

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

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**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.

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

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### 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 introduction 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 immunological challenges and clinical condition.

**Manuscript source:** Invited manuscript

**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

**Received:** November 22, 2020

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

**First decision:** January 11, 2021

**Revised:** January 22, 2021

**Accepted:** March 19, 2021

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

**Published online:** April 18, 2021

**P-Reviewer:** Gonzalez FM

**S-Editor:** Fan JR

**L-Editor:** A

**P-Editor:** Yuan YY



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

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**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.

**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>

## 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<sup>[1-3]</sup>. 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<sup>[4,5]</sup>. Steroids have been used since the early days of organ transplantation to prevent the loss of transplanted organs by the recipient immune system<sup>[1,4]</sup>. 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<sup>[1,4]</sup>. Variable approaches were adopted by different transplant centers to decrease the burden of steroid side effects either by steroids withdrawal or total steroid avoidance<sup>[6]</sup>. 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<sup>[1]</sup>. 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<sup>[6]</sup>. 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<sup>[6]</sup>.

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 immunosuppression<sup>[7]</sup>. 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<sup>[8]</sup> and pediatric recipients<sup>[9]</sup>.

Early results from randomized controlled studies (RCS) showed a significant improvement in cardiovascular risk profiles in transplant recipients with steroid-free protocols<sup>[10,11]</sup>. 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<sup>[11]</sup>. Nevertheless, long term benefits and consequences of steroid avoidance were not confirmed<sup>[10,11]</sup>.

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## STEROID-FREE PROTOCOLS IN SPECIAL POPULATIONS

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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<sup>[1,10]</sup>. 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<sup>[12]</sup>. High-risk transplantation is considered in the presence of one or more of the following risk factors<sup>[12]</sup>: (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<sup>[13]</sup>.

### ***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<sup>[14]</sup>. Several studies have shown that African American recipients have immune hyper-responsiveness, more HLA polymorphisms, in addition to several important cytokine polymorphisms<sup>[13]</sup>.

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<sup>[14,15]</sup>. 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<sup>[13]</sup>. Ten years patient and allograft outcomes were comparable in both groups<sup>[13]</sup>.

### ***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<sup>[16]</sup>. 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)<sup>[17]</sup>.

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 implemented<sup>[16,17]</sup>. Few studies focused on the outcome of ESW in the setting of kidney retransplantation<sup>[18,19]</sup>. 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<sup>[18,19]</sup>.

### ***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<sup>[20]</sup>. Sensitised patients may have antibodies to HLA antigens secondary to previous blood transfusion, pregnancy, or prior failed transplants<sup>[20]</sup>. 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%<sup>[20]</sup>.

### ***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<sup>[1]</sup>. The introduction of desensitisation protocols has changed this concept over the past few decades making ABO incompatible (ABOi) kidney transplantation relatively a realistic option<sup>[21]</sup>. Nevertheless, potent maintenance immune suppression utilising triple agents was commonly used to achieve excellent patient and graft survival<sup>[22]</sup>. Several centres investigated the challenge of early withdrawal<sup>[23,24]</sup> and the late withdrawal of steroids<sup>[25,26]</sup>. 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<sup>[24-26]</sup>.

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

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

### ***Steroid withdrawal in older patients***

Kidney transplant recipients older than 60 years are commonly defined as elderly patients<sup>[30,31]</sup>. The prevalence of ESRD in older people is substantial<sup>[6]</sup>. 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<sup>[30]</sup>. 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<sup>[30,31]</sup>. 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<sup>[31]</sup>.

### ***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<sup>[32,33]</sup>. Factors associated with catch up growth includes recipients less than six years old, well-functioning allograft and steroid-free immune suppression<sup>[32,33]</sup>. 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<sup>[34,35]</sup>.

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## **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<sup>[36]</sup>. Low-quality RCT with poor methodology may carry a significant bias which will result in misleading conclusions<sup>[36]</sup>. Therefore, RCT articles included in our study will be subjected to a further evaluation process utilizing the modified Jadad scale<sup>[37]</sup>.

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<sup>[38]</sup>. 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](#)<sup>[37]</sup>.

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<sup>[37]</sup>. 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](#).

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## **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<sup>[1,2]</sup>. 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<sup>[1]</sup>. 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<sup>[1,3]</sup>.

### **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<sup>[1,2]</sup>. 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<sup>[1-3]</sup>.

### **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).



**Table 1** The modified Jadad scale<sup>[37]</sup>

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<sup>[37]</sup>. 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](#).

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<sup>[11]</sup>.

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<sup>[39,40]</sup>.

