Chapter 10

Overview of Immunosuppression in Renal Transplantation

M. Ghanta, J. Dreier, R. Jacob and I. Lee

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54865

1. Introduction

The use of potent induction agents and maintenance immunosuppression has substantially decreased the risk of acute rejection. One year graft survival is greater than 92% in deceased donor and 96% in living donor transplant recipients with current immunosuppressive strategies according to the Scientific Registry of Transplant Recipients, (SRTR, 2009).

Half life appears to be the best way to give the patient a general understanding of how long their transplant may last. The graft half life for deceased donor transplants has increased from 6.6 years in 1989 to 8.8 years by 2005. Significant progress has also been made in high risk transplants where graft half life has improved from 3 years in 1989 to 6.4 years in 2005 for expanded criteria donor recipients. For the standard low risk patient receiving a living donor kidney, current immunosuppression should guarantee a graft half life of at least 11.9 years. [1]

However, the problems of chronic rejection and chronic allograft dysfunction still remain, often leading to graft loss and shortened long-term graft survival.[2] The 5 and 10 year adjusted graft survival for deceased donor transplants were 70% and 43% respectively. The adjusted 5 year and 10 year graft survival for living donor transplant were 82% and 60% respectively. (SRTR, 2009)

Humoral rejection and sensitized patients continue to be a clinical challenge. The management and clinical impact of subclinical rejection also remains unclear. Although there are numerous clinical trials testing different immunosuppressive strategies, a lack of large prospective randomized clinical trials has decreased our ability to generate consensus on the best immunosuppressive strategies for preserving long-term allograft function. This chapter will focus on reviewing multiple aspects of immunosuppressive therapy, such as; 1) mechanism of action, 2) how therapies are being utilized in practice, 3) the advantages and/or disadvantages

of different therapies and 4) major clinical trials evaluating the effectiveness of specific regimens. New emerging strategies and therapeutic agents that are being investigated will also be discussed.

2. Induction agents

The goal of induction therapy is to suppress both cellular and humoral responses to prevent episodes of acute rejection. Rabbit anti-thymocyte globulin (rATG), IL-2 receptor blockers, and Alemtuzumab (Campath), are the primary antilymphocyte antibody preparations that are currently used for induction. More than 80% of the transplant centers in the United States use induction agents immediately post transplantation.[3] The specific agent utilized is often based on multiple factors which include recipient risk for rejection, recipient race, presence of chronic infections such as Hepatitis B or C, HIV, and center preference. See Table 1. for common induction agents.

2.1. Thymoglobulin

Thymoglobulin (rATG) is the most commonly used induction agent in United States. (rATG), is an antilymphocyte polyclonal antibody that is derived by injecting rabbits with human thymocytes. rATG contains polyclonal cytotoxic antibodies mainly targeted against various epitopes on human T lymphocytes and works primarily by complement mediated depletion of T lymphocytes. However, the multiple specificities of rATG against a broad range of T-cell antigens can affect multiple pathways involved in T-cell trafficking, adhesion, activation and promotion of certain T-cell subsets that may be more favorable for transplantation such as T-regulatory cells. [4-6] Although primarily a T-cell directed agent, the development of humoral responses which are dependent on T-cell help are likely compromised by rATG as well.

2.1.1. Side effects

Secondary to potential infusion reactions and other toxicities, administration of rATG requires patient monitoring and is administered in an inpatient setting or in an established infusion center. The typical dose is 1.5mg/kg/dose and involves 3-5 doses of rATG, depending on center protocols.

The antibodies in rATG can bind to proteins on the surface of granulocytes as well as platelets and hence leucopenia and thrombocytopenia are commonly encountered after rATG administration. Cytopenias are handled either by dose reduction or holding the dose. Despite premedication, infusion reactions do occur including fevers, chills and arthralgias. Serious reactions such as anaphylaxis, acute respiratory distress syndrome (noncardiogenic pulmonary edema) occur rarely. Typically these reactions are a result of intense cytokine release from lysis of T lymphocytes. Since rATG is obtained from rabbit sera, serum sickness can occur which presents with fever, malaise, diffuse arthralgias and rash. rATG results in prolonged T cell depletion, up to 6 months post administration and recipients are at increased risk for

http://dx.doi.org/10.5772/54865

opportunistic infections and lymphoma. Patients are typically prophylaxed for cytomegalovirus infection and pneumocystis carinii infection post rATG administration.

2.2. Alemtuzumab

Alemtuzumab or Campath is a recombinant humanized monoclonal antibody directed against CD52. It binds to CD52 receptor on the surface of T and B lymphocytes leading to antibody mediated cell lysis. CD52 is present on virtually all B and T cells as well as macrophages, NK cells and some granulocytes. It was initially approved for use in B-cell lymphocytic leukemia and is now used in transplantation. Alemtuzumab induces a rapid and profound depletion of peripheral and central lymphoid cells. It is typically administered as a single 30 mg dose either subcutaneously or intravenously. Just like rATG patients receive premedication to prevent infusion reactions. When used as an induction agent it is given intraoperatively. Single dose administration makes Campath a more convenient option to administer compared to rATG which is typically administered daily for 3-5 days.

