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Chapter 7

Modern Immunosuppression Regimens in Kidney Transplantation

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Historical Background of Induction Therapy

The initial results of kidney transplantation were significantly affected by a high rate of acute rejection as well as significant perioperative morbidity. Historically, the armamentarium of the transplant physician consisted of glucocorticoids and azathioprine. Significant improvements in the science and understanding of kidney transplantation immunology have lead to the development of induction therapy agents. Early induction therapy agents possessed little specificity and delivered a broad spectrum of effects; however, their potent ability to prevent early acute rejection episodes led to their widespread use [1].

The extensive use of these formulations exposed their flaws. The cross-reactivity with hematopoietic cells revealed dose-limiting side effects including thrombocytopenia, anemia, and neutropenia [2, 3]. Moreover, the lack of standardized preparation led to variations in dosing. In addition, these formulations had significant antigenic properties as a result of using horse or rabbit based formulations, which lead to significant side effects, such as serum sickness, cytokine release syndrome, or even anaphylaxis [4-6].

The development of specific, monoclonal antibodies by Kohler and Milstein circumvented many of the drawbacks of polyclonal formulations, including lack of specificity and variability in preparation [7]. Muromonab, or OKT3, was the first monoclonal antibody prepared from mouse specific for cluster of differentiation 3 (CD3) [8]. OKT3 was effective at specifically depleting T cells from the circulation, and became widely used as a valuable tool to combat acute rejection episodes [9, 10]. Nevertheless, these monoclonal formulations still maintained some of the similar side effect profile of the polyclonal formulations, including an antigenic response to the protein or cytokine release syndrome, which lead to limited dosing in some patients [11].

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The 1980's marked an important era in transplantation with new advances in genetic engineering. Monoclonal antibodies became more sophisticated, targeting specific T cell populations and allowing blockade of T cell activation, such as the interleukin 2 receptor (IL-2R) or CD25 [12]. Moreover, the ability to avoid antigenic proteins by encoding genetic sequences of DNA binding sites of animal proteins onto human antibodies led to the development of chimeric monoclonal antibodies [13-15]. Using these techniques, soluble fusion proteins can be formed by merging nonantibody receptors with the Fc portion of antibodies.

1.2. Antibodies

Understanding the structure and function of antibodies is critical to understanding the efficacy of antibody induction therapy. Antibodies are composed of two identical heavy chains (either μ, γ, α, ε, or δ) and two identical light chains (either κ or λ). The heavy and light chain portions create two identical antigen binding sites (Fab fragment) which are held together by the common region, termed the Fc portion [16]. The type of heavy chain differentiates the immunoglobulin type as IgM, IgG, IgA, IgE, and IgD. In clinical transplantation, the IgG molecule is typically utilized, as it's readily produced and structurally feasible to manipulate (Fig. 1).

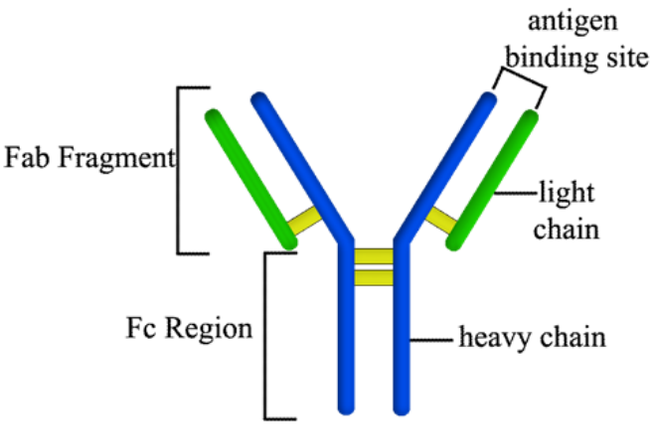


Figure 1. Basic antibody structure. Depicted is a standard IgG molecule. The heavy chains are colored in blue, while the light chains are colored in green. The yellow lines signify the disulfide bonds.

Antibodies are present on the surface of B cells. Upon secretion into the serum, antibodies are able to neutralize circulating antigens. Antibodies maintain their effector functions irrespective of species. Antibodies are capable of various functions, including mimicking activating ligands of receptors and serving as receptor inhibitors by blocking the ligand binding site [17, 18]. In some instances, antibody binding can lead to both activation and inhibition by inducing surface molecule internalization, whereby the molecule is removed from the surface of the cell [19]. This results in a negligible net effect. A major limitation of antibody use is the inability to directly bind intracellular molecules.