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

Table 2 Summary of randomised controlled trials articles

Ref.	Cases included	Aim of the study	Results and conclusions	Modified Jadad score
van Sandwijk <i>et al</i> <sup>[43]</sup> , 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  Steroid withdrawal group has better cardiovascular risk profile and lower rates of infection	6
Andrade-Sierra <i>et al</i> <sup>[44]</sup> , 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)  Steroid free group has higher eGFR and better blood pressure control with fewer anti-hypertensive drugs (8% versus 50%; $P < 0.001$ ).	4
Nagib <i>et al</i> <sup>[45]</sup> , 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  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	4
Thierry <i>et al</i> <sup>[46]</sup> , 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  There were no significant differences in kidney functions, proteinuria, or documented rejection between both groups	6
Ponticelli <i>et al</i> <sup>[47]</sup> , 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  NODAT was reported in 13.2% of steroid withdrawal group compared to 1.9% in the control group	6
Krämer <i>et al</i> <sup>[48]</sup> , 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  Steroid free regimens were associated with a better cardiovascular risk profile	6
Thierry <i>et al</i> <sup>[49]</sup> , 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 <i>et al</i> <sup>[50]</sup> , 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  The higher costs associated with steroid use was attributed to the cost of management of steroid-related comorbidities	4
Sandrini <i>et al</i> <sup>[51]</sup> , 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  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%, $P < 0.03$ )	5
Delgado <i>et al</i> <sup>[52]</sup> , 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 <i>et al</i> <sup>[53]</sup> , 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 <i>et al</i> <sup>[11]</sup> , 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  Steroid withdrawal was associated with better metabolic and cardiovascular risk profiles	8
Vincenti <i>et al</i> <sup>[54]</sup> , 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  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	6
Pelletier <i>et al</i> <sup>[55]</sup> , 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  Steroid withdrawal was associated with a significant improvement in bone density and total cholesterol levels	5
Rostaing <i>et al</i> <sup>[56]</sup> , 2005	538 patients with follow up for six months	Short term outcome with a steroid-free protocol using Tac, 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  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	6
Laftavi <i>et al</i> <sup>[57]</sup> , 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
Vitko <i>et al</i> <sup>[58]</sup> , 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 ( $P < 0.001$ )]  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) ( $P = 0.007$ )	6
Kumar <i>et al</i> <sup>[59]</sup> , 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 <i>et al</i> <sup>[60]</sup> , 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  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 ( $P = 0.0082$ )	5
Vincenti <i>et al</i> <sup>[61]</sup> , 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 <i>et al</i> <sup>[62]</sup> , 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 <i>et al</i> <sup>[63]</sup> , 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 <i>et al</i> <sup>[64]</sup> , 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  Serum triglycerides, cholesterol and mean arterial blood pressure levels were also similar in both groups	4
Vanrenterghem <i>et al</i> <sup>[65]</sup> , 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  Steroid withdrawal was associated with a better lipid profile, blood pressure measurements and bone densitometry measurements at 12 mo	6
Matl <i>et al</i> <sup>[66]</sup> , 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  LSW was associated with a significantly lower serum cholesterol level. However, no significant changes were observed in serum triglycerides or blood pressure measurements	2
Ahsan <i>et al</i> <sup>[67]</sup> , 1999	266 patients were followed up for one year	The effect of LSW <i>vs</i> 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  There is an increased risk of Acute rejection among steroid withdrawal group 30.8% <i>vs</i> 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 ( $P < 0.001$ )	7
<b>Steroid free immune suppression in paediatrics</b>				
Höcker <i>et al</i> <sup>[68]</sup> , 2019	42 paediatric patients (aged $11.2 \pm 3.8$ yr) were followed for 15 mo	The effect of steroid withdrawal on the recipient's blood pressure measured <i>via</i> ABPM	After 15 mo of follow up, there were no significant differences between both study groups in terms of allograft functions  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 ( $P = 0.002$ )	6
Tönshoff <i>et al</i> <sup>[69]</sup> , 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  No statistically significant differences in the incidence of BPAR, proteinuria, and longitudinal growth	6
Webb <i>et al</i> <sup>[70]</sup> , 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  Patient and graft survival, the incidence of rejection and eGFR were comparable in both groups	5
Mericq <i>et al</i> <sup>[71]</sup> , 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 <i>et al</i> <sup>[72]</sup> , 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 ( $P = 0.017$ )  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	5

			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 <i>et al</i> <sup>[73]</sup> , 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 <i>et al</i> <sup>[74]</sup> , 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 <i>et al</i> <sup>[75]</sup> , 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; 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.

based on meticulous evaluation of the patient medical history, associated comorbidities, 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<sup>[41,42]</sup>. 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<sup>[41]</sup>. 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,  $P = 0.001$ )<sup>[41]</sup>.

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<sup>[41]</sup>.

## 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.

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