Induction Therapy in Pediatric Renal Transplant Recipients

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Olga Charnaya, Asha Moudgil, and Dechu Puliyanda

9.1 Introduction

Induction therapy is the initiation of intense immunosuppression at the time of, or prior to, transplantation intended to prevent allograft rejection upon contact of the recipient's immune system with the donor antigens. Induction therapies have been divided into biological agents that include monoclonal and polyclonal antibodies and chemical agents such as calcineurin inhibitors (CNI), antiproliferative agents including mycophenolate mofetil (MMF), and methylprednisolone (MP). Other induction therapies include plasmapheresis and intravenous immunoglobulin (IVIG). Most data comes from adult studies and pediatric data is provided when available.

Historically, induction therapy was primarily intended to provide intensive T-cell depletion at the time of transplantation. Recently, newer induction agents and strategies have also targeted B-cells, particularly in the highly sensitized recipients.

O. Charnaya
Department of Pediatrics, Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: ocharna1@jhmi.edu

A. Moudgil
Department of Nephrology, Children's National Medical Center, Washington, DC, USA
e-mail: amoudgil@childrensnational.org

D. Puliyanda (✉)
Department of Pediatrics, Division of Pediatric Nephrology and Transplant Immunology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: dechu.puliyanda@cshs.org

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9.2 Aims of Induction Therapy

The main purpose of induction therapy has been to decrease the incidence, severity, and frequency of acute rejection (AR) episodes after transplantation with the intent of prolonging the life of the allograft. This is accomplished by interfering with the anticipated immune response to foreign antigens.

The immune response mounted against a transplanted allograft occurs due to the cognate interaction between the innate and adaptive immune systems, which is most intense at the time of transplant and continues throughout the entire life of the allograft. At the time of transplant, the innate immune system is activated in response to tissue injury sustained during organ retrieval and resultant ischemia, known as ischemia-reperfusion injury (IRI), which initiates and amplifies the adaptive response. Production of inflammatory cytokines (IL-1, IL-6, TNF-α, and γ-interferon), chemokines, and P-selectins induces permeability changes in endothelial cells causing release of antigens from the graft and stimulating migration of donor-derived antigen-presenting cells (APCs) from the transplant to the recipient's lymphoid tissue. Both donor-derived and recipient APCs present foreign antigens in the form of peptides present on their cell surface in the groove of the histocompatibility antigen (HLA) molecules to the recipient CD4+ T-cells. This ensures that all allopeptides are presented to T-cells with the optimal T-cell receptor (TCR) specificity and affinity. Proliferation of CD4+ T-cells is driven by further co-stimulatory signaling from APCs [1]. Activated CD4+ cells stimulate many other types of cells that include effector cytotoxic T-lymphocytes (CD8+), inflammatory T-cells (Th17), and B-cells to generate cell-mediated graft destruction and develop HLA antibodies and long-term immunological memory. The adaptive immune response further directs innate immune components such as complement, neutrophils, and phagocytic cells to the site of allograft injury [2]. T-regulatory (Treg) cells are also produced during this interaction which helps regulate these inflammatory responses to limit the destruction.

The aim of induction therapy is to prevent these inflammatory responses at the time of transplantation and to provide adequate immunosuppression until the oral immunosuppressive agents can take over this task. In patients with delayed graft function (DGF), defined as the need for dialysis within the first week after transplantation, there is an upregulation of HLA molecules on the allograft causing an increased propensity for AR and therefore, the need for intensification of immunosuppression [3]. Successful induction therapy agents and protocols need to be safe and cost-effective and should not cause excessive immunosuppression, with the goal of minimizing the risk of infectious complications and malignancies, such as posttransplant lymphoproliferative disease (PTLD). The effect of any induction agent on long-term patient and graft survival should be assessed prior to its widespread use.

9.3 Historical Induction Agents

Total lymphoid irradiation (TLI) was one of the first induction modalities used in the early transplantation era in human organ transplantation [4, 5]. TLI caused lympholysis and produced sufficient immunosuppression to prolong the survival of a variety of organ allografts in experimental animals [6, 7]. The length of effective immunosuppression was dose-dependent and was limited by the toxicity that occurred with the higher doses. The next step in evolution of induction immunosuppression came with utilization of polyclonal antibodies, obtained by immunizing laboratory animals with human lymphoid cells from cell cultures, peripheral lymphocytes, thymus, or spleen. The pooled sera are pre-absorbed on erythrocytes and platelets and purified to extract the IgG fraction. Polyclonal antibody agents have evolved over time and are the most commonly utilized induction agents today.

9.4 Currently Utilized Induction Agents

Current induction therapies can be broken down into three broad categories: lymphocyte-depleting, non-lymphocyte-depleting, and chemical agents. Numerous studies have compared different induction immunosuppression regimens. However, these studies are often underpowered, are predominantly performed in adult patients, and have not demonstrated a superiority of a single optimal induction regimen. Therefore, most pediatric transplant centers use induction agents based on their clinical experience rather than guided by the available data.

9.4.1 Lymphocyte-Depleting Agents

Rabbit antithymocyte globulin (rATG) under the brand name Thymoglobulin® received FDA approval in 1998 for the treatment of steroid-resistant AR in transplant recipients; in the last few years, it was also approved as an induction agent. It is created by immunizing rabbits with human thymocytes and purifying the resulting IgG fraction. The antibodies in Thymoglobulin are polyclonal, and although their effect is predominantly anti T-cell, it also has a lesser degree of activity against B-cells, monocytes, and neutrophils due to shared antigens between different immune cells [8]. Data show that rATG induces a proportionally larger decrease of CD4+ Foxp3- cells compared to CD4 + CD25 + Foxp3+ Treg cells resulting in relative preservation of Treg cells [9].

Brennan et al. performed the first studies to demonstrate the safety, effectiveness, and superiority of Thymoglobulin over another polyclonal horse-derived preparation (ATGAM) and basiliximab [10–12]. These landmark studies changed the clinical approach to induction immunosuppression as evidenced by a persistent and

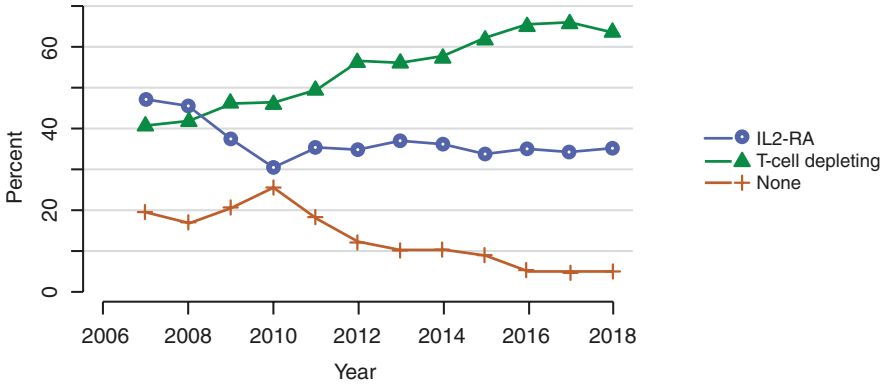

Fig. 9.1 2018 SRTR/OPTN annual report. Use of induction immunosuppression by agent in pediatric kidney transplant by year [133]

steady increase in rATG induction compared to no-induction or basiliximab (Fig. 9.1). While pediatric studies are limited, rATG induction followed by CNI, MMF, and prednisone was demonstrated to be a safe and effective immunosuppression regimen in pediatric patients with 1 year of follow-up, with a low incidence of AR, symptomatic cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection, or PTLD [13]. A single-center study of 198 children and adolescents showed decreased rates of AR when compared to an ATGAM-induction historical cohort; however, there were increased rates of EBV viremia with Thymoglobulin® but similar patient and graft survival [14].

Thymoglobulin® can be administered through a large peripheral vein or central venous access and is usually given daily (1.5–2.0 mg/kg/day) to achieve total cumulative dose ranging from 4.5 to 7.5 mg/kg [11, 15–17]. The current FDA dosing guidance recommends a minimum of four doses of rATG at 1.5 mg per kg for a cumulative dose exposure minimum of 6 mg per kg for induction purposes [18]. Individual centers use varying doses of rATG for induction based on the center's experience and preferences.