Antibodies have the ability to deplete target cells through two basic mechanisms. First, antibodies can activate the complement system resulting in complement-mediated lysis of target cells. Second, certain cells with Fc region receptors have the ability to phagocytose

cells covered with antibodies through a mechanism termed antibody-dependent cellular cytotoxicity (ADCC) (Fig.2). The efficacy with which this occurs depends upon the Fab fragment and the Fc region [20]. It is important to note that cells which have significantly matured, or memory cells, are somewhat resistant to antibody-dependent depletion mechanisms, possibly due to increased expression of anti-apoptotic or complement regulatory genes [21].

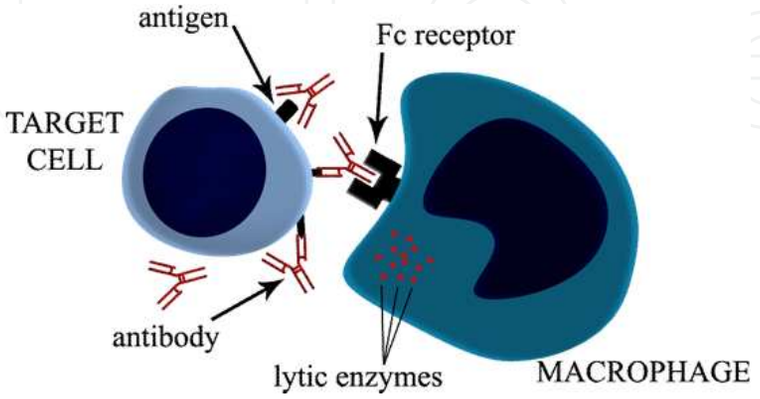


Figure 2. Antibody-dependent cellular cytotoxicity (ADCC). The Fc receptor on the macrophage is used to bind the constant Fc portion of antibodies to facilitate engulfment of cells coated with antibodies.

1.3. Classifying induction therapy agents

Induction therapy agents can be classified into two groups: depleting agents and non-depleting agents (Table 1). This distinction is based on the ability to target specific antigens or cells, leading to a decrease in the total expression or cell count. Most depleting agents are relatively potent with potential for toxicity with prolonged administration, while non-depleting agents are generally well-tolerated. In addition, the use of induction therapy agents has decreased the rates of acute rejection in the first 6 months compared to no induction therapy [22]. Although these short-term benefits appear promising, long-term outcomes, including patient and graft survival rates, have not been shown to be altered by the use of induction therapy, possibly the effect of long-term maintenance immunosuppressive therapy or even patient co-morbidities.

The overall success of a kidney transplant is contingent on both surgical technique and potent immunosuppressive medications. Although induction therapy has not affected surgical morbidity, the rate of allograft thrombosis has been shown to be reduced in children with the use of induction agents [23, 24]. However, not all medications used are FDA-approved for induction therapy. Additionally, these medications are not without risks, including infectious complications and the development of post-transplant lymphoproliferative disorder (PTLD), which has been well-described with the use of OKT3 and maintenance immunosuppression [25, 26]. Because of the effects of depleting agents on T cells, appropriate infectious prophylaxis should be instituted for all transplant recipients.

In 1995 induction therapy was used in less than half of all kidney transplants in the United States, while 10 years later, approximately 70% of all kidney transplant recipients received

Agent	Clonality	Targets	Dosing	Halflife	Duration of effects	Cytokine Release Syndrome?
rATG[1]	Polyclonal	Various immune targets, especially T cells	Multiple doses (POD[2]#0-4)	29.8-37.7 days	Months to years	Yes
Basiliximab	Monoclonal	CD25 (predominantly activated T cells)	2 doses (POD[2]#0 & 4)	7.2 days	Weeks	No
Daclizumab	Monoclonal	CD25 (predominantly activated T cells)	Multiple doses (POD[2]#0, then every 2 weeks)	20 days	Weeks	No
Alemtuzumab	Monoclonal	CD52 (naïve T cells, some B cells, and monocytes)	Typically 1 dose (POD[2]#0)	12 days	Months to years	Yes (less than rATG[1])

[1]rabbit Antithymocyte globulin, [2]post operative day

Table 1. Pharmacological Comparison of Induction Therapy

induction therapy [27]. Given the availability of various potent, specific induction agents in modern transplantation, the clinical dilemma lies in selecting the most appropriate agent for a given patient, taking into account co-morbidities, donor quality, immunological status, and planned immunosuppression maintenance therapy.