2.2.1. Side effects

Potential side effects include thrombocytopenia, vomiting, diarrhea, headache and rarely autoimmune hemolytic anemia. Infection and lymphoma risk is similar to rATG, and patients are similarly prophylaxed for potential infections.

2.3. IL-2 receptor blockers (IL-2RA)

IL-2 receptor blockers, Basiliximab (Simulect) and daclizumab (Zenapax) are humanized anti-CD25 monoclonal antibody preparations. They are targeted against the α-chain (CD25) of the IL-2 receptor. Rather than working by lymphocyte depletion, these agents block IL-2 signaling which is required for T-cell growth, differentiation and expansion. Because both agents are derived from mice and partly humanized, they cause far less infusion reactions compared to rATG. Daclizumab is currently not available for use in United States. Basiliximab is used in the U.S. and is typically administered as 20mg intravenous infusion intraoperatively with subsequent doses given on the third or fourth post operative day. Neither drug has major side effects. Risk of infection and lymphoma is far less than that of lymphocyte depleting agents.

3. Which induction agent?

According to the annual report from SRTR 2009, 83% of transplant recipients received induction agents at the time of kidney transplant. The majority of patients received a T-cell depleting agent, 58%, and 21.2% received an IL-2 receptor blocking agent.

How agents are used in practice is dependent on a number of factors which range from center specific protocols to tailored immunosuppression based on recipient factors. The risks and benefits of each agent must be assessed in every patient individually based on the individuals' immunologic risk and susceptibility to infectious complications. Induction agents clearly

possess different mechanisms of action that will have different effects on modulating cellular and humoral immune responses. It may be more advantageous to use more potent induction therapies such as the lymphocyte depleting agents, in those recipients at higher risk for rejection. On the other hand, utilizing such agents may be of concern in recipients with chronic infections such as hepatitis B and/or C or HIV. [7-10]

Induction Agents	Thymoglobulin
	Basiliximab
	Daclizumab
	Alemtuzumab
	Rituximab
Maintenance Agents	Tacrolimus
	Cyclosporine
	Sirolimus
	Mycofenolate Mofetil
	Azathioprine
	Corticosteroids
	Belatacept
	Leflunomide

Table 1. Immunosuppressive agents

Lymphocyte depleting agents such as rATG and Alemtuzumab primarily differ in their ability to deplete specific types of leukocytes. rATG contains polyclonal antibodies directed at thymic antigens and is more T-cell directed, and has little direct effect on B-cell depletion. Alemtuzumab contains a specific monoclonal antibody against CD52 which is expressed by both T and B cells as well as antigen presenting cells (APCs). The effect of Alemtuzumab mechanistically is directed at disabling several arms of the immune response, such as cell mediated (T-cell responses) and humorally mediated (B-cells) responses, as well as affecting antigen presenting cells.

Existing studies however, fail to show greater efficacy of Alemtuzumab compared to rATG in clinical trials. However, case series and other small trials speak of the benefit of utilizing Alemtuzumab in refractory rejection, and in instances of mixed rejection where an agent with activity against both cell mediated and humoral responses are required. Finally, both Alemtuzumab and rATG are agents of choice in patients that are considered higher risk such as African American race, repeat renal transplant, and sensitized patients with high panel reactivity to multiple HLA antigens.

The IL-2 receptor blocker, Basiliximab (Simulect), provides an option for induction therapy in those recipients with history of chronic infections with hepatitis B and or C and HIV, as Simulect is associated with less infectious complications post-transplant compared to lymphocyte depleting agents. Less immunosuppression is also an attractive option for those patients who may not require potent induction therapy, such as recipients that are older,

http://dx.doi.org/10.5772/54865

Caucasian, and those receiving living donor kidneys. When compared to lymphocyte depleting agents, clinical trials suggest more acute rejection episodes with IL-2RA. [11]

Utilizing data from the United Network For Organ Sharing Data Registry, a recent study examining a large cohort of HIV recipients demonstrated higher risk of DGF and death censored graft loss with IL-2 receptor agents.[12] HIV patients also have higher rates of acute rejection with one recent study reporting a 31% incidence at one year.[7] Questions remain as to whether this is driven in part by choosing a less potent induction agent such as Simulect or issues with achieving therapeutic levels and/or avoiding toxic levels of maintenance drugs that interact with many anti-retroviral HIV medications. Thymoglobulin has been used in HIV recipients but can lower the CD4+ cell count dramatically, with recovery occurring as far out as two years. [13] Thymoglobulin use in HIV has also been associated with increased risk of infections requiring hospitalizations. Clearly, more studies are needed to weigh the risks and benefits of IL-2 receptor blockers on long-term graft function and post-transplant infectious complications.

4. Comparison of induction agents; clinical trials

A study by Terasaki et al analyzed the various induction immunosuppression strategies used across centers in the United States [3]. From 2003 onwards, the majority of centers were utilizing Simulect, rATG or Alemtuzumab. According to the OPTN database, recipients who received alemtuzumab had the lowest risk of graft failure, followed by rATG and basiliximab. However, the benefit of one induction agent over the other is not entirely clear because conclusions from small single center studies and retrospective studies utilizing database reviews are often mixed. In addition, studies may be difficult to evaluate secondary to different maintenance regimens that are used after induction.