Rounding the daily dose to the nearest 25 mg increment (but still ensuring the complete total dose), dosing guided by CD3+ T cell counts as well as delayed administration of doses can help to reduce the cost of this therapy [19]. More recently, low-dose (3–4.5 mg/kg) Thymoglobulin induction regimens have been studied in adult patients and shown to have similar rates of biopsy proven AR, delayed or slow graft function, graft loss, and leukopenia [20, 21].

Alemtuzumab (Campath-1H®, Genzyme, Cambridge, MA), a monoclonal antibody targeted at the CD52 antigen present on T- and B-lymphocytes and monocytes, received FDA approval in 1998 for the treatment of chronic lymphocytic leukemia. It has been used extensively off label in solid organ transplantation as an induction agent. The nature and kinetics of lymphocyte repopulation depends on the maintenance immunosuppression. Similar to rATG, alemtuzumab also proportionally increased CD4 + CD25 + Foxp3+ Treg cell population independent of the

maintenance immunosuppression regimen [22, 23]. This suggests that repopulation of the lymphoid compartment after T-cell depletion with alemtuzumab results in long-term increases of Treg cells.

Initial adult trials were aimed at CNI and steroid avoidance with alemtuzumab induction; however, they resulted in an unacceptably high incidence of acute cellular and humoral rejection [24–26]. Five-year follow-up results of alemtuzumab induction in 33 renal transplant recipients with half-dose CSA monotherapy compared with patients treated with conventional immunosuppression with CSA, azathioprine (AZA), and steroids showed comparable patient and graft survival, graft loss, incidence of infections, and serious adverse events and incidence of AR [27]. The results of this study suggested that alemtuzumab induction was safe in the long term. However, it was noted that it may cause delayed onset of AR, and therefore continued surveillance for AR is needed.

As with most induction agents, pediatric data are limited by small sample size and short follow-up. Alemtuzumab induction was first shown to be safe and effective with tacrolimus monotherapy immunosuppression in a pilot study of 17 unselected pediatric patients. Tacrolimus was begun posttransplantation with subsequent lengthening of intervals between doses with the hypothesis that heavy posttransplant immunosuppression may contribute to long-term immunosuppression dependence by subverting tolerogenic mechanisms [28]. Steroids were added temporarily to treat rejection in two patients (both rATG subgroup) or to treat hemolytic anemia in two others. After a mean follow-up of 22 months, patient and graft survival were 100% and 94%, respectively. Following the same protocol, Sung et al. reported data on 25 pediatric patients receiving alemtuzumab induction with 100% actuarial patient and graft survival at 3 years, and only one graft was lost at 4 years due to nonadherence [29]. At the 4-year follow-up, 48% remained on tacrolimus monotherapy maintenance immunosuppression, 32% on dual therapy (tacrolimus and an antiproliferative agent), and 16% on triple therapy (tacrolimus, antiproliferative agent, and glucocorticoids). Early acute rejection (< 12 months) occurred in 12%, late acute rejection episodes occurred in 16% of patients, and 20% of patients developed de novo donor-specific antibodies (dnDSA). Similarly, Tan et al. showed favorable 4-year outcomes in patients receiving a living donor kidney transplant with alemtuzumab induction and tacrolimus monotherapy [30]. Acute cellular rejection was seen in 4.8% of patients and no antibody-mediated rejection (AMR) was seen; 17% developed dnDSA. The mean HLA mismatch in the cohort was only 2.6, notably better than many transplants done today.

Alemtuzumab is given at the time of organ reperfusion (0.3–0.6 mg/kg, max 30 mg) IV or as a subcutaneous injection at similar doses [31]. Most commonly, a single dose is used in pediatric patients; however, in some adult protocols, a second dose is administered after 24 hours resulting in prolonged lymphocyte depletion [32]. In 2013, the manufacturer changed their distribution model for alemtuzumab and it is no longer commercially available. It is now provided only through the Campath® Distribution Program free of charge for patients deemed appropriate. While this is an economic advantage to centers at the present time, concern remains for the future and availability of alemtuzumab in the long term [19].

A recent Cochrane review analyzed 99 studies (8956 adult and pediatric participants) with the aim of evaluating the relative and absolute effects of lymphocyte-depleting agents and to determine differences in adverse effects. They found that both rATG and alemtuzumab reduce AR rates compared to no-induction, at the cost of increased CMV infections, while patient-centered outcomes (death and toxicity) do not appear to be improved [33].

9.4.2 Non-lymphocyte-Depleting Agents

Basiliximab (Simulect®, Novartis Pharmaceuticals Corp, East Hanover, NJ) is a chimeric (75% human, 25% murine) monoclonal antibody that targets the CD25 molecule on the IL-2 receptor and selectively prevents the clonal expansion of activated T-cells. Daclizumab is a humanized monoclonal antibody, which is no longer on the market and will not be discussed in this chapter.

The IL-2 receptor is comprised of three chains: α chain (CD25), β chain (CD122), and γ chain (CD132). Only the β and the γ chain are expressed on the surface of the resting T-cells. In response to antigenic stimulation, the activated T helper lymphocyte (CD4) can induce activation of the IL-2 receptor α chain (CD25) and form the activated IL-2 receptor heterotrimeric complex. This leads to the clonal expansion of activated helper and cytotoxic T-cells. An important caveat to consider is that Treg cells are depended on IL-2 signaling for ongoing activity and therefore their function can be impaired by this therapy. Studies have shown that basiliximab therapy led to a profound, but transient, reduction in $CD4^+CD25^+FOXP3^+$ Treg within 7 days of treatment lasting for approximately 90 days after transplant [34].

Several single-center and a few multicenter studies have reported their experience with IL-2 receptor antagonist (IL2-RA) induction in pediatric renal transplantation, with triple immunosuppression consisting of CSA or tacrolimus, and MMF or AZA and steroids, as maintenance immunosuppression. Although most of the reports have a small sample size, the incidence of AR at 1 year has varied between 6% and 17%, with 1-year graft survival between 86 and 98% [35–37]. Pooled data from NAPRTCS reported 284 patients treated with daclizumab, 166 with basiliximab, and 711 with no-induction therapy as controls [38]. One-year incidence of AR was 23–26%, lower than 34% observed in no-induction controls. Graft survival was significantly higher with 95–97% versus 93% in no-induction controls. There was no increase in the incidence of side effects in those treated with IL2-RA compared to no-induction control group. Smith et al. reported decreased incidence of graft thrombosis in those treated with IL2-RA induction (1.07%) compared with those treated with no-induction therapy (2.40%, OR 0.44, 95% CI 0.23, 0.84, $p = 0.014$) in a retrospective analysis of data reported to NAPRTCS [39]. All these studies, though mostly single-center and/or retrospective, point to the fact that IL2-RA can prevent AR without increasing side effects.

A 2010 Cochrane review compared basiliximab with no-induction or rATG [40]. When compared to rATG, there was no difference in graft loss at any time point, but there was a reduction of biopsy-proven AR at 1 year (RR 1.30, 95% CI 1.01 to 1.67)

with rATG but a 75% increase in malignancy and 32% increase in CMV disease. Notably in this review, despite the homogeneity of results across the populations of the pooled studies, there was underrepresentation of high-risk participants and in particular of children.

Basiliximab is given on day 0 and day 4 of transplant as 20 mg/dose in adults and 12 mg/m^2/dose in children. In a cost comparison between basiliximab and placebo (including steroid therapy), no significant differences in costs were seen in terms of immunosuppressive therapies, total hospitalization, laboratory tests, outpatient visits, postoperative dialysis, or total costs at 6 or 12 months from an institutional perspective [41].

Belatacept (Nulojix®), approved in June of 2011, is indicated for the prophylaxis of organ rejection in adult patients receiving a renal transplant. A soluble fusion protein, it binds to CD80 and CD86 on APC inhibiting CD28-mediated costimulation of T-lymphocytes [42]. Unlike the lymphocyte-depleting agents, the effect on circulating Treg cells is unclear with studies showing both decreased and increased counts and function [34, 43–45].