2. Induction therapy agents

2.1. Depleting agents

2.1.1. Rabbit Antithymocyte globulin (rATG)

2.1.1.1. Mechanism of Action

Rabbit antithymocyte globulin (rATG) is a polyclonal heterologous antibody produced from immunizing rabbits with human thymocytes, which serve as the immunogens (Fig. 3) [28]. The rabbit serum is then gathered and purified to remove antibodies with potentially detrimental effects and only the IgG isotypes are collected. Despite these purification techniques, it is possible that the majority of antibodies in these formulations serve no therapeutic purpose [29, 30]. When administered to humans, the rATG antibody formulations bind all antigens that the rabbits were exposed to during the immunization process.

rATG binds multiple T cell surface antigens and receptors involved in antigen recognition, adhesion and costimulation, including CD2, CD3, CD4, CD5, CD8, CD28, CD45, and CD40L. In addition, rATG may also bind non-T cell molecules such as CD16, CD20, CD56, and the major histocompatibility molecules (class I and II) [28-30]. The depleting effect of rATG occurs within 24 hours of administration and can persist with a prolonged serum half-life of several weeks [31, 32]. The effects of lymphocyte depletion are persists for years following administration, as evidenced by selectively low $CD4^+$ T cell counts [33, 34].

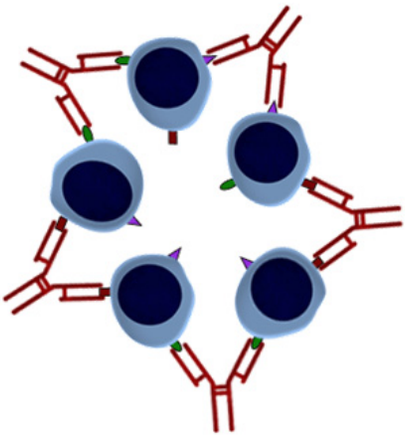


Figure 3. Polyclonal antibodies. Polyclonal antibodies are non-specific and bind multiple antigens as shown in the figure.

2.1.1.2. Clinical applications

rATG has been approved for use as an induction agent and for the treatment of acute rejection in Europe since 1984 [35]. However, in the United States, it is only indicated for the treatment of acute rejection. Nevertheless, it is routinely administered as induction therapy in many centers in the United States. Although early studies demonstrated an increased infectious risk and post-transplant malignancy when administered in conjunction with cyclosporine [36], improvements in infectious prophylaxis and lower doses have significantly alleviated these risks.

rATG administration improves early outcomes in kidney transplantation. Although the exact mechanism leading to this is unclear, rATG may minimize ischemia-reperfusion injury and potentially prevent the development of delayed graft function, which has been associated with poorer outcomes [37]. rATG has been used in patients at higher risk of developing delayed graft function, including recipients of donation after cardiac death donors, and recipients of extended criteria donors [38-40]. It is also administered in patients at higher immunologic risk, such as retransplants. Finally, it may help minimize the need for maintenance immunosuppression therapy facilitating early corticosteroid withdrawal [40, 41].

2.1.1.3. Adverse effects

Patients treated with rATG may experience a variety of side effects. It has been associated with a syndrome called cytokine release syndrome (Fig. 4), which is common to many polyclonal antibody formulations. Patients may experience mild flu-like symptoms, such as fever, chills, nausea, urticaria, rash, and headache [32]. This occurs as a result of increased production of tumor necrosis factor-α, IL-1, and IL-6 [28, 32, 42]. Premedication with corticosteroids, antipyretics, and antihistamines can prevent or treat these flu-like symptoms. In some cases, patients may develop more severe shock-like reactions, such as dyspnea, severe hypotension, pulmonary edema, or even anaphylaxis. Although patients frequently experience the mild flu-like symptoms and not the more severe reactions, recipient co-morbid conditions, such as cardiac or pulmonary disease, should be considered when selecting rATG as an induction agent. Serum sickness has also been associated with rATG administration in up to 7-10% of patients [43, 44].

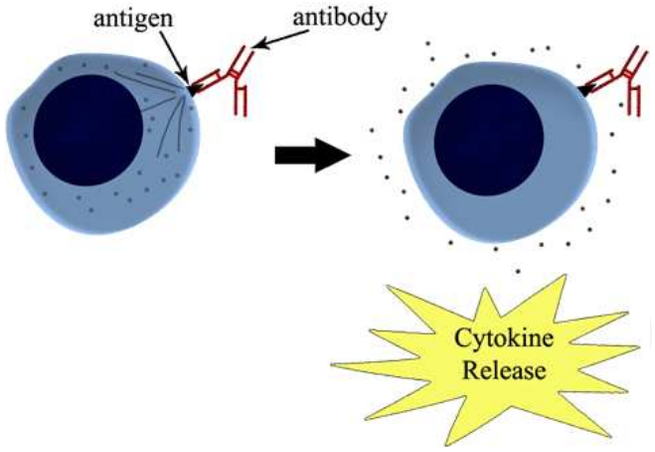


Figure 4. Antibody activation and cytokine release. Antibodies can bind antigens resulting in activation of the cell and cytokine release as illustrated in the figure.