Larger randomized trials and multicenter trials have been conducted and generally demonstrate that cell-depleting agents are generally more efficacious than IL2RA induction. [3] In a randomized controlled trial, rATG was superior to IL2RA in preventing acute rejection in recipients with high-immunologic risk, and with standard criteria donor kidneys. Two prospective randomized trials demonstrated rATG was superior to basiliximab in preventing biopsy proven acute rejection in standard criteria donor kidney recipients. When comparing Alemtuzumab to rATG, studies are mixed. In a separate single center randomized trial comparing alemtuzumab with rATG induction, Farney et al have shown that alemtuzumab is superior to rATG in preventing biopsy proven acute rejection.[14] However, in a larger randomized multicenter study (INTAC), Hanaway et al compared induction therapy with alemtuzumab to conventional induction (basiliximab or rATG). At one year post transplant, the incidence of biopsy proven acute rejection was lower in the alemtuzumab arm compared to basiliximab induction in low immunologic risk recipients. However in the high immunologic risk recipients, alemtuzumab was as efficacious but not superior to rATG.

5. Induction agents in sensitized patients

Rituximab (Rituxan) is used in the following clinical scenarios; 1) ABO incompatible or positive cross match transplantation, 2) treatment of antibody mediated rejection and 3) desensitization by decreasing titers of preformed alloantibodies prior to transplantation. [15-17] It is an anti-CD20 monoclonal antibody directed against the CD20 antigen present on naive B-cell lymphocytes. It creates a rapid and sustained depletion of circulating naive B cells for approximately 6 months. Because of its specific activity against B-cells, Rituxan is used to target the humoral arm of the immune response by limiting B-cell activity and antibody production. Although widely used in transplantation, the efficacy of this drug when compared with other newer agents in treating humoral responses and decreasing alloantibody production remains to be seen.

Eculizumab, is an anti C5 antibody which leads to terminal complement blockade and prevents formation of the membrane attack complex. Eculizumab protects allografts from complement mediated injury which occurs when pathogenic alloantibodies directed against donor allograft tissue activate complement. Although not widely used yet, the Mayo Clinic published an open label study demonstrating that blockade of terminal complement decreases antibody mediated rejection in sensitized patients and allows for positive crossmatch transplantation to occur. Eculizumab reduced antibody mediated rejection (AMR) to 7.7% compared to historical control groups where the incidence of AMR was 30-40% in the first few months.[18] Compared to long-standing protocols widely used for sensitized patients (e.g, plasmapharesis, IVIG and Rituximab), Eculizumab looks more promising in decreasing AMR rates.

Bortezomib, is a proteasome inhibitor that has specific activity against high affinity antibody producing plasma cells (PC), and induces apoptosis of circulating PC (a small percentage of the PC population) but in addition is able to effect PC that remain in survival niches such as the bone marrow and spleen.[19] Besides affecting the humoral arm, Bortezomib has multiple effects on immune cell function. Proteosome inhibition prevents the function of NFκB, an important transcription factor that transcribes multiple genes important for immune cell function and disrupts the regulation of cell cycle proteins, cell survival signals and expression of adhesion molecules.[20, 21] In transplantation it is used to treat refractory antibody mediated rejection as well as to reduce the burden of preformed alloantibodies to facilitate transplantation of highly sensitized individuals. Studies and case series evaluating the use of Bortezomib for desensitization and treatment of acute rejection have been mixed.[22-25] Although used by some centers, it has not been widely adopted into practice.

6. Maintenance immunosuppression

Maintenance therapy is used to prevent acute rejection and promote long term graft survival. Conventionally, combinations of 2-3 drugs with different mechanisms of action targeting various immune responses are used. Maintenance regimens vary according to the center, immunological risk of the patient, and individual susceptibility to adverse reactions. The

http://dx.doi.org/10.5772/54865

introduction of calcineurin inhibitors (CNI) together with anti-proliferative agents like mycophenolate mofetil has resulted in major improvements in acute rejection rates and short term graft survival over the last three decades in kidney transplant recipients. However, long term graft outcomes have not improved dramatically, partly because of nephrotoxicities associated with the long term use of these drugs. In the year 2009, the initial maintenance regimen for 81% of kidney transplant recipients included tacrolimus and mycophenolate mofetil, per SRTR report, 2009. At one year post transplantation, 72.1% of the kidney transplant recipients remained on tacrolimus and mycophenolate moefetil and only 5.3% were receiving cyclosporine and mycophenolate mofetil. See Table 1 for common maintenance agents.

Although the majority of US centers utilize CNI in combination with mycophenolate moefetil for maintenance, different dosing strategies for CNI, as well as new agents are being explored. A recently FDA approved medication for use in renal transplant, Belatacept, may have a promising role in widescale maintenance immunosuppression in the future. The basic pharmacology, clinical uses, major drug interactions and toxicity profiles of commonly used and new maintenance agents will be discussed in this section.