Belatacept was introduced as a CNI-sparing agent for maintenance immunosuppression. Early studies (BENEFIT trial) showed an increased risk of early ACR episodes and increased risk for PTLD in EBV-seronegative patients [42, 46]. In both a Cochrane review and the 7-year follow-up studies, patients treated with belatacept were shown to have more AR but better renal function, less hypertension, improved lipid parameters, and less new-onset diabetes compared to patients receiving CSA-based maintenance immunosuppression [47–50]. To address the increased risk for AR, Wojciechowski et al. studied a protocol of low-dose rATG combined with belatacept induction followed by belatacept and everolimus maintenance therapy. This study of 44 adult patients showed an 11.3% 1-year AR rate, which was numerically lower than that seen in the BENEFIT study [51]. Kirk et al. showed that the increased early acute rejection risk could be overcome with a CNI and steroid-free regimen when belatacept is paired with alemtuzumab induction and sirolimus maintenance in adult patients [52]. The initial cohort consisted of 20 living donor kidney transplant recipients. Half of the cohort received donor bone marrow infusion as there is evidence that mTORi can promote the effects of co-stimulatory blockade, especially with high levels of circulating donor antigen. No patients in this trial developed DSA or had clinical rejection (three patients with subclinical rejection) in the first year, and 7/20 patients were able to successfully wean to belatacept monotherapy after 1 year. The 5-year follow-up study of an expanded cohort of 40 patients including deceased donor transplant recipients, expanded criteria donors, and those with pre-formed alloantibody did not include donor bone marrow infusions [53]. DSA developed in 5/40 patients, 4 had subclinical rejection detected on protocol biopsy in the first year, and only 2 patients experienced a clinical rejection event. There were no grafts lost due to rejection and 12/40 patients were able to wean to monotherapy with belatacept. These two studies showed that co-stimulatory blockade could successfully be employed at the time of transplant with comparable complication rates to standard induction protocols.

9.4.3 Comparison of Antibody Induction Agents

A prospective study compared the effects of alemtuzumab, rATG, and basiliximab on AR in high- and low-immunological risk patients. All patients had the same early steroid withdrawal, and CNI/MMF maintenance immunosuppression regimen. High-risk patients received either alemtuzumab or rATG, and low-risk patients received either alemtuzumab or basiliximab. By the first year after transplant, biopsy-confirmed AR was less frequent with alemtuzumab than with conventional therapy in the low-risk group, but no apparent difference was detected in the high-risk group [54]. Koyawala et al. compared outcomes in adult KT recipients based on induction agent utilizing OPTN data linked with Medicare claims data. The study showed higher mortality risk and odds ratio of AR with alemtuzumab and basiliximab, and higher risk of allograft failure in the alemtuzumab group compared to matched rATG recipients [55]. Similarly, Tanriover et al. compared outcomes based on induction regimen in adult living and deceased donor KT recipients. They showed that compared with no-induction therapy, IL2-RA induction was not associated with better outcomes when TAC/MPA/steroid maintenance was used. However, rATG appears to offer better graft survival compared to IL2-RA in steroid avoidance protocols [56, 57].

For patients considered to be at high-immunological risk including African Americans (AA), high HLA mismatch, and DGF, lymphocyte-depleting induction therapy as compared with IL2-RA reduces the risk of rejection, graft loss, and death [12, 58–61].

9.4.4 Chemical Agents (CNI, Corticosteroids)

Chemical agents for induction include corticosteroids, CSA, and tacrolimus. These are the same drugs that are used for maintenance immunosuppression except they may be used intravenously and usually in higher doses.

Corticosteroid induction followed by maintenance therapy has played a central role in the evolution of renal transplantation. It was and remains a cornerstone of immunosuppression in the majority of patients. Most studies have used 10–15 mg/kg of methylprednisolone (MP) in the operating room followed by steroid taper. Corticosteroids prevent T-cell activation by preventing release of T-cells and APC-derived cytokines such as IL-1, IL-2, IL-3, IL-6, TNF-α, and γ-interferon. In addition, corticosteroids are beneficial in reducing IRI, especially in deceased donor organ transplantation. In steroid avoidance protocols, steroids are still used for the first 5 days after transplant to help reduce IRI.

Tacrolimus is a highly protein-bound drug that binds to the immunophilin, FK-binding protein, within the cytoplasm of the cell. This causes inhibition of the calcineurin pathway preventing the generation of IL-2 and therefore inhibiting the proliferation of T-lymphocytes. The drug was introduced in the late 1980s and has been extensively used as a maintenance immunosuppressive drug since the mid-1990s. The side effects of tacrolimus are similar to those of cyclosporine,

except that fewer cosmetic side effects such as hirsutism and gingival hyperplasia are observed with tacrolimus. However, tacrolimus has more pronounced side effects on the neurological system and may have an increased incidence of post-transplant diabetes and PTLD as compared to CSA [62].

Studies with the use of IV tacrolimus as an induction agent are extremely limited and are really of historic interest only.

Mycophenolate mofetil (MMF) has been administered anywhere from 12 hours up to 14 days prior to transplant to allow for lower maintenance CNI doses [63]. Initial pharmacokinetic studies were done with patients on CSA and determined an ideal starting dose of 1200 mg/m2/day. Tacrolimus does not have the same effect on MMF metabolism and therefore lower starting doses (600–900 mg/m2/day) should result in similar AUC [64].

Other than IV methyl prednisolone, chemical agents are rarely used for induction.

9.5 Induction Strategies Based on Patient Risk

9.5.1 Induction Therapy in Standard-Risk Group

In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) guideline for "Care of Kidney Transplant Recipients" recommended induction therapy in all kidney transplant recipients (Level 1A) [65]. This guideline recommended children with standard immunological risk receive IL2-RA (basiliximab) as first-line therapy, but children at high-immunological risk receive lymphocyte-depleting induction. There is presently no consensus among pediatric kidney transplant centers regarding the use and optimal regimen for immunosuppressive induction therapy.

9.5.2 Induction Therapy with Steroid Avoidance

Sarwal et al. from Stanford University subsequently conducted single-center pilot trial that enrolled 57 pediatric renal transplant recipients in a steroid-free protocol using extended daclizumab induction followed by tacrolimus and MMF maintenance [66]. Study patients underwent serial protocol biopsies. The control group included 50 historical-matched steroid-based children receiving tacrolimus. In this study, 98% graft and patient survival was achieved in the steroid avoidance group. At 1 year of analysis, steroid-free recipients showed significant improvements in clinical AR, graft function, hypertension, and growth without an increase in infectious complications. Since that time, numerous studies have been published showing long-term (up to 5 years) safety and efficacy with early steroid withdrawal protocols utilizing lymphocyte depletion induction [67–72]. The benefits seen in all of these protocols are improved cardiovascular risk factors (blood pressure and lipids) and improved growth with comparable rates of AR and graft survival.

A direct comparison of alemtuzumab and rATG induction with complete steroid avoidance protocols was recently completed and showed no difference in 1-year

graft survival, low corticosteroid conversion in both groups, similar incidence of DSA, and biopsy-proven AR [73]. Notable differences between the groups included more leukopenia in the alemtuzumab group and more CMV viremia in the rATG group. However, there were other center-specific practices regarding MMF and valganciclovir dosing that may have contributed to the differences; therefore, they cannot be attributed to induction agent alone.

9.5.3 Induction Therapy in Diseases with a High Risk of Recurrence

9.5.3.1 Focal Segmental Glomerulosclerosis (FSGS)

Primary idiopathic FSGS recurs in 30% of patients receiving their first kidney transplant, >80% in a second transplant, and is associated with a high risk of graft failure [74]. The current theory that a humoral circulating factor is responsible for the disease has led to the specific targeted therapies added to standard induction immunosuppression [75].

Plasma exchange (PLEX) removes the patient's plasma and replaces it with pooled donor fresh frozen plasma (FFP) or albumin with the aim of removing the suspected offending circulating agent. This therapy is currently the mainstay of treatment of posttransplant FSGS recurrence. Two of the first prospective studies of preemptive use of PLEX in kidney transplant in adult and pediatric patients, utilizing varying numbers of PLEX treatments with differing time of initiation depending on living donor or deceased donor transplant, showed a reduced rate of FSGS recurrence; however, the numbers in both studies were very small (n = 10 and n = 21) [76, 77]. More recently, pediatric-specific data has not shown a benefit of preemptive PLEX in reducing recurrence of FSGS [78–80]. Given the cost and potential complications of this therapy, careful consideration of the risk/benefit in each individual patient is recommended as we await better powered studies to provide evidence-based guidance.