Hematological adverse events may occur, including leucopenia and thrombocytopenia. It is important to monitor white blood cell, lymphocyte, and platelet counts daily. Effectively, these adverse events may lead to an increase in infectious complications, including cytomegalovirus (CMV), herpes simplex virus, Epstein-Barr virus (EBV), and varicella [45, 46].

2.1.2. Alemtuzumab

2.1.2.1. Mechanism of action

Alemtuzumab, or Campath-1H, is a monoclonal antibody to rat antihuman CD52 (Fig. 5). It is an IgG1 humanized molecule [47]. CD52 is present in high abundance on most lymphocytes, including T cell, B cells, and monocytes, but not hematopoietic precursors [48]. It effectively depletes T cells, and some B cells and monocytes in the circulation as well as the allograft [49].

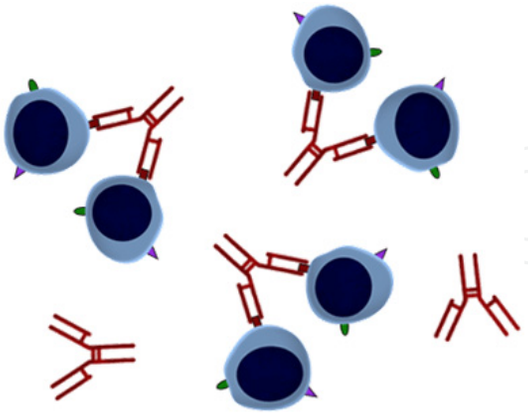


Figure 5. Monoclonal antibodies. Monoclonal antibodies are specific and bind a single antigen as shown in the figure.

2.1.2.2. Clinical applications

Alemtuzumab has not been approved for use as an induction agent; however, this is a common off-label use. At this time, it is only approved to treat lymphogenous malignancies.

As an off-label induction agent, it's been used with various immunosuppression regimens, including steroid-sparing regimens. Effectively, it depletes lymphocytes at the time of transplantation and last for several months to a year before the immune system is reconstituted [50]. Alemtuzumab is given at a dose of 30 mg or 0.3 mg/kg through a peripheral line over 3 hours. Sometimes 2 doses are given, although T cells are expectedly removed within 1 hour of initial administration [21, 49].

Alemtuzumab depletes all T cell subsets, but has a predilection for more naïve T cells [21]. Memory T cell subsets may not be depleted with this therapy, but these cell types are especially susceptible to calcineurin inhibitors. Because of the prompt and intense depletion, alemtuzumab is especially appealing to use in patients with delayed graft function, as calcineurin inhibitor therapy can be withheld to avoid concomitant calcineurin-induced renal insults.

Early studies of alemtuzumab demonstrated its efficacy as a treatment therapy for acute rejection; however, it was associated with significant infectious morbidity and mortality [47]. Patients were significantly over-immunosuppressed, especially on a triple maintenance therapy. More recent literature has been small studies or anecdotal data [51-53]. Because its efficacy is greatest against naïve T cells, its use in sensitized patients may-be limited.

In a recent study, alemtuzumab was prospectively compared to basiliximab and rATG as an induction agent in patients on a steroid-sparing immunosuppressive regimen [54]. Alemtuzumab demonstrated lower short-term rates of acute rejection compared to basiliximab in patients at low-risk of developing acute rejection. At 3-years, however, the rates of acute rejection were no different between alemtuzumab and rATG. Patients receiving alemtuzumab did not experience an increased incidence of adverse events.

2.1.2.3. Adverse effects

Similar to rATG, alemtuzumab has been associated with cytokine release syndrome, but to a lesser extent. With adequate premedication with methylprednisolone, acetaminophen, and diphenhydramine, the cytokine release is blunted. Rash is one of the most common manifestations, while anaphylaxis and hypotension have been reported. It has been linked to the development of autoimmune thyroiditis in patients treated with alemtuzumab for multiple sclerosis [55]. This has also been reported in a renal transplant recipient treated with alemtuzumab [56].

2.2. Non-depleting agents

2.2.1. Basiliximab

2.2.1.1. Mechanism of action

Basiliximab is a chimeric mouse-human monoclonal IgG1 antibody to CD25, the α-subunit of the IL-2 receptor. Basiliximab inhibition of IL-2 binding occurs through steric hindrance (Fig. 6). Effectively, basiliximab causes prevention of early T cell activation, as opposed to T cell depletion [50].