6.1. Calcineurin inhibitors

Since their introduction in the 1970s, CNI have been the fundamental agents used for maintenance immunosuppression in solid organ transplantation. They played a revolutionary role in transplantation by dramatically reducing the incidence of acute rejection episodes and prolonging allograft survival post-transplant. Cyclosporine and tacrolimus are the available CNI preparations with both having a unique role in maintenance. Currently, tacrolimus is more widely used compared to cyclosporine primarily because there is less nephrotoxicity associated with tacrolimus. Based on recent SRTR reporting, the use of cyclosporine has declined from 66.3% in 1998 to 5.7% in 2009. Notably the use of tacrolimus has increased from 25.9% to 87.8%.

6.2. Mechanism of action of CNI

The target protein of both tacrolimus and cyclosporine is CNI which is a calcium-dependent phosphatase. This enzyme is ubiquitously expressed and associates with calmodulin to form an active enzyme complex that dephosphorylates and activates the transcription factor, nuclear factor of activated T cells (NFAT), after T-cell receptor signaling. Dephosphorylated NFAT can then translocate to the nucleus and initiate transcription of several key cytokine genes (e.g., IL-2, IL-4, TNF- and IFN-γ). Blockade of calcineurin leads to decreased NFAT activity and transcription of critical cytokines affecting T cell function, activation and proliferation. Both these drugs bind to cytoplasmic proteins to mediate their action. Cyclosporin binds to cyclophilin, while tacrolimus binds to FKBP-12.

6.3. Clinical use

Recommended starting dose for tacrolimus is 0.15-0.30 mg/kg, while that of cyclosporine is 6-10 mg/kg. For both drugs, total dose is administered in two divided doses. Intravenous

dosing is 1/3rd of the total oral dose, administered as a continuous 24 hour infusion. Patient variability in drug kinetics can be attributed to the heterogeneity of metabolic activity of the enzyme responsible for calcineurin metabolism; the liver enzyme, CYP3A. In general, African Americans may require higher doses of tacrolimus, whereas patients with liver disease and elderly patients may need lower doses. Because of wide patient variability in metabolism, therapeutic drug monitoring is routinely performed with these agents. Most centers check a 12 hr trough level prior to the morning dose. More sophisticated monitoring with area under the curve (AUC) measurements is available but is not routinely performed because of technical and clinical difficulties. During the first 3 months post transplant, our center aims for a 12 hr tacrolimus trough in the range of 8-12 ng/dl, followed by a level of 6-10 ng/dl for months 4 to 12. After the first year, we reduce tacrolimus dosing aiming to achieve maintenance levels of of 4-6 ng/dl. For cyclosporine, a 12 hour trough of 250-350 mg/dl are maintained for the first few months and then target levels are gradually decreased. After the first year post transplantation the usual cyclosporine trough is between 100-200mg/dl. Targeted drug ranges vary across centers and are driven by center protocols that take into account patient risk, type of induction used and the strength of other agents used for maintenance.

6.4. Metabolism of CNIs and major drug interactions

Both tacrolimus and cyclosporine are metabolized by cytochrome P450 (CYP3a) enzymes that are located in the GI tract and liver. Both drugs are excreted in bile so dosage adjustment is not needed in renal insufficiency. Many medications are metabolized by P450 system and therefore many potential and significant drug interactions with CNI can occur. Classes of drugs that induce CYP3a can reduce CNI levels, such that increased dosing may be required to reach therapeutic and adequate ranges. On the other hand, drugs that block the action of CYP3a can lead to increased levels of CNI, which can lead to acute nephrotoxicity among other side effects. Specific blood pressure medications, antibiotics, anti-fungals, anti-convulsants and HIV medications need to be reviewed for p450 interactions, and both CNI and medications need to be adjusted accordingly. Commonly used medications that affect P450, and the subsequent impact on CNI levels are shown in Table 2.

Agents that are not often considered in practice, but having an effect on CNI include, steroids which when withdrawn can lead to increases in drug levels of CNIs, and binders such as cholestyramine and sevelamer which can bind CNIs and prevent absorption leading to sub therapeutic levels. Grape fruit juice increases absorption of tacrolimus and hence it is generally recommended to avoid its use with CNIs. Several herbal medications can also alter the metabolism of these drugs.

Because of the sensitive interactions between CNI and antiretrovirals, mangagement of CNI in HIV recipients can be challenging. CNI toxicity and supra therapeutic levels of CNI are common issues in HIV recipients and most likely contributes to allograft dyfunction. Reduced dosing of Tacrolimus is required with some protease inhibitors, particularly Ritonavir, the most potent blocker of CYP3A, and is dosed once to twice a week as opposed to the normal twice a day dosing.

Increases CNI level by inhibition of P450	Decreases CNI level by induction of P450
* Verapamil	Rifampin
Amlodipine	Rifabutin
* Diltiazem	Barbiturates
Nicardipine	Phenytoin
* Ketoconazole	Carbamazepine
Fluconazole	
Itraconazole	
Voriconazole	
Erythromycin	
Ritonavir	

*Significant increases in CNI level

Table 2. CNI-Drug Interactions

6.5. Adverse effects and toxicities of CNI

CNIs have facilitated the success of transplantation and a greater number of patients are living with functioning transplants for longer periods of time. This has made long term CNI exposure and the associated side effects inevitable. Cyclosporine and tacrolimus possess unique side effect profiles which play an important role in agent selection for individual patients.