Rituximab is an anti-CD20 monoclonal antibody that depletes B-cells and suppresses antibody production. The mechanism of action in FSGS is not completely understood but thought to be through interference with the production of a circulating factor involved in FSGS pathogenesis, either through its direct effects on B-cells or through its indirect effects on T-cells [81]. In addition, some direct effect on podocyte structure has been theorized [82]. Rituximab has been used for treatment of documented recurrence and has been shown to help sustain remission in combination with PLEX; however, its use as an induction agent is limited [83]. Case reports have shown effectiveness of rituximab to prevent posttransplant FSGS [80, 81]. Rituximab was used successfully in a patient receiving a second kidney transplant, and in another patient, it was used as the only induction agent in an actively nephrotic patient with no disease recurrence with up to 30 months of follow-up [84, 85]. Ofatumumab (a fully humanized monoclonal antibody to CD20) has been used in three children with recurrent FSGS with attainment of full or partial remission after failing PLEX, CSA, and rituximab [86, 87]. This drug has not been used as part of an initial induction regimen and needs to be studied further.

Protein adsorption column and LDL apheresis have been described as treatment options for recurrence in a few case reports [88, 89]. There is one case report of five adult patients with primary FSGS who received perioperative LDL apheresis with a short follow-up time (60 days–22 months) with no recurrence events in this cohort [90].

Cyclosporine A has shown some degree of efficacy in pediatric patients with an up to 81% percent reduction in proteinuria in patients with recurrent disease. However, this is usually in combination with other therapies such as PLEX, and therefore the individual effect of this drug is difficult to determine [91, 92]. Unless we have reliable biomarkers of FSGS recurrence or these therapies are tried in a large number of patients in a randomized manner, the role of preemptive therapies remains anecdotal and speculative since only 30% patients have recurrence.

9.5.3.2 Atypical Hemolytic Uremic Syndrome (aHUS)

The unifying pathogenesis of aHUS is dysregulation of the alternative complement pathway caused by one or a combination of genetic mutations in the various regulatory proteins required to suppress this constitutively active pathway. Risk of recurrence is very high, up to 80% within the first 2 years, depending on which mutation is identified. There are three primary strategies to minimize risk of recurrence: [1] kidney transplant + PLEX, [2] kidney transplant + eculizumab, and [3] combined liver-kidney transplant [93].

PLEX with FFP replacement can ameliorate symptoms of aHUS by replacing the missing factor where the underlying pathophysiology is a deficiency of regulatory proteins. However, this therapy will be ineffective in the mutations caused by membrane cofactor protein (MCP) and can exacerbate aHUS in gain-of-function mutations. This regimen is associated with a high rate of complications and therefore is not an ideal option for patients with aHUS.

Eculizumab, a recombinant humanized monoclonal antibody that binds C5 and effectively stops its cleavage thus inhibiting the formation of terminal membrane attack complex (C5b-9), has revolutionized the care of adults and children with complement disorders. This drug should be used in combination with a standard induction regimen, the first dose to be given either given prior to surgery or within the first 24 hours following reperfusion. It should be continued indefinitely after transplant [94–96].

9.5.3.3 C3 Glomerulopathy (C3GN)

C3GN is a membranoproliferative glomerulonephritis mediated by alternative complement pathway dysregulation and has an estimated 50% risk of recurrence in the allograft. Recurrence usually occurs within the first 1–2 years and is characterized by decreasing renal function, proteinuria, hematuria, and/or hypocomplementemia [97]. Eculizumab has been used to treat recurrent C3GN; however, there are no data to support the prophylactic use of this drug as part of an induction regimen [94, 98].

9.5.4 Induction Therapy in Immunologically High-Risk (HLA-Sensitized) Patients

Patients are considered HLA sensitized if their panel reactive antibody (PRA) is greater than 30%. They are considered broadly sensitized if their PRA is >80% [99]. These antibodies make it difficult for them to receive a kidney transplant with a negative crossmatch (both with living and deceased donors); and wait times on dialysis are longer than the average low-risk patients. After transplant, they are at high risk for AMR and have a higher risk of graft loss [100]. Therefore, this group of patients presents a unique challenge to the transplant physicians.

Prior to consideration for transplantation, measures are undertaken to remove these antibodies and to suppress their production. This process is referred to as desensitization or immunomodulation. Several protocols for immunomodulation are available and have been studied; however, this is beyond the scope of this chapter [101–104].

Once the patient has undergone immunomodulation, and a kidney with an acceptable crossmatch is available, the induction immunosuppression regimen is intense and may consist of one or more of the following agents [105]. It is important to note that almost all studies of induction therapies in highly sensitized patients are in adults. It is also important to note that most studies are with a combination therapy, and therefore it is difficult to assess the efficacy of individual induction agents.

9.5.4.1 Intravenous Immunoglobulin: IVIg

IVIg has been the mainstay in the repertoire of induction agents used for HLA-sensitized patients. It was the very first agent used for desensitization and continues to be used as an induction agent in combination with other agents. IVIg is efficacious in reducing anti-HLA antibodies in vitro and in vivo [106]. This action is perhaps mediated through an anti-idiotypic antibody-blocking effect; it is also a modifier of complement activation and injury [107].

The IG02 placebo-controlled study assessed the use of IVIg vs placebo as an induction agent in 24 highly sensitized adult kidney transplant recipients. Patients received 2grams/kg IVIg (maximum dose of 140 grams). IVIg was superior to placebo for the reduction of HLA antibodies and improving the rates of transplantation, with similar rates of adverse events in both groups [101]. A single pediatric study showed the efficacy of IVIg along with rATG induction in successful transplantation of a 7-year-old highly sensitized child [108].

IVIg products are derived from pooled human sera, and several IVIg preparations are currently available on the market, differing with regard to excipient compounds. The adverse effects of each preparation differ based on the excipient used, and therefore proper product selection is important [109]. In general, sucrose-free products decrease the risk of acute kidney injury (AKI), and splitting the dose of IVIg and giving over a longer period of time might mitigate the risk of thrombosis seen with these products [110].

9.5.4.2 Alemtuzumab

Alemtuzumab has been used for induction in highly sensitized pediatric patients. In a pediatric study, 15 highly sensitized patients underwent induction with alemtuzumab (15–30 mg as a one-time subcutaneous injection) [111]. This group was compared to 35 non-sensitized patients who had received basiliximab induction. Although there was a higher risk of acute cellular rejection in the highly sensitized group, the rates of AMR were comparable. WBC count and absolute lymphocyte count were significantly lower in the alemtuzumab group at 30 days and 1 year; however, the rates of viral, bacterial, and fungal infections were comparable. Patient survival was 100% with excellent graft survival in both groups. In another pediatric study, three highly sensitized patients were successfully transplanted after desensitization and alemtuzumab induction with stable 3-year graft function [112].

9.5.4.3 Antithymocyte Globulin

Various dosing regiments of rATG have been used in highly sensitized patients ranging from a single dose at 9 mg/kg given in the perioperative period to 1.5 mg/kg/day for 4–5 days for a total of 6 mg/kg [113, 114]. The incidence of AR was comparable to low-risk patients receiving non-lymphocyte-depleting agents for induction [115]. A study comparing rATG to alemtuzumab induction in adult highly sensitized patients showed a significantly lower incidence of AR and DGF with alemtuzumab [116]. However, the incidence of AR decreased when rATG was combined with rituximab for induction therapy [21].

There are reports of two highly sensitized children treated with rATG induction who had stable graft function and no detectable CMV, EBV, and BK viremia, at 1-year posttransplantation [108, 112].

9.5.4.4 Rituximab

Rituximab has been successfully used in desensitization protocols in combination with IVIg and PLEX. The typical dose for induction is 375 mg/m2 as a one-time dose given in the perioperative period. Several adult studies have shown beneficial effect and stable allograft function with the use of rituximab alone or in combination with IVIG or rATG [21, 117, 118].

Rituximab may be associated with increased risk of hypogammaglobulinemia and infections. However, two reports did not show increased risk of infectious complications in highly sensitized renal transplant recipients treated with rituximab either for induction or for the treatment of AMR [119, 120].

9.5.4.5 Eculizumab

In a rat model of acute AMR after kidney transplant, terminal complement blockade preserved allograft function resulting in significantly longer graft survival than in those not treated with C5 blockade [121]. Eculizumab has been used as an induction agent in highly sensitized adult patients to mitigate the risk of AMR. Nine weeks of eculizumab (starting on the day of transplant) was used in 80 highly sensitized

patients in combination with rATG induction, and the drug was well tolerated [111, 122]. At 36 months, graft and patient survival rates were 83.4% and 91.5%, respectively. Similar results have been noted in other studies [123, 124].