2.2.1.2. Clinical applications

Basiliximab targets naïve T cells, limiting its role to induction therapy. The first dose is administered on the day of transplant with the final dose administered on postoperative day 4 (20 mg per dose) via a peripheral line. Its use has been associated with decreased rates of acute cellular rejection compared to no formal induction agent on either triple or double drug immunosuppression regimens [57, 58]. Additional studies comparing basiliximab induction to polyclonal antibody depleting induction agents in the setting of triple maintenance immunosuppression regimens have shown similar outcomes with respect to acute rejection rates and delayed graft function [59, 60]. Basiliximab induction therapy has been successfully used in steroid avoidance immunosuppression regimens [61]. In the setting of monotherapy or calcineurin inhibitor free regimens; however, basiliximab has not been shown to be effective in preventing early immunologic events [62, 63]. In cases of excellent human leukocyte antigen (HLA)-matching (i.e. 2-haplotype matches), it's been used as an effective induction agent with steroid avoidance immunosuppressive regimens [61]. Given the relatively mild side effect profile, basiliximab is well-tolerated in all patients, even those with significant cardiac or pulmonary co-morbidities.

2.2.1.3. Adverse effects

The side effect profile of basiliximab is relatively mild [57, 58]. Because of the lack of T cell activation or stimulation, cytokine release syndrome does not occur. The most serious adverse event is hypersensitivity, which is rare (<1%) [50]. There is no increased risk of infectious complications or PTLD compared to no induction therapy [64].

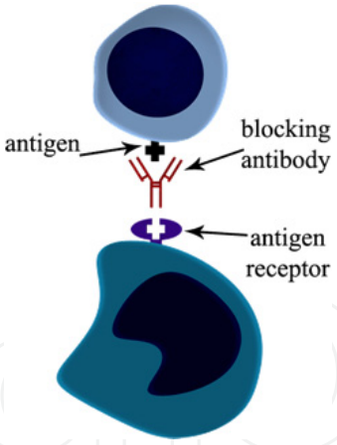


Figure 6. Antibody blockade. In this figure the antibody functions by blocking the antigen from binding to the receptor.

2.2.2. Daclizumab

2.2.2.1. Mechanism of Action

Daclizumab, like basiliximab, is a CD25 antagonist; however, it is a humanized IgG1 antibody. The CD25 molecule was the first humanized monoclonal antibody to be successfully targeted in the field of transplantation [65]. The mechanism of action of daclizumab essentially duplicates that of basiliximab.

2.2.2.2. Clinical applications

Daclizumab has been shown to decrease the incidence of acute cellular rejection when administered as an induction agent [66, 67]. Given the favorable side effect profile, it is well tolerated, irrespective of co-morbid conditions. The main disadvantage of daclizumab, as compared to basiliximab, is that it is more costly and requires repeated administrations [50]. Given the low demand for the medication, it has been discontinued by the manufacturer.

2.2.2.3. Adverse effects

The generally favorable side effect profile resembles that of basiliximab. Cytokine release is not typically associated with this agent [66, 67]. Like basiliximab, the risk of infectious complications or PTLD is not significantly increased with use [64].

3. Desensitizing agents

3.1. Rituximab

3.1.1. Mechanism

Rituximab is a monoclonal chimeric antibody to the CD20 molecule. CD20 is a glycoprotein on the cell surface of circulating, mature B cells. Rituximab effectively depletes CD20+ cells from the circulation by inducing apoptosis [68]. These cells are precursors to antibody-producing plasma cells, and their role in transplantation is only partially characterized. They may play a role in acute rejection, as B cells can act as antigen presenting cells.

3.1.2. Applications

Rituximab is approved for use in various lymphomas, leukemias, PTLD, and rheumatoid arthritis [50, 69]. Peripheral veins can be used for administration and dosing is dependent on the indication. A recent study examining the role of rituximab as an induction agent found no benefit compared to placebo [70]. However, it does play a role as a desensitizing agent in patients with preformed donor specific antibodies (DSA), in conjunction with total plasmapheresis and/or intravenous immunoglobulin (IVIG) [71, 72].

Additionally, it has been used to aid in transplanting across blood group barriers in donor recipient pairs and in patients with positive crossmatches following antibody elimination.

Rituximab is increasingly being used to treat episodes of vascular rejection and antibody mediated rejections [73, 74]. Finally, rituximab is a proven and effective agent in the treatment of PTLD [75]. Administration does not replace immunosuppression reduction or chemotherapy, but rather supplements the other modalities.

3.1.3. Adverse effects

Rituximab is generally well-tolerated with minimal side effects. Anaphylaxis remains a theoretical concern, as is the case with most agents. Reports on infectious complications

related to rituximab have been variable [76-78]. In some instances there was no difference in bacterial, viral, or fungal infections in kidney transplant recipients treated with rituximab, however, this remains controversial.