One of the most significant side effects of CNIs is nephrotoxicity which contributes to chronic allograft dysfunction and late allograft loss. Acute CNI toxicity is functionally mediated by vasoconstriction of the afferent arteriole leading to reduction in renal blood flow and glomerular filtration rate. Studies demonstrate that CNI increases renin production in the kidney leading to angiotensin II mediated vasoconstriction. [26] Chronic exposure can lead to prolonged vasoconstriction and acute tubular necrosis. Chronic CNI nephrotoxicity can mediate vascular injury, glomerular ischemia, tubular atrophy and chronic interstitial fibrosis. Basic studies do demonstrate that excess production of fibrosing cytokines like transforming growth factor beta (TGF-β) is in part driven by CNI direct role on renin secretion in the kidney. [27] The development of calcineurin minimization and withdrawal protocols as well as the development of new maintenance agents are an attempt to prevent/minimize CNI nephrotoxicity and its impact on long-term allograft survival.

Other adverse renal manifestations of CNIs include thrombotic microangiopathy, which presents with renal dysfunction, microangiopathic hemolytic anemia and thrombocytopenia. CNI can also cause isolated tubular toxicity which manifests in many forms of electrolyte disturbances. The most prominent and clinically significant of these are renal tubular acidosis (RTA) type 4 (typically associated with metabolic acidosis and hyperkalemia) and hypomag-

nesemia. Proposed mechanisms mediating this effect includes, decreased aldosterone production secondary to cyclosporine, as well as decreased transcription and expression of mineralocorticoid receptor due to prograf.

Since calcineurin is a ubiquitous enzyme, there are other non-renal toxicities associated with CNI use. Tacrolimus is associated with neurotocity, GI side effects and pancreatic islet toxicity. Neurotoxicity can be as benign as tremors, but in some cases can be quite severe and lead to seizures and altered mental status. Finally, Tacrolimus use has been associated with posterior reversible encephalopathy syndrome (PRES) which can present with various neurological manifestations.[28] Another important clinical issue is the development of new onset post-transplant diabetes, or worsening diabetes post-transplant, particularly with tacrolimus. Neuro and pancreatic toxicity of tacrolimus are clinically handled by either dose reduction or conversion to cyclosporine. Cyclosporine use however can cause gingival hyperplasia, hirsutism, hypercholesterolemia, hypertension, salt retention and an increased incidence of gout. Both CNIs have been linked to increased risk of infectious complications as well as post transplant malignancies. Differences in adverse effects among the CNIs as well as other maintenance agents are shown in Table 3.

The current challenge is to mitigate the side effects of CNIs without sacrificing overall graft outcomes. Several novel protocols are recently designed and studied to overcome CNI toxicity. We have summarized these in the section of new evolving protocols.

6.6. Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a maintenance immunosuppressant used often in combination with CNIs and steroids. MMF was introduced in 1995 and has largely replaced azathioprine in transplantation, as clinical trials showed superiority of MMF when compared to azathioprine. [29] Based on a recent SRTR report in 2009, MMF was part of the initial maintenance regimen in 89.9% of kidney transplant recipients.

6.7. Mechanism of action

Mycophenolate mofetil is an inactive prodrug with mycophenolic acid (MPA) being its active component. The mofetil entity significantly increases bioavailability of MPA. There is an enteric coated form of MPA also available for use that may be better tolerated in some patients. MPA is a selective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) which is the rate-limiting enzyme in the denovo synthesis of purines. T- and B-lymphocytes are more dependent on this pathway than other cell types for proliferation since they do not have a salvage pathway for purine synthesis. Moreover, MPA is a more potent inhibitor of the type II isoform of IMPDH, which is predominatly expressed in activated lymphocytes.

6.8. Clinical use

MMF was initially approved for standard dose administration of 1 gram twice daily in adult kidney transplant recipients. Therapeutic drug monitoring for MMF/MPA is not performed routinely since several factors can impact the MPA AUC (detailed in the section below). Recent

http://dx.doi.org/10.5772/54865

studies however have shown an association between MPA exposure and clinical outcomes (rejection and toxicity) and therapeutic drug monitoring (TDM) in certain circumstances may be warranted. [30] [31] The APOMYGRE study has shown decreased incidence of acute rejection with individualized MMF dosing based on drug exposure. [32]

When a serious infection develops, MMF or MPA is typically held since the drug's impact on lymphocyte proliferation is reversible and the immunosuppressive effects disappear within a few days. Intravenous formulations are available for MMF and intravenous dosing is the same as oral dosing with 1:1 conversion. Dose adjustment is not necessary in renal insufficiency. These drugs are not dialyzable. Use of MMF in pregnancy is contraindicated since it is associated with congenital malformations in the fetus especially facial abnormalities.[33] Mycophenolate should be discontinued before planned pregnancy in both male and female transplant recipients.

