CHAPTER 5
Specific immunosuppressive protocols

CHAPTER 5.1 Steroid minimisation strategies

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1 Introduction

Glucocorticoids, developed in the early 1950s, are one of the main agents used for both maintenance immunosuppression and treatment of acute rejection. Glucocorticoids have both anti-inflammatory and immunosuppressive effects. They also induce lymphopenia and monocytopenia that result from inhibition of lymphocyte proliferation, survival, activation, homing, and effector functions. The main glucocorticoids used are prednisone or prednisolone (given orally with comparable efficacy) and methylprednisolone (given orally or intravenously with 25% greater potency). These agents are rapidly absorbed and have short plasma half-lives (60–180 minutes), but long biological half-lives (18–36 hours).

In many transplant centres, the initial dose of glucocorticoids is usually given during surgery as intravenous methylprednisolone, at doses between 2 and 10 mg/kg body weight per day. The oral dose of glucocorticoids used for maintenance therapy varies between 15 and 60 mg/m^2 per day (0.5 to 2 mg/kg per day), which is gradually tapered over time to approximately 3 mg of prednisolone per m^2 of body surface area, usually taken as a single morning dose. Alternate day dosing is often used 6 to 12 months post-transplant to minimise the effect of glucocorticoids on growth.

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2 Side effects of glucocorticoids

Glucocorticoids have numerous side effects in children, including impaired growth, susceptibility to infection, cushingoid appearance, body disfigurement, acne, cardiovascular complications, arterial hypertension, hyperglycaemia, lipid disorders, aseptic bone necrosis, osteopenia, cataracts, poor wound healing, and psychological effects. The negative effect of glucocorticoids on appearance may play a role in poor adherence, particularly in body image-conscious adolescents. The risk of infection is excessive with prolonged high-dose pulse therapy (typically > 3 g per 1.73 m^2). Glucocorticoid dosage should, therefore, be tapered during rejection treatment, even if kidney function does not improve. Interestingly, glucocorticoids are not associated with an increased risk of malignancy. One of the most important reasons for discontinuing glucocorticoids or switching to alternate day therapy is impaired longitudinal growth, which is often seen in those on continuous treatment. Steroids are the major cause of growth failure in paediatric kidney transplant recipients, in addition to suboptimal allograft function [Tönshoff 2023]. Pharmacological doses of steroids disrupt longitudinal growth by inhibiting growth hormone secretion and insulin-like growth factor activity, and by suppressing the local synthesis of growth factors and matrix proteins in the growth plate [Tönshoff et al. 2005].

3 Steroid minimisation strategies

Because of the many adverse effects of maintenance glucocorticoid therapy, attempts have been made to withdraw or minimise glucocorticoid (steroid) therapy in paediatric kidney transplant recipients [Benfield et al. 2010, Sutherland et al. 2009, Barletta et al. 2009, Höcker et al. 2009, Höcker et al. 2010, Sarwal et al. 2003, Chavers et al. 2009, Grenda et al. 2010, Webb et al. 2015, Sarwal et al 2012, Pape et al. 2010, Tönshoff et al. 2019, Tönshoff et al. 2021]. There are four main approaches to steroid minimisation: (i) complete steroid avoidance or early steroid withdrawal (< 7 days post-transplant), (ii) an intermediate approach combining elements of early and late withdrawal protocols that sometimes uses antibody induction, (iii) late steroid withdrawal (≥ 1 year post-transplant, and (iv) alternate day steroids.

Nevertheless, steroid withdrawal or avoidance following renal transplantation remains a controversial issue. Although the benefits of using steroid-free protocols in paediatric patients are promising, further studies are needed to determine the impact on long-term allograft function and to identify patients (e.g., low immunological risk) who can be successfully switched to steroid-free immunosuppression without increasing the risk of acute rejection.

The efficacy of steroid withdrawal may depend in part on adequate exposure to the remaining drugs, such as tacrolimus, MMF or mTOR inhibitors in order to sufficiently suppress the anti-allograft immune response. Thorough therapeutic drug monitoring of these immunosuppressants and targeting the appropriate therapeutic ranges to achieve sufficient immunosuppressive activity is therefore recommended (see Chapter 4.3). Unfortunately, there is currently no immunological test that can reliably predict the success or the risk of steroid withdrawal.

Complete steroid avoidance or early steroid withdrawal

Some centres in North America argue that complete steroid avoidance is a more promising approach than steroid withdrawal, because a completely steroid-free immunosuppressive milieu from the outset should not lead to steroid-dependent suppression of the immune response, which would make either steroid withdrawal or alternate day dosing hazardous for rebound rejection. However, an empirical or experimental support for this hypothesis is still lacking.

Steroid avoidance protocols have been used successfully and have been extensively evaluated in the United States. These protocols have selected low-risk individuals and used intensive induction therapy with thymoglobulin, tacrolimus, and MMF [Sarwal et al. 2012]. The results of the North American randomised controlled multicentre trial with a follow-up of 3 years post-transplant showed that the steroid-free group showed lower systolic blood pressure and lower cholesterol levels. The authors concluded that complete steroid avoidance is safe and effective in non-sensitised children undergoing primary kidney transplantation [Sarwal et al. 2012].