Because of the association between terminal complement inhibition and *Neisseria meningitidis* infection, patients are required to be vaccinated for it at least 14 days before receiving the first dose of eculizumab or to be vaccinated at the time of transplant and receive prophylaxis with an appropriate antibiotic for 14 days after the vaccination.

9.5.4.6 C1-INH (Berinert; CSL Behring, King of Prussia, Penn)

C1-INH is a serine protease inhibitor which inhibits complement activation by interrupting C1s and C1r in the classic complement pathway [125]. It is also a potent inhibitor of the lectin complement pathway by neutralizing lipopolysaccharides, thereby inhibiting both sepsis and endotoxin shock in animal models. It plays an important role in vascular permeability and its deficiency leads to hereditary angioedema [126].

In a placebo-controlled trial in highly sensitized adult transplant recipients, C1-INH used with alemtuzumab induction was noted to be safe with no significant adverse events. No AMR episodes were observed, and C1-INH therapy led to reductions in levels of C1q HLA antibodies, thus indicating its role in prevention of AMR. It has also been shown to prevent DGF in a randomized placebo-controlled trial [127].

9.5.4.7 Bortezomib

The drug works by inhibiting proteasomes, cellular complexes that break down proteins, and specifically target antibody-producing plasma cells. It has been used in conjunction with pheresis to treat AMR and for desensitization, but reports of its use as an induction agent are very limited. Bortezomib is associated with peripheral neuropathy in 30% of patients [128].

9.5.4.8 Imlifidase

Imlifidase contains the IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS), an endopeptidase that cleaves human IgG into $F(ab')_2$ and Fc fragments inhibiting both complement-dependent and antibody-dependent cytotoxicity. Imlifidase therefore can be useful as an induction agent in highly sensitized patients.

IdeS was administered to 25 highly HLA-sensitized patients (11 patients in Stockholm, Sweden, and 14 in Los Angeles, USA) before the transplantation of a kidney from an HLA-incompatible donor. Frequent monitoring for renal function, adverse events, outcomes, donor-specific antibodies, and renal biopsies were performed. Maintenance immunosuppression consisted of tacrolimus, MMF, and steroids. IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients [129]. In a study by Lonze et al., Ides was used in seven highly sensitized patients prior to renal transplantation. Three out of seven patients had rebound in DSA and ABMR that responded to standard of care. Therefore, patients in the Ides study in the USA also received IVIg and rituximab after transplantation to prevent antibody rebound [130].

Very few highly sensitized pediatric patients have received renal transplant after desensitization due to availability of other options for children including receiving an organ though donor exchange registries or by preferentially allocating kidneys to these children as was done in a recent Italian study [131]. However, there are a few patients who are running out of dialysis access due to prolonged time on dialysis and may benefit from such therapies. Due to lack of sufficient data, most treatments in children are guided by adult studies. However, it is very important to have long-term follow-up data in children to assess if these therapies have unique effects on growth and development in children and young adults.

9.6 Current Practices in the USA

The KDIGO guidelines recommended induction therapy in all kidney transplant recipients (Level 1A) [65]. They recommend children with standard immunological risk receive IL2-RA (basiliximab) as first-line therapy and that polyclonal agents be reserved for patients determined to have high-immunological risk (black race, allosensitization, younger age). Peritransplant events such as DGF, prolonged cold ischemia time, high number of HLA mismatches, and in recipients of donors with higher kidney disease profile index (KDPI) may also warrant antibody induction therapy [12].

Despite these recommendations to stratify induction immunosuppression based on patient risk, this is not reflected in an analysis of practice patterns. Dharnidharka et al. evaluated induction immunosuppression for all adult and pediatric patients who received a kidney transplant from 2005 to 2014 utilizing the SRTR database and found that only a minority of variation in induction immunosuppression choice was a result of donor/patient factors, and the majority was a result of center-practice patterns [132].

The 2018 UNOS/OPTN report shows that the most commonly used induction agents are T-cell-depleting preparations, followed by IL2-RA, and no-induction agent staying static over the last 2 years [133, 134].

9.7 Conclusions

The goal of available induction therapies in conjunction with maintenance immunosuppression is to prevent AR and its deleterious effects on the allograft. It is pertinent to find the least toxic, steroid-sparing, and cost-effective induction regimen. Currently, induction is commonly used for most pediatric transplants and for all high-risk patients including those who are receiving a re-transplant, highly sensitized, cross-match positive and with DGF or those at risk for DGF, and those at risk of recurrence of their native kidney disease. Most recently, innovative induction protocols are being used to minimize maintenance immunosuppression. However, more pediatric data is needed to ensure risks and safety profile in growing children and adolescents.

References

1. Yatim KM, Lakkis FG. A brief journey through the immune system. Clin J Am Soc Nephrol CJASN. 2015;10(7):1274–81.
2. Murphy K. Paul travers, mark Walport, and Charles Janeway. Janeway's Immunobiology. New York: Garland Science; 2008.
3. Shoskes DA, Parfrey NA, Halloran PF. Increased major histocompatibility complex antigen expression in unilateral ischemic acute tubular necrosis in the mouse. Transplantation. 1990;49(1):201–7.
4. Najarian JS, Ferguson RM, Sutherland DE, Slavin S, Kim T, Kersey J, et al. Fractionated total lymphoid irradiation as preparative immunosuppression in high risk renal transplantation: clinical and immunological studies. Ann Surg. 1982;196(4):442–52.
5. Levin B, Hoppe RT, Collins G, Miller E, Waer M, Bieber C, et al. Treatment of cadaveric renal transplant recipients with total lymphoid irradiation, antithymocyte globulin, and low-dose prednisone. Lancet (London, England). 1985;2(8468):1321–5.
6. Slavin S, Strober S, Fuks Z, Kaplan HS. Immunosuppression and organ transplantation tolerance using total lymphoid irradiation. Diabetes. 1980;29(Suppl 1):121–3.
7. Myburgh JA, Smit JA, Stark JH, Browde S. Total lymphoid irradiation in kidney and liver transplantation in the baboon: prolonged graft survival and alterations in T cell subsets with low cumulative dose regimens. J Immunol. 1984;132(2):1019–25.
8. Wiseman AC. Immunosuppressive Medications. Clin J Am Soc Nephrol. 2016;11(2):332–43.
9. Tang Q, Leung J, Melli K, Lay K, Chuu EL, Liu W, et al. Altered balance between effector T cells and FOXP3+ HELIOS+ regulatory T cells after thymoglobulin induction in kidney transplant recipients. Transplant Int. 2012;25(12):1257–67.
10. Brennan DC, Flavin K, Lowell JA, Howard TK, Shenoy S, Burgess S, et al. A randomized, double-blinded comparison of thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. Transplantation. 1999;67(7):1011–8.
11. Hardinger KL, Schnitzler MA, Miller B, Lowell JA, Shenoy S, Koch MJ, et al. Five-year follow up of thymoglobulin versus ATGAM induction in adult renal transplantation. Transplantation. 2004;78(1):136–41.
12. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355(19):1967–77.
13. Ault BH, Honaker MR, Osama Gaber A, Jones DP, Duhart BT Jr, Powell SL, et al. Short-term outcomes of thymoglobulin induction in pediatric renal transplant recipients. Pediatr Nephrol. 2002;17(10):815–8.
14. Khositseth S, Matas A, Cook ME, Gillingham KJ, Chavers BM. Thymoglobulin versus ATGAM induction therapy in pediatric kidney transplant recipients: a single-center report. Transplantation. 2005;79(8):958–63.
15. Klem P, Cooper JE, Weiss AS, Gralla J, Owen P, Chan L, et al. Reduced dose rabbit antithymocyte globulin induction for prevention of acute rejection in high-risk kidney transplant recipients. Transplantation. 2009;88(7):891–6.
16. Nafar M, Dalili N, Poor-Reza-Gholi F, Ahmadpoor P, Samadian F, Samavat S. The appropriate dose of thymoglobulin induction therapy in kidney transplantation. Clin Transpl. 2017;31(6)
17. Marvin MR, Droogan C, Sawinski D, Cohen DJ, Hardy MA. Administration of rabbit antithymocyte globulin (thymoglobulin) in ambulatory renal-transplant patients. Transplantation. 2003;75(4):488–9.
18. Purohit-Sheth T. FDA Approval Letter 2017 [Available from: https://www.fda.gov/media/104907/download.
19. James A, Mannon RB. The cost of transplant immunosuppressant therapy: is this sustainable? Curr Trans Rep. 2015;2(2):113–21.