6.9. MMF exposure and metabolism

Mycophenolate moefetil is rapidly absorbed and hydrolysed to yield the active component MPA mainly in the liver, which is detectable in peripheral blood within 1-2 hours. MPA is then converted to 7-0-MPA glucuronide also referred to as MPAG (an inactive metabolite) by UDP-glucuronosyl transferase (UDPGT) in the liver and intestine. MPAG is excreted through the bile and urine. Both MPA and MPAG are protein bound. So factors such as low albumin concentration and high urea levels can decrease protein binding and lead to rapid clearance of the drug. MPAG accumulation in renal failure displaces MPA from protein binding and can lead to an increase in the free fraction of the drug. Once MPAG is excreted in the bile it can be converted back to MPA by bacterial glucuronidases and lead to increased levels of MPA (enterohepatic recirculation). This leads to a second peak in the drug concentration 6 to 12 hours after administration which contributes to more than 30% of the area under the curve. Cyclosporine leads to inhibition of this second peak by blocking the transporters involved in biliary excretion of MPAG. So typically patients on cyclosporine need higher doses of MMF or MPA compared to patients on tacrolimus. Antibiotic therapy is also known to have a similar impact by inhibiting bacterial proliferation in the gut and hence inhibiting enterohepatic recirculation.

There is no significant drug interaction with medications that induce or block the CYP3A pathway. When used in combination with sirolimus both agents can lead to cytopenias. Generally co administration with antacids and cholestyramine should be avoided as they interfere with absorption of MMF.

6.10. Toxicity

The main dose limiting toxicity of MMF or enteric coated MPA is related to gastrointestinal (GI) side effects. More than one third of patients develop diarrhea and in addition some patients have nonspecific GI intolerance in the form of dyspepsia, nausea and vomiting. Indeed, there is evidence demonstrating a correlation between drug exposure and GI toxicity. [31] Most of these side effects are handled with either dose reduction or splitting the dose into 3 to 4 divided doses. Although patients may tolerate enteric coated MPA better, studies

curiously do not demonstrate major differences in the GI side effect profile of MMF and enteric coated MPA. [34]

Another major side effect of these preparations is bone marrow suppression mainly manifesting with leucopenia. Typically the dose of MMF is reduced based on the severity of leucopenia. There appears to be a correlation between the incidence of leucopenia and drug exposure. [31] Anemia and thrombocytopenia can occur as well.

6.11. Azathioprine

Azathioprine (Imuran) has been in use in transplantation for more than three decades. With introduction of CNIs and MMF, many centers have moved away from using azathioprine as a first line maintenance agent. SRTR reports from 2009 demonstrate that only 0.6% of the kidney transplant recipients were on Azathioprine. It is commonly used now primarily in patients who are intolerant to MMF. Usual daily dose administered is 2-3 mg/kg once daily.

6.12. Mechanism of action, metabolism and major drug interactions

Azathioprine is an antimetabolite a derivative of 6-mercaptopurine. It gets incorporated into cellular deoxyribonucleic acid (DNA). Once incorporated into DNA it interferes with transcription, purine and ribonucleic acid (RNA) synthesis which are important for T cell activation. Azathioprine is metabolized by xanthine oxidase inhibitor to 6–thiouric acid. Hence allopurinol which is a xanthine oxidase inhibitor should be used with great caution with azathioprine as it can lead to significant toxicity. Typically the dose of azathioprine is reduced when used in combination with allopurinol.

6.13. Adverse drug reactions

The single most severe toxicity of azathioprine is related to suppression of bone marrow. Patients can develop profound leucopenia and thrombocytopenia. It is recommended to monitor white count and platelet count carefully every 2 weeks at initiation. The dose of the drug will need to be decreased if leucopenia occurs and severe leucopenia might necessitate discontinuation of the drug. Cholestasis, hepatic veno occlusive disease, hepatitis and rare cases of pancreatitis have been described with azathioprine use.

6.14. Sirolimus

Sirolimus (Rapamycin) was introduced to transplantation in the late 1990s. It has antitumor, antiproliferative and immunosuppressive actions. Sirolimus plays a key role in immunosuppression especially as an alternative to CNIs to minimize long term CNI induced nephrotoxicity. SRTR database reported that the use of sirolimus as part of initial maintenance regimen peaked in 2001; however it gradually declined to only 3% of kidney transplant recipients receiving it in 2009. In the same report at 1 year post transplantation, 6.5% of recipients were receiving sirolimus. The declining use of sirolimus can be attributed to the side effects encountered with medication usage.

http://dx.doi.org/10.5772/54865

The unique antitumoral properties of sirolimus, however, make it an attractive option for immunosuppression in patients with post transplant malignancies. Recent study reported by Euvrard et al (Tumorapa study) has shown that sirolimus conversion has provided protection against recurrence of skin cancers in patients with squamous cell carcinomas of the skin post transplant. [35]

6.15. Mechanism of action

Similar to CNIs sirolimus binds to cytoplasmic protein FKBP-12 to mediate its action. The sirolimus/FKBP-12 complex then inhibits mTOR (mammalian target of rapamune). This enzyme is a kinase that plays a key role in cell cycle progression (G1-S transition). Blocking mTOR has a profound effect on inhibiting T-cell proliferation and expansion. mTOR is expressed ubiquitously so the antiproliferative effects of sirolimus is not limited to lymphocytes and attributes to several adverse effects of the drug which are detailed below.