3.2. Bortezomib

3.2.1. Mechanism

Bortezomib is a proteasomal inhibitor that causes apoptosis of plasma cells. It binds the 26S subunit of the proteasome [79]. Proteasome inhibition ultimately leads to apoptosis during mitosis. Bortezomib selectively causes apoptosis in CD138+ plasma cells [80]. Additionally, Bortezomib may block T cell cycling and decrease the number of circulating B cells by reducing bone marrow levels of IL-6 [81].

3.2.2 .Applications

Bortezomib has not been approved for use in kidney transplantation; however, it has been used in sensitized patients [80]. Bortezomib has been successfully used to decrease DSA levels, which may play a role in acute antibody-mediated rejection (AMR) Induction Therapy in Renal Transplant Recipients [82]. Furthermore, in vivo data has demonstrated a decrease in the percentage of bone marrow plasma cells, antibody production, and allospecificities of plasma cells in bone marrow aspirates of patients treated with bortezomib i in the setting of AMR [80].

3.2.3. Adverse events

Bortezomib has been associated with various side effects. Although gastrointestinal side effects are the most common, peripheral neuropathy has also been reported, especially in patients with a pre-existing history of neuropathy [79]. Moreover, myelosuppression and shingles has been reported.

3.3. Intravenous Immunoglobulin (IVIG)

3.3.1. Mechanism

Intravenous immunoglobulin, or IVIG, is pooled polyclonal antibodies from different human donors. These are high-dose human IgG fractions with a wide range of specificities. These are non-T cell specific formulations and have no specific cell targets [83]. It is able to bind activated complement components or even inhibit complement activation [84]. IVIG may also modulate the alloimmune response by binding to the Fc receptor of antigen-presenting cells, effectively quelling the alloimmune response [85].

3.3.2. Applications

Despite the inability to deplete T cells, IVIG is an effective treatment of acute cellular rejection. Early studies showed that IVIG was as effective as OKT3 in reversing steroid

resistant acute rejection episodes [86]. In the setting of antibody-mediated rejection, IVIG has been shown to be beneficial when used in conjunction with plasmapheresis and/or rituximab [87-88]. As a desensitization agent alone, no study has demonstrated a clear benefit [88, 89]. Definitive reduction of antibody was not shown and a survival advantage was not evident.

3.3.3. Adverse effects

The side-effect profile of IVIG increases with dosing. High-dose IVIG is associated with more infusion-related complications, such as headache, thrombotic incidents, hemolysis, bronchospasms, osmotic nephropathy, or even aseptic meningitis [83, 90]. Sucrose-based and high osmolality products have a higher risk of developing osmotic nephropathy as opposed to other preparation. Nevertheless, it is typically well-tolerated, especially at lower doses and most patients report only headache.

4. Maintenance immunosuppression regimens

4.1. Historical background

The initial transplant armamentarium consisted only of azathioprine and steroids for maintenance immunosuppression in renal transplantation until the 1980's, when the first calcineurin inhibitor, cyclosporine became available. Over the next 20 years, azathioprine had been largely replaced by mycophenolate (MMF), an antiproliferative agent. Standard therapy in most modern immunosuppression regimens now consists of a calcineurin inhibitor, mycophenolate, with or without steroid maintenance.

Minimizing global immunosuppression in the modern era of transplantation has become an important goal. The use of induction therapy has allowed for steroid avoidance immunosuppression regimens. The goal of steroid avoidance immunosuppression is to decrease the negative cardiovascular profile associated with long-term administration of steroids. Specifically, steroid-free regimens should decrease the negative effects on blood pressure control as well serum glucose and lipid metabolism [91]. Moreover, the leading cause of death in kidney transplant patients is cardiovascular events [92].

4.2. Steroid maintenance versus withdrawal

Advocates of steroid-maintenance regimens suggest that steroids may allow for lower doses of calcineurin inhibitors, such as cyclosporine or tacrolimus. Moreover, steroids may decrease the incidence of nephrotoxicity perioperatively. However, there has been insufficient data to support either conclusion [93].

The effectiveness of steroid-withdrawal and cyclosporine-based therapy has been clearly associated with timing. Early studies of cyclosporine-based regimens demonstrated that cessation of steroids prior to the 6 month period post-transplantation increased the risk of acute rejection [94]. Furthermore, a meta-analysis of seven randomized-controlled trials of

steroid avoidance and/or withdrawal demonstrated an increased risk of acute rejection with steroid avoidance or early withdrawal (most steroids were withdrawn in the first 3 months post-transplant) [95]. However, patient and graft survival were not adversely affected in the meta-analysis.