20. Martinez-Mier G, Moreno-Ley PI, Budar-Fernandez LF, Mendez-Lopez MT, Allende-Castellanos CA, Jimenez-Lopez LA, et al. Low-dose thymoglobulin vs Basiliximab induction therapy in low-risk living related kidney transplant recipients: a prospective randomized trial. Transplant Proc. 2020;53:1005.
21. Laftavi MR, Pankewycz O, Feng L, Said M, Patel S. Combined induction therapy with rabbit antithymocyte globulin and rituximab in highly sensitized renal recipients. Immunol Investig. 2015;44(4):373–84.
22. Ciancio G, Burke GW, Gaynor JJ, Carreno MR, Cirocco RE, Mathew JM, et al. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. Transplantation. 2005;80(4):457–65.
23. Bloom DD, Chang Z, Fechner JH, Dar W, Polster SP, Pascual J, et al. CD4+ CD25+ FOXP3+ regulatory T cells increase de novo in kidney transplant patients after immunodepletion with Campath-1H. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2008;8(4):793–802.
24. Calne R, Moffatt SD, Friend PJ, Jamieson NV, Bradley JA, Hale G, et al. Campath IH allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. Transplantation. 1999;68(10):1613–6.
25. Knechtle SJ, Pirsch JD, Fechner JH, Becker BN, Friedl A, Colvin RB, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation: results of a pilot study. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2003;3(6):722–30.
26. Flechner SM, Friend PJ, Brockmann J, Ismail HR, Zilvetti M, Goldfarb D, et al. Alemtuzumab induction and sirolimus plus mycophenolate mofetil maintenance for CNI and steroid-free kidney transplant immunosuppression. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2005;5(12):3009–14.
27. Watson CJ, Bradley JA, Friend PJ, Firth J, Taylor CJ, Bradley JR, et al. Alemtuzumab (CAMPATH 1H) induction therapy in cadaveric kidney transplantation--efficacy and safety at five years. Am J Transplant. 2005;5(6):1347–53.
28. Shapiro R, Ellis D, Tan HP, Moritz ML, Basu A, Vats AN, et al. Antilymphoid antibody preconditioning and tacrolimus monotherapy for pediatric kidney transplantation. J Pediatr. 2006;148(6):813–8.
29. Sung J, Barry JM, Jenkins R, Rozansky D, Iragorri S, Conlin M, et al. Alemtuzumab induction with tacrolimus monotherapy in 25 pediatric renal transplant recipients. Pediatr Transplant. 2013;17(8):718–25.
30. Tan HP, Donaldson J, Ellis D, Moritz ML, Basu A, Morgan C, et al. Pediatric living donor kidney transplantation under alemtuzumab pretreatment and tacrolimus monotherapy: 4-year experience. Transplantation. 2008;86(12):1725–31.
31. Vo AA, Wechsler EA, Wang J, Peng A, Toyoda M, Lukovsky M, et al. Analysis of subcutaneous (SQ) alemtuzumab induction therapy in highly sensitized patients desensitized with IVIG and rituximab. Am J Transplant. 2008;8(1):144–9.
32. Haynes R, Harden P, Judge P, Blackwell L, Emberson J, Landray MJ, et al. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C study): a randomised trial. Lancet (London, England). 2014;384(9955):1684–90.
33. Hill P, Cross NB, Barnett ANR, Palmer SC, Webster AC. Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. Cochrane Database Syst Rev. 2017;1
34. Bluestone JA, Liu W, Yabu JM, Laszik ZG, Putnam A, Belingheri M, et al. The effect of costimulatory and interleukin 2 receptor blockade on regulatory T cells in renal transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2008;8(10):2086–96.
35. Garcia CD, Barros VR, Schneider L, Alves MD, Silveira CG, Garcia VD. IL-2 antibody induction and the outcome of pediatric renal transplants. Transplant Proc. 2002;34(7):2914–5.

36. Garcia Meseguer C, Vila Lopez A, Luque de Pablos A, Vallo Boado A, Simon JM. Immunoprophylaxis with Simulect (basiliximab) in pediatric kidney transplant recipients: results from routine clinical practice at 5 kidney transplant units. Transplant Proc. 2003;35(5):1697–8.
37. Ciancio G, Burke GW, Suzart K, Mattiazzi A, Rosen A, Zilleruello G, et al. Effect of daclizumab, tacrolimus, and mycophenolate mofetil in pediatric first renal transplant recipients. Transplant Proc. 2002;34(5):1944–5.
38. Benfield M, tA, Ping-Leung H. Comparative study of the safety, efficacy, and practice patterns of monoclonal antibodies in pediatric renal transplantation (abstract). Washington, DC, USA: American Transplant Congress; 2002. 2002.
39. Smith JM, Stablein D, Singh A, Harmon W, McDonald RA. Decreased risk of renal allograft thrombosis associated with interleukin-2 receptor antagonists: a report of the NAPRTCS. Am J Transplant. 2006;6(3):585–8.
40. Webster AC, Ruster LP, McGee R, Matheson SL, Higgins GY, Willis NS, et al. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev. 2010;2010(1):CD003897.
41. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. Drugs. 2003;63(24):2803–35.
42. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2010;10(3):535–46.
43. Alvarez Salazar EK, Cortes-Hernandez A, Aleman-Muench GR, Alberu J, Rodriguez-Aguilera JR, Recillas-Targa F, et al. Methylation of FOXP3 TSDR underlies the impaired suppressive function of Tregs from long-term Belatacept-treated kidney transplant patients. Front Immunol. 2017;8:219.
44. Tang Q, Henriksen KJ, Boden EK, Tooley AJ, Ye J, Subudhi SK, et al. Cutting edge: CD28 controls peripheral homeostasis of CD4+CD25+ regulatory T cells. J Immunol. (Baltimore, Md : 1950). 2003;171(7):3348–52.
45. Grimbert P, Audard V, Diet C, Matignon M, Plonquet A, Mansour H, et al. T-cell phenotype in protocol renal biopsy from transplant recipients treated with belatacept-mediated co-stimulatory blockade. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011;26(3):1087–93.
46. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2010;10(3):547–57.
47. Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. Cochrane Database Syst Rev. 2014;2014(11):CD010699.
48. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med. 2016;374(4):333–43.
49. Durrbach A, Pestana JM, Florman S, Del Carmen RM, Rostaing L, Kuypers D, et al. Long-term outcomes in Belatacept- versus cyclosporine-treated recipients of extended criteria donor kidneys: final results from BENEFIT-EXT, a phase III randomized study. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2016;16(11):3192–201.
50. Woodle ES, Kaufman DB, Shields AR, Leone J, Matas A, Wiseman A, et al. Belatacept-based immunosuppression with simultaneous calcineurin inhibitor avoidance and early corticosteroid withdrawal: A prospective, randomized multicenter trial. Am J Transplant. 20(4):1039–55.
51. Wojciechowski D, Chandran S, Yang JYC, Sarwal MM, Vincenti F. Retrospective evaluation of the efficacy and safety of belatacept with thymoglobulin induction and maintenance everolimus: a single-center clinical experience. Clin Transpl. 2017;31(9)