The anti-tumor effect of sirolimus is mediated by inhibiting the PI3K-AKT pathway which plays a critical role in cell proliferation, survival, migration and angiogenesis. [36] In addition it inhibits growth of endothelial cells and tumor angiogenesis by interfering with synthesis of vascular endothelial growth factor.

6.16. Clinical use

Sirolimus has a long half life of 60 to 70 hours so consideration is needed when initiating the drug or making dose adjustments. Usually patients receive a loading dose of 3-15mg followed by once daily dosing of 1-5mg per day. The loading and maintenance dose are generally determined by patient weight and immunologic risk. The dose is then adjusted based on drug levels. Therapeutic drug monitoring is routinely used with sirolimus. It is recommended to check 24 hour trough levels several days after initiation or dosage adjustment of sirolimus since it takes longer to achieve a steady state.

The drug is available as oral tablet at 0.5mg, 1mg and 2mgs dose. In addition there is also liquid formulation with strength of 1mg/ml. It is metabolized by CYP3A and hence dose needs to be adjusted in liver disease, but not in renal impairment.

6.17. Metabolism and drug interactions

As both sirolimus and CNIs are metabolized by CYP3A enzyme pathway, concomitant use of both agents can increase exposure to sirolimus 2 to 3 fold. It is generally recommended that sirolimus be administered a few hours after CNI dosing. Similar to CNIs, it interacts with drugs that induce and block the CYP3A pathway. Sirolimus is not renally excreted so dose adjustment is not needed in renal failure. However dose adjustment is recommended in patients with hepatic dysfunction.

6.18. Adverse reactions

Sirolimus is considered to be less nephrotoxic than CNIs, however there are some unique renal side effects related to its use. Sirolimus potentiates CNI nephrotoxicity and can be tubulotoxic

leading to hypomagnesemia and hypokalemia. De novo development of proteinuria, or exaggeration of preexisting proteinura is seen with conversion to sirolimus.[37] Use of sirolimus is in fact contraindicated if patient has 24 hour urine protein exceeding 1 gram/day. Sirolimus has been reported to have a direct toxic effect on podocytes. [38] [39] Sirolimus associated cast nephropathy has been reported as well. [40] Thrombotic microangiopathy has also been observed with sirolimus use, likely mediated by its inhibition of VEGF pathway. [41] The discontinuation rate of Sirolimus was as high as 30% in clinical studies due to adverse reactions. [42-44]

Use of sirolimus is not recommended immediately after transplant surgery as sirolimus impairs wound healing (by inhibiting fibroblast proliferation). Sirolimus can increase the risk of lymphocele formation and is also associated with prolonged recovery from delayed graft function. [45]. Due to its effects on tissue repair, sirolimus is generally stopped few weeks prior to any anticipated elective surgery. Metabolic side effects of sirolimus include hyperlipidemia and hyperglycemia. Sirolimus use is also associated with non-infectious atypical pneumonitis. Bactrim is typically prescribed for one year as there are studies observing fatal pneumocystis pneumonia with sirolimus use. Sirolimus also suppresses bone marrow leading to cytopenias. Cell counts should be closely monitored especially when used in combination with MMF. Patients also can develop oral ulcers with this agent.

Adverse Effects	Tac	CsA	mTORi	MMF	Steroids
Nephrotoxicity	↑	↑			
Proteinuria			↑↑		
Hypertension		↑↑			↑↑
Hyperlipidemia		↑	↑↑		↑
New Onset Diabetes	↑↑	↑	↑		↑
Delayed Wound Healing			↑		
Osteopenia	↑	↑			↑↑
Hyperuricemia					
Anemia/Leukopenia			↑	↑	
GI side effects	↑			↑↑	

Tac, Tacrolimus; CsA, Cyclosporine; mTORi, mammalian target of rapamycin inhibitor; MMF, mycophenolate mofetil

↑: mild-moderate adverse effect on the complication

↑↑: moderate-severe adverse effect on the complication

Table 3. Adverse Effects Of Maintenance Immunosuppressive agents

http://dx.doi.org/10.5772/54865

6.19. Everolimus

There are recent studies on use of everolimus in kidney transplant recipients. [46] It is similar to sirolimus in terms of mechanism of action and side effect profile. The only major difference from sirolimus is its shorter half life.

6.20. Corticosteroids

Since the early 1960's, corticosteroids were used in kidney transplantation both as maintenance agents and to treat acute rejections. [47-49]. Corticosteroids down-regulate cytokine gene expression through interference with transcription. Since they are lipophilic they first translocate into cytoplasm and bind to receptors. The steroid –receptor complex then translocates to the nucleus to bind to glucocorticoid responsive elements on DNA to regulate transcription. By dampening cytokine production they blunt the immune response generated by T cells. Long-term steroid use is associated with several adverse effects including hypertension, new onset diabetes after transplantation, osteoporosis, fractures, hyperlipidemia, growth retardation, weight gain, avascular necrosis, cataracts, cosmetic changes, depression, and psychotic behavior. With the advent of potent maintenance and induction agents the transplant community is now moving more and more towards steroid sparing strategies.