Regarding the efficacy and safety of early steroid withdrawal, a randomised controlled trial, the TWIST trial, in 196 paediatric kidney transplant recipients, showed that two doses of daclizumab in patients treated with a regimen of tacrolimus and MMF allowed early steroid withdrawal on day 5 post-transplant [Grenda et al. 2010]. There was a comparable rate of biopsy-proven acute rejection rates at six months in steroid-free patients compared with controls (10.2% vs. 7.1%). In addition, prepubertal patients with early steroid withdrawal showed improved growth and lipid and glucose metabolism profiles compared to controls, without an increase in graft rejection or loss. These beneficial effects were confirmed in a 2-year follow-up study [Webb et al. 2015]. The TWIST study has been criticised for reporting only biopsy-proven acute rejection episodes

≥ Banff I and not the rate of borderline rejection and/or treated rejection episodes in the two study arms, leaving some uncertainty about the immunosuppressive efficacy of this protocol.

Intermediate approach of steroid withdrawal at 6-9 months post-transplant

This intermediate approach combines elements of early and late withdrawal protocols, using antibody induction, but delaying the decision to withdraw steroids until 6–9 months post-transplant, when stable renal graft function (sometimes combined with a normal protocol biopsy) allows identification of suitable candidates (as in the late withdrawal approach) [Pape et al. 2010, Pape et al. 2019]. For example, the CRADLE study was a 36-month multicentre prospective randomised trial in paediatric kidney transplant recipients who were randomised at 4 to 6 weeks post-transplant to receive everolimus plus reduced-exposure tacrolimus with glucocorticoid withdrawal at 6 months post-transplant or to continue MMF and standard-exposure tacrolimus with glucocorticoids (Tönshoff et al. 2019, Tönshoff et al. 2021). The incidence of composite efficacy failure (biopsy-proven acute rejection, graft loss, or death) at month 36 was similar between groups (9.8% vs. 9.6%). Mean estimated glomerular filtration rate at month 36 was comparable between groups (68.1 vs. 67.3 mL/min/1.73 m^2). Growth was better in prepubertal patients on everolimus and reduced-exposure tacrolimus without glucocorticoids. The authors concluded that although the rate of study drug discontinuation due to adverse events was higher in the everolimus group, an everolimus plus reduced-exposure tacrolimus regimen is an alternative treatment option that allows the withdrawal of glucocorticoids and the reduction of calcineurin inhibitors.

Late steroid withdrawal

In the late steroid withdrawal approach, patients suitable for minimisation are identified by a stable post-transplant clinical course and renal function. Late steroid withdrawal does not require antibody induction in the perioperative period [Höcker et al. 2009, Höcker et al. 2010]. Steroid withdrawal has the advantage over steroid avoidance that immunologically high-risk patients and those with unstable graft function can be easily identified in advance and excluded from steroid-free immunosuppression. For example, in one study, 42 paediatric kidney transplant recipients at low or standard immunological risk were randomly assigned, at ≥ 1 year post-transplant, to continue taking or to withdraw steroids over 3 months. Two years after steroid withdrawal, longitudinal growth was superior to controls. The prevalence of the metabolic syndrome declined significantly. Steroid-free patients had less frequent arterial hypertension (50% versus 93%) and required less antihypertensive medication. They also had significantly improved carbohydrate and lipid metabolism with less hypercholesterolaemia and hypertriglyceridaemia. Patient and graft survival was 100%. Allograft function remained stable 2 years after steroid withdrawal. The incidence of acute rejection was similar in the steroid withdrawal group (4%) and controls (11%). The authors concluded that late steroid withdrawal in selected cyclosporine- and MMF-treated paediatric kidney transplant recipients improves growth, mitigates cardiovascular risk factors and reduces the prevalence of the metabolic syndrome without increasing the risk of acute rejection or graft dysfunction [Höcker et al. 2010].

Alternate-day steroids

One way to ameliorate or avoid steroid-specific side effects in paediatric kidney transplant recipients is to administer steroids on alternate days, as a cumulative dose of steroids has a significantly reduced inhibitory effect on growth velocity when administered on alternate days compared to a daily regimen without adversely affecting graft survival or long-term graft function [Broyer et al. 1992, Jabs et al. 1996]. However, the effect on longitudinal growth is only moderate and limited to the first 2 years post-transplant. For example, in a large study reported from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry, relative height increased by 0.50 ± 0.06 SDS in the first 2 years post-transplant, but no additional height gain was observed in subsequent years [Jabs et al. 1996]. Therefore, it is thought that alternate-day steroid dosing may provide catch-up growth in young paediatric kidney transplant recipients with well-preserved graft function only in the first 2 years post-transplant.

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