52. Kirk AD, Guasch A, Xu H, Cheeseman J, Mead SI, Ghali A, et al. Renal transplantation using belatacept without maintenance steroids or calcineurin inhibitors. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2014;14(5):1142–51.
53. Schmitz R, Fitch ZW, Xu H, Ghali A, Mehta AK, Guasch A, et al. Kidney transplantation using alemtuzumab, belatacept, and sirolimus: five-year follow-up. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2020;20:3609.
54. Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, et al. Alemtuzumab induction in renal transplantation. N Engl J Med. 2011;364(20):1909–19.
55. Koyawala N, Silber JH, Rosenbaum PR, Wang W, Hill AS, Reiter JG, et al. Comparing outcomes between antibody induction therapies in kidney transplantation. J Am Soc Nephrol JASN. 2017;28(7):2188–200.
56. Tanriover B, Zhang S, MacConmara M, Gao A, Sandikci B, Ayvaci MU, et al. Induction therapies in live donor kidney transplantation on tacrolimus and mycophenolate with or without steroid maintenance. Clin J Am Soc Nephrol CJASN. 2015;10(6):1041–9.
57. Tanriover B, Jaikaransingh V, MacConmara MP, Parekh JR, Levea S-L, Ariyamuthu VK, et al. Acute rejection rates and graft outcomes according to induction regimen among recipients of kidneys from deceased donors treated with tacrolimus and mycophenolate. Clin J Am Soc Nephrol CJASN. 2016;11(9):1650–61.
58. Padiyar A, Hricik DE. Immune factors influencing ethnic disparities in kidney transplantation outcomes. Expert Rev Clin Immunol. 2011;7(6):769–78.
59. Taber DJ, McGillicuddy JW, Bratton CF, Rohan VS, Nadig S, Dubay D, et al. Cytolytic induction therapy improves clinical outcomes in African-American kidney transplant recipients. Ann Surg. 2017;266(3):450–6.
60. Sureshkumar KK, Chopra B. Induction type and outcomes in HLA-DR mismatch kidney transplantation. Transplant Proc. 2019;51(6):1796–800.
61. Lentine KL, Schnitzler MA, Xiao H, Brennan DC. Long-term safety and efficacy of antithymocyte globulin induction: use of integrated national registry data to achieve ten-year follow-up of 10-10 study participants. Trials. 2015;16:365.
62. Torres A, Hernández D, Moreso F, Serón D, Burgos MD, Pallardó LM, et al. Randomized controlled trial assessing the impact of tacrolimus versus cyclosporine on the incidence of Posttransplant diabetes mellitus. Kidney Int Rep. 2018;3(6):1304–15.
63. Maamoun H, Soliman A, Zayed B. Cyclosporine and mycophenolate mofetil 48 hours before renal transplantation enables the use of low cyclosporine doses and achieves better graft function. Transplant Proc. 2010;42(10):4033–6.
64. Ettenger R, Sarwal MM. Mycophenolate mofetil in pediatric renal transplantation. Transplantation. 2005;80(2 Suppl):S201–10.
65. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2009;9(Suppl 3):S1–155.
66. Sarwal MM, Vidhun JR, Alexander SR, Satterwhite T, Millan M, Salvatierra O Jr. Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. Transplantation. 2003;76(9):1331–9.
67. Supe-Markovina K, Melquist JJ, Connolly D, DiCarlo HN, Waltzer WC, Fine RN, et al. Alemtuzumab with corticosteroid minimization for pediatric deceased donor renal transplantation: a seven-yr experience. Pediatr Transplant. 2014;18(4):363–8.
68. Warejko JK, Hmiel SP. Single-center experience in pediatric renal transplantation using thymoglobulin induction and steroid minimization. Pediatr Transplant. 2014;18(8):816–21.
69. Sarwal MM, Ettenger RB, Dharnidharka V, Benfield M, Mathias R, Portale A, et al. Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2012;12(10):2719–29.
70. Barletta GM, Kirk E, Gardner JJ, Rodriguez JF, Bursach SM, Bunchman TE. Rapid discontinuation of corticosteroids in pediatric renal transplantation. Pediatr Transplant. 2009;13(5):571–8.

71. Grenda R, Watson A, Trompeter R, Tonshoff B, Jaray J, Fitzpatrick M, et al. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2010;10(4):828–36.
72. Li L, Chang A, Naesens M, Kambham N, Waskerwitz J, Martin J, et al. Steroid-free immunosuppression since 1999: 129 pediatric renal transplants with sustained graft and patient benefits. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2009;9(6):1362–72.
73. Puliyanda DP, Pizzo H, Rodig N, Somers MJG. Early outcomes comparing induction with antithymocyte globulin vs alemtuzumab in two steroid-avoidance protocols in pediatric renal transplantation. Pediatr Transplant. 2020;2020:e13685.
74. Artero M, Biava C, Amend W, Tomlanovich S, Vincenti F. Recurrent focal glomerulosclerosis: natural history and response to therapy. Am J Med. 1992;92(4):375–83.
75. Savin VJ, McCarthy ET, Sharma M. Permeability factors in nephrotic syndrome and focal segmental glomerulosclerosis. Kidney Res Clin Pract. 2012;31(4):205–13.
76. Gohh RY, Yango AF, Morrissey PE, Monaco AP, Gautam A, Sharma M, et al. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. Am J Transplant. 2005;5(12):2907–12.
77. Ohta T, Kawaguchi H, Hattori M, Komatsu Y, Akioka Y, Nagata M, et al. Effect of pre-and postoperative plasmapheresis on posttransplant recurrence of focal segmental glomerulosclerosis in children. Transplantation. 2001;71(5):628–33.
78. Gonzalez E, Ettenger R, Rianthavorn P, Tsai E, Malekzadeh M. Preemptive plasmapheresis and recurrence of focal segmental glomerulosclerosis in pediatric renal transplantation. Pediatr Transplant. 2011;15(5):495–501.
79. Verghese PS, Rheault MN, Jackson S, Matas AJ, Chinnakotla S, Chavers B. The effect of peri-transplant plasmapheresis in the prevention of recurrent FSGS. Pediatr Transplant. 2018;22(3):e13154.
80. Mahesh S, Del Rio M, Feuerstein D, Greenstein S, Schechner R, Tellis V, et al. Demographics and response to therapeutic plasma exchange in pediatric renal transplantation for focal glomerulosclerosis: a single center experience. Pediatr Transplant. 2008;12(6):682–8.
81. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2006;6(5 Pt 1):859–66.
82. Fornoni A, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med. 2011;3(85):85ra46.
83. Hickson LJ, Gera M, Amer H, Iqbal CW, Moore TB, Milliner DS, et al. Kidney transplantation for primary focal segmental glomerulosclerosis: outcomes and response to therapy for recurrence. Transplantation. 2009;87(8):1232–9.
84. Kolonko A, Piecha G, Więcek A. Successful preemptive kidney transplantation with rituximab induction in a patient with focal segmental glomerulosclerosis and massive nephrotic syndrome: a case report. Transplant Proc. 2016;48(9):3092–4.
85. Audard V, Kamar N, Sahali D, Cardeau-Desangles I, Homs S, Remy P, et al. Rituximab therapy prevents focal and segmental glomerulosclerosis recurrence after a second renal transplantation. Transpl Int. 2012;25(5):e62–e6.
86. Solomon S, Zolotnitskaya A, Del Rio M. Ofatumumab in post-transplantation recurrence of focal segmental glomerulosclerosis in a child. Pediatr Transplant. 2019;23(4):e13413.
87. Colucci M, Labbadia R, Vivarelli M, Camassei FD, Emma F, Dello Strologo L. Ofatumumab rescue treatment in post-transplant recurrence of focal segmental glomerulosclerosis. Pediatr Nephrol. 2020;35(2):341–5.
88. Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jacques Y, et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med. 1994;330(1):7–14.