The ability to withdrawal steroids appears to be better with tacrolimus-based immunosuppression regimens. An early report by Shapiro et al. demonstrated that patients receiving tacrolimus and steroid-sparing immunosuppression had excellent early and intermediate-term patient and graft survival compared to kidney transplant recipients receiving standard steroid-maintenance immunosuppression [96]. Later, various randomized-controlled trials were undertaken to assess the initial outcomes. A meta-analysis of six randomized, controlled-trials comparing a calcineurin inhibitor-based immunosuppression regimen with MMF demonstrated a slightly increased risk of acute rejection once steroids were discontinued; however, this did not affect the incidence of graft failure [97]. Shortly thereafter, a randomized trial from Europe assigned low immunologic risk patients to receive either triple immunosuppression with tacrolimus, MMF, and steroids, a tacrolimus-based steroid withdrawal regimen, or a tacrolimus-based steroid-maintenance regimen without MMF [98]. At 6 months, the incidence of acute rejection was not different between the groups. Furthermore, the steroid withdrawal group benefited from an improved lipid profile. Kumar et al. reported on a series of 300 kidney transplant recipients receiving basiliximab induction therapy followed by steroid maintenance or withdrawal at 2 days post-transplant [99]. Maintenance therapy for all patients consisted of a calcineurin inhibitor and MMF or sirolimus. At 3 years, the incidence of biopsy-proven acute rejection, patients and graft survival, chronic allograft nephropathy, or graft function was not significantly different. Moreover, the steroid withdrawal group benefited from a lower rate of new-onset diabetes after transplantation.

Successful avoidance of steroids is contingent upon the use of calcineurin inhibitors. In 2006 Gelens and colleagues performed a single-center, randomized, trial of three parallel groups, which were: tacrolimus and sirolimus (group one), tacrolimus and MMF (group two), and sirolimus and MMF with daclizumab induction [100]. During an interim analysis when 50% of the patients were included, group one had a significantly increased rejection free survival (82%) compared to group three (34%, P=0.03) and between groups one and two (tacrolimus-based, 76%) and group three (34%, P=0.04). The study was halted prematurely. Despite the current armamentarium of antibody-depleting medications, steroid withdrawal seems feasible only with a calcineurin inhibitor-based regimen.

4.3. Induction therapy and steroid withdrawal

The possible minimization of maintenance immunosuppression has been studied using basiliximab and rATG without compromising allograft outcomes. In the Astellas Steroid Withdrawal Study, patients assigned to the steroid-withdrawal arm and treated with rATG experienced a lower cumulative incidence of biopsy-proven acute rejection at 5 years compared to patients treated with basiliximab [101]. Selection bias; however, may have marred this study, given that the investigators selected which antibody induction agent was

used. Our transplant center's experience utilizing induction therapy to enable steroid withdrawal has been very successful in a diverse population, using rATG in the majority of patients [102] and basiliximab in well-matched living donor recipients [61]. In a study by Cantarovich et al., patients administered rATG and steroid-maintenance immunosuppression had significantly lower acute rejection rates compared to patients on a steroid-free immunosuppression regimen, although the incidence of malignancy, *de novo* diabetes, and hyperlipidemia were higher in steroid-maintenance group [103]. Patient survival, graft survival, and infection rates were not significantly different between the two groups at 1 year.

Alemetuzumab and steroid-free regimens have been compared to both basiliximab and rATG. In the study by Hanaway et al., acute rejection rates were relatively low in low-risk patients receiving alemtuzumab compared to basiliximab, although the reduced immunologic risk profile of alemtuzumab was not evident in high risk patients treated with rATG [54]. The overall rate of adverse events with alemtuzumab was similar to that of basiliximab or rATG over the 3 year study period (53% versus 50%, respectively; p=0.46). Moreover, the rate of cardiovascular events of all alemtuzumab treated patients compared to basiliximab or rATG was also similar (7% versus 10%, respectively; p=0.26), although the similarity was less evident in the high-risk immunologic group treated with rATG compared to alemtuzumab (12% versus 3%, respectively; p=0.06). Cai et al. analyzed the United Network for Organ Sharing registry and found that recipients of alemtuzumab in conjunction with steroid-maintenance therapy had the lowest risk of graft failure, while patients administered an interleukin-2 receptor antagonist on a steroid-free immunosuppression regimen had the highest risk of graft failure [104]. In a single-center, open-label randomized trial of 200 kidney transplant recipients, low dose dual induction therapy of rATG and daclizumab was compared to lose dose dual therapy of rATG and alemtuzumab in patients maintained on steroid-free maintenance immunosuppression [105]. Patient and graft survival rates as well as acute rejection and infectious complication rates were not significantly different. In addition, no patient developed post-transplant lymphoproliferative disorder.

