up |
| Non-significant lower incidence of NODAT was recorded in steroid free group (1.7% versus 5.7%; *P* = 0.373) |
| Incident of BPAR, patient survival and graft outcome were comparable between both groups |
| Benfield *et al*[73], 2010 | 132 paediatric cases with data collected for up to 3 yr | Evaluating the outcome of LSW (6 mo post-transplantation) in comparison to low dose maintenance steroids | LSW resulted in a significant improvement of the Cushingoid facies compared to the control group | 6 |
| The standardised height velocity was higher in the withdrawal group (*P* = 0.033) |
| The allograft survival rate at 3 yr was higher in the withdrawal group (98.6% *vs* 84.5%; *P* = 0.002) |
| Lipid profile, systolic and diastolic blood pressures showed no statistical differences between both groups |
| The study was terminated prematurely due to high incidence of PTLD |
| Grenda *et al*[74], 2010  | 196 paediatric recipients follow up data of the first 6 mo post-transplantation | Evaluating the short-term outcome of ESW (at day 4 post-transplant) | ESW significantly improved the growth, especially in prepubertal recipients | 6 |
| Parameters of lipid and glucose metabolism were significantly better in the withdrawal group. However, they suffered a higher incidence of infection and anaemia (*P* < 0.05 for all mentioned comparisons) |
| Incident of BPAR, allograft function, patient and graft survival were similar for both groups |
| Höcker *et al*[75], 2010 | 42 paediatric patients with follow up for 2 yr after the withdrawal of steroids | Evaluating the effect of LSW (1 yr post-transplant) in comparison to maintenance steroids | LSW was associated with superior longitudinal growth (*P* < 0.001) | 6 |
| Steroid withdrawal was associated with a significant decrease in the prevalence of metabolic syndrome, better control of blood pressure, and improved lipid and carbohydrate metabolism |
| Patient survival, graft function and graft survival were not affected by steroid withdrawal |

IL-2: Interleukin-2; Dac: Daclizumab; Tac: Tacrolimus; MMF: Mycophenolate mofetil; ABPM: Ambulatory blood pressure monitoring; PTLD: Post-transplant lymphoproliferative disorder; ESW: Early steroid withdrawal; eGFR: Epidermal growth factor receptor; LSW: Late steroid withdrawal; NODAT: New-onset diabetes after transplantation; CMV: Cytomegalovirus; DSA: Donor-specific antibody; HLA: Human leukocyte antigens; BPAR: Biopsy-proven acute rejection.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**