89. Shah L, Hooper DK, Okamura D, Wallace D, Moodalbail D, Gluck C, et al. LDL-apheresis-induced remission of focal segmental glomerulosclerosis recurrence in pediatric renal transplant recipients. Pediatr Nephrol. 2019;34(11):2343–50.
90. Sannomiya A, Murakami T, Koyama I, Nitta K, Nakajima I, Fuchinoue S. Preoperative low-density lipoprotein apheresis for preventing recurrence of focal segmental glomerulosclerosis after kidney transplantation. Journal of transplantation. 2018;2018:8926786.
91. Salomon R, Gagnadoux M-F, Niaudet P. Intravenous cyclosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. Transplantation. 2003;75(6):810–4.
92. Raafat RH, Kalia A, Travis LB, Diven SC. High-dose oral cyclosporin therapy for recurrent focal segmental glomerulosclerosis in children. Am J kidney Dis. 2004;44(1):50–6.
93. Sanghera P, Ghanta M, Ozay F, Ariyamuthu VK, Tanriover B. Kidney diseases associated with alternative complement pathway dysregulation and potential treatment options. Am J Med Sci. 2017;354(6):533–8.
94. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V. On behalf of the French study group for a HCG. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012;8(11):643–57.
95. Zuber J, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012;12(12):3337–54.
96. Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with Eculizumab: a systematic review and meta-analysis. J Clin Med. 2019;8(7)
97. Zand L, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, Gandhi MJ, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol JASN. 2014;25(5):1110–7.
98. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Fremeaux-Bacchi V, Kavanagh D, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference. Kidney Int. 2017;91(3):539–51.
99. Jordan SC, Reinsmoen N, Lai CH, Cao K, Kahwaji J, Peng A, et al. Desensitizing the broadly human leukocyte antigen-sensitized patient awaiting deceased donor kidney transplantation. Transplant Proc. 2012;44(1):60–1.
100. Lee KW, Kim SJ, Lee DS, Lee HH, Joh JW, Lee SK, et al. Effect of panel-reactive antibody positivity on graft rejection before or after kidney transplantation. Transplant Proc. 2004;36(7):2009–10.
101. Jordan SC, Tyan D, Stablein D, McIntosh M, Rose S, Vo A, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol JASN. 2004;15(12):3256–62.
102. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242–51.
103. Vo AA, Petrozzino J, Yeung K, Sinha A, Kahwaji J, Peng A, et al. Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab. Transplantation. 2013;95(6):852–8.
104. Jordan SC, Choi J, Vo A. Kidney transplantation in highly sensitized patients. Br Med Bull. 2015;114(1):113–25.
105. Reinsmoen NL, Lai CH, Vo A, Cao K, Ong G, Naim M, et al. Acceptable donor-specific antibody levels allowing for successful deceased and living donor kidney transplantation after desensitization therapy. Transplantation. 2008;86(6):820–5.
106. Tyan DB, Li VA, Czer L, Trento A, Jordan SC. Intravenous immunoglobulin suppression of HLA alloantibody in highly sensitized transplant candidates and transplantation with a histoincompatible organ. Transplantation. 1994;57(4):553–62.

107. Jordan SC, Toyoda M, Vo AA. Intravenous immunoglobulin a natural regulator of immunity and inflammation. Transplantation. 2009;88(1):1–6.
108. Al-Uzri AY, Seltz B, Yorgin PD, Spier CM, Andreoni K. Successful renal transplant outcome after intravenous gamma-globulin treatment of a highly sensitized pediatric recipient. Pediatr Transplant. 2002;6(2):161–5.
109. Vo AA, Cam V, Toyoda M, Puliyanda DP, Lukovsky M, Bunnapradist S, et al. Safety and adverse events profiles of intravenous gammaglobulin products used for immunomodulation: a single-center experience. Clin J Am Soc Nephrol. 2006;1(4):844–52.
110. Kahwaji J, Barker E, Pepkowitz S, Klapper E, Villicana R, Peng A, et al. Acute hemolysis after high-dose intravenous immunoglobulin therapy in highly HLA sensitized patients. Clin J Am Soc Nephrol. 2009;4(12):1993–7.
111. Kim IK, Choi J, Vo AA, Kang A, Patel M, Toyoda M, et al. Safety and efficacy of Alemtuzumab induction in highly sensitized pediatric renal transplant recipients. Transplantation. 2017;101(4):883–9.
112. Pirojsakul K, Desai D, Lacelle C, Seikaly MG. Management of sensitized pediatric patients prior to renal transplantation. Pediatr Nephrol. 2016;31(10):1691–8.
113. Ribeiro MP, Sandes-Freitas TV, Sato KH, Ribeiro Junior MA, Silva-Junior HT, Medina-Pestana JO. Effect of induction therapy in kidney transplantation in sensitive patients: analysis of risks and benefits. J Bras Nefrol. 2016;38(1):82–9.
114. Itabashi Y, Aikawa A, Muramatsu M, Hyoudou Y, Shinoda K, Takahashi Y, et al. Living-donor kidney transplant with preformed donor-specific antibodies. Exp Clin Transplant. 2019;17(Suppl 1):43–9.
115. Mai ML, Ahsan N, Wadei HM, Genco PV, Geiger XJ, Willingham DL, et al. Excellent renal allograft survival in donor-specific antibody positive transplant patients-role of intravenous immunoglobulin and rabbit antithymocyte globulin. Transplantation. 2009;87(2):227–32.
116. Shamsaeefar A, Roozbeh J, Khajerezae S, Nikeghbalian S, Kazemi K, Motazedian N, et al. Effects of induction therapy with alemtuzumab versus antithymocyte globulin among highly sensitized kidney transplant candidates. Saudi J Kidney Dis Transpl. 2016;27(4):665–70.
117. Yin H, Wan H, Hu XP, Li XB, Wang W, Liu H, et al. Rituximab induction therapy in highly sensitized kidney transplant recipients. Chin Med J. 2011;124(13):1928–32.
118. Querido S, Weigert A, Adragao T, Henriques J, Birne R, Matias P, et al. Intravenous immunoglobulin and rituximab in HLA highly sensitized kidney transplant recipients. Transplant Proc. 2018;50(3):723–7.
119. Scemla A, Loupy A, Candon S, Mamzer MF, Martinez F, Zuber J, et al. Incidence of infectious complications in highly sensitized renal transplant recipients treated by rituximab: a case-controlled study. Transplantation. 2010;90(11):1180–4.
120. Jackson AM, Kraus ES, Orandi BJ, Segev DL, Montgomery RA, Zachary AA. A closer look at rituximab induction on HLA antibody rebound following HLA-incompatible kidney transplantation. Kidney Int. 2015;87(2):409–16.
121. Yu ZX, Qi S, Lasaro MA, Bouchard K, Dow C, Moore K, et al. Targeting complement pathways during cold ischemia and reperfusion prevents delayed graft function. Am J Transplant. 2016;16(9):2589–97.
122. Glotz D, Russ G, Rostaing L, Legendre C, Tufveson G, Chadban S, et al. Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. Am J Transplant. 2019;19(10):2865–75.
123. Stegall MD, Diwan T, Raghavaiah S, Cornell LD, Burns J, Dean PG, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011;11(11):2405–13.
124. Cornell LD, Schinstock CA, Gandhi MJ, Kremers WK, Stegall MD. Positive crossmatch kidney transplant recipients treated with eculizumab: outcomes beyond 1 year. Am J Transplant. 2015;15(5):1293–302.
125. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513–22.

126. Heydenreich N, Nolte MW, Gob E, Langhauser F, Hofmeister M, Kraft P, et al. C1-inhibitor protects from brain ischemia-reperfusion injury by combined antiinflammatory and antithrombotic mechanisms. Stroke. 2012;43(9):2457–67.
127. Vo AA, Zeevi A, Choi J, Cisneros K, Toyoda M, Kahwaji J, et al. A phase I/II placebo-controlled trial of C1-inhibitor for prevention of antibody-mediated rejection in HLA sensitized patients. Transplantation. 2015;99(2):299–308.
128. Ejaz NS, Shields AR, Alloway RR, Sadaka B, Girnita AL, Mogilishetty G, et al. Randomized controlled pilot study of B cell-targeted induction therapy in HLA sensitized kidney transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2013;13(12):3142–54.
129. Jordan SC, Lorant T, Choi J. IgG endopeptidase in highly sensitized patients undergoing transplantation. N Engl J Med. 2017;377(17):1693–4.
130. Lonze BE, Tatapudi VS, Weldon EP, Min ES, Ali NM, Deterville CL, et al. IdeS (Imlifidase): a novel agent that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. Ann Surg. 2018;268(3):488–96.
131. Dello Strologo L, Murer L, Guzzo I, Morolli F, Pipicelli AM, Benetti E, et al. Renal transplantation in sensitized children and young adults: a nationwide approach. Nephrol Dial Transpl. 2017;32(1):191–5.
132. Dharnidharka VR, Naik AS, Axelrod DA, Schnitzler MA, Zhang Z, Bae S, et al. Center practice drives variation in choice of US kidney transplant induction therapy: a retrospective analysis of contemporary practice. Transpl Int. 2018;31(2):198–211.
133. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, et al. OPTN/SRTR 2018 annual data report: kidney. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2020;20(Suppl s1):20–130.
134. Hellemans R, Bosmans JL, Abramowicz D. Induction therapy for kidney transplant recipients: do we still need anti-IL2 receptor monoclonal antibodies? Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2017;17(1):22–7.