5. New and experimental agents

5.1. Siplizumab (MEDI-507)

Originally described as BTI-322, siplizumab is a monoclonal humanized antibody to CD2. It is an IgG1k molecule derived from rat [106]. CD2, or lymphocyte function-associated antigen-2 (LFA-2) is an important T cell adhesion molecule that binds to CD58, or LFA-3. This is a transmembrane signal transduction molecule that facilitates T cell receptor binding. Early studies examined the use of siplizumab as an induction agent and treatment modality for acute rejection in solid organ transplantation as well as graft-versus-host disease [106, 107]. The first human study of siplizumab demonstrated the safety and feasibility in kidney transplantation, as compared to placebo; however, current endeavors are focused on investigating its use in nonmyeloablative conditioning regimens to achieve mixed chimerism [106, 108, 109]. In addition, it is being investigated for the treatment of plaque psoriasis [110].

5.2. Alefacept

Alefacept is a dimeric fusion protein (Fig.7) constituted from LFA-3 and the human Fc portion of IgG1. Studies have demonstrated inhibition of T cell proliferation and depletion of effector memory T cells [111, 112]. Currently, alefacept is approved to treat plaque psoriasis. Preclinical studies in nonhuman primates have demonstrated a survival benefit of alefacept, when used in conjunction with costimulatory blockade, but not alone; however in human trials have never shown a benefit [113].

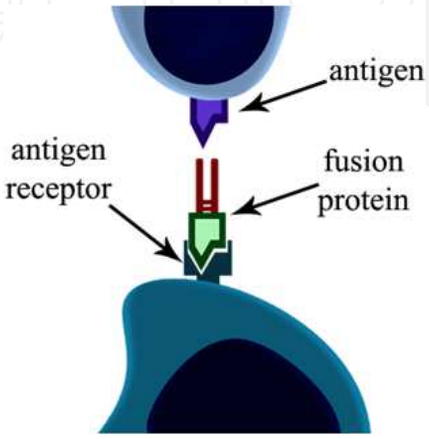


Figure 7. Mimicry. In this figure, the antibody is fused with a protein structural similar to the intended antigen, which can serve as activating or inhibitory.

5.3. Costimulatory blockade

5.3.1. Abatacept

Abatacept is a recombinant cytotoxic T-lymphocyte antigen 4 (CTLA4) fused with the Fc portion of IgG1 [114, 115]. Animal models demonstrated its ability to delay or even prevent the onset of allograft rejection, which is comparable to basiliximab and some polyclonal antibody therapies [114-116]. It has been approved for treatment of rheumatoid arthritis [117, 118]. Further investigations of this medication are not currently under development.

5.3.2. Belatacept

Belatacept is the improved version of abatacept, providing selective blockade of T cell activation as a fusion protein. Two amino acids have been changed to improve dissociation rates when binding to CD80 and CD86 [119, 120]. In the phase II trial comparing belatacept to cyclosporine, acute rejection rates were similar, while allograft function was significantly improved in patients receiving belatacept [119]. In the phase III trial of kidney transplantation, patients receiving belatacept experienced improved allograft function at 12 months; however, acute rejection rates and severity of acute rejection episodes were significantly higher in the belatacept arm of the study. Additionally, the incidence of PTLD was greater in patients receiving belatacept [120]. An additional study investigating the efficacy of belatacept in kidney transplantation of extended criteria donors demonstrated

similar results, with a predilection towards central nervous system (CNS) forms of PTLD [121]. The novelty of costimulation blockade is the ability to avoid calcineurin inhibitors, especially in allografts at increased risk of delayed graft function. Belatacept has recently been approved for the prophylaxis of organ rejection in adult patients receiving a kidney transplant, in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids [122]. Current recommendations include using it only in patients who are EBV seropositive; however, patients should be monitored for an increased risk of infectious complications and Progressive Multifocal Leukoencephalopathy.

5.4. Eculizumab

Recently, a new medication called eculizumab has emerged as a humanized monoclonal antibody to complement component 5 (C5) to mediate complement-mediated injury [123]. Blocking complement activation, especially the last step of the complement cascade, has important implications in kidney transplantation. However, the role of eculizumab appears to be more applicable to cases of clear complement-mediated destruction, such as antibody-mediated rejection and desensitization protocols [124]. Furthermore, the logistics of administration may further hinder its' use as a maintenance immunosuppression agent, as it must be administered biweekly or weekly intravenously at least for the first 1-2 months upon initiation of therapy. Currently, it is only approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria [123].

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