6.21. Leflunomide

Leflunomide is used for maintenance immunousppression especially in patients with BK nephropathy. [50, 51] It has both imunosuppressive properties and antiviral activity against BK. It blocks pyramidine synthesis in lymphocytes. The common adverse effects with its use are GI toxicity and neuropathy. There are no major drug interactions with leflunomide.

7. Alternative maintenance regimens

Different immunosuppressive strategies and protocols have evolved over time to address several major concerns with maintenance regimens. Major concerns include the long term side effects of chronic steroid use, as well as long term calcineurin nephrotoxicity which contribute to decreased long-term graft survival. Protocols that have been studied and published include steroid withdrawal and avoidance, as well as studies where calcineurin use is avoided, minimized or replaced with other agents.

7.1. Steroid withdrawal/avoidance (SAW)

Steroid withdrawal typically involves discontinuing steroids several months post transplantation whereas steroid avoidance involves no corticosteroid maintenance at all and only a brief exposure to steroids in the immediate post operative period. Studies demonstrate that early steroid withdrawal is safer than late withdrawal as late withdrawal was associated with increased risk of acute rejections. [52, 53] A recent meta-analysis of 34 randomized controlled studies using SAW regimens published by Knight et al concluded that SAW is associated with

increased risk of acute rejection, however this did not impact long term patient or graft survival. [54] There is a more favorable cardiovascular profile with SAW most likely secondary to decreased incidence of hypertension, new onset diabetes and dyslipidemia. As many studies have shown increased risk of acute rejections with SAW it is generally implemented with caution in high immunologic risk recipients (high PRA, repeat transplants, young African American recipients, patients with prior rejections and/or unstable graft function). With use of more potent induction regimens more US centers are currently implementing SAW in immunologically low risk recipients.

7.2. Calcineurin inhibitor avoidance/minimization/withdrawal

Several studies have looked at minimizing exposure to CNIs to over come nephrotoxicity. Complete calcineurin avoidance with de novo use of sirolimus has not been successful and was associated with higher incidence of rejections and graft loss. [43]. Due to this, more centers and studies have favored calcineurin minimization and withdrawal (at 3 to 6 months post transplant) as opposed to complete avoidance. The ELITE-symphony trial was a land mark trial comparing different regimens of calcineurin minimization and withdrawal demonstrating better allograft outcomes at three years of follow up in patients on low dose tacrolimus (in addition to steroids and MMF) than standard dose cyclosporine, reduced dose cyclosporine or low dose sirolimus as primary maintenance agent. [44] A recent meta-analysis evaluating calcineurin minimization strategies concluded that calcineurin minimization decreases rates of graft failure, incidence of delayed graft function, and new onset diabetes post transplant while avoiding an increased risk of acute rejection. [55].

8. Antirejection therapies

Rejection is a common problem with renal allografts, and can be of cellular (lymphocyte) and/or humoral (circulating antibody) origin. It is well known that if acute rejection is left untreated, eventually graft failure ensues. Rejection can be acute or subclinical. Acute rejection is clinically evident and often presents as a decline in kidney function associated with a rise in creatinine and classic histologic changes seen on renal biopsy. On the other hand, subclinical rejection is subtle; where histologic changes of rejection may be present in grafts that otherwise appear to have stable renal function. Immunosuppressive management for subclinical rejection has not been well delineated. [56-58] Finally, rejection may be mixed and have both cellular and humoral components.

Overall the incidence of acute rejection post-transplant has decreased. However, survival of allografts has not increased to the extent predicted, mostly due to the universal development of chronic allograft dysfunction and late graft loss. Chronic allo-immune injury has been recognized as a major contributor to late graft loss and can present early on in transplantation as demonstrated by several protocol biopsy studies. [59, 60] Compared to cell-mediated rejections, humoral rejection and chronic rejection can be challenging to treat. In addition, the

http://dx.doi.org/10.5772/54865

optimal treatments for humoral rejection, subclinical rejection and chronic rejection have yet to be defined by the transplant community..

8.1. Treatment of cellular rejection

Acute cellular rejection is a T-cell–mediated process, is usually easy to treat, and responds well to therapy. T-cell directed induction therapies, and calcineurin maintenance has substantially decreased the overall incidence of cell-mediated acute rejections. Low grade cellular rejection with out vascular involvement is treated with high dose, intravenous steroids. The dose and duration of treatment with corticosteroids has not been well defined by studies, and is often left to physician discretion. Thymoglobulin in combination with steroids is used to treat severe and high grade acute cellular rejections with a vascular component. Although Thymoglobulin is most widely used for high grade cellular rejections, there are small case series and small studies that favor the use of alemtuzumab for treatment of cellular rejections. [61]

8.2. Treatment of humoral rejection

Humoral rejection mediated by alloreactive B-cells, alloantibodies and complement are more challenging to treat. Humoral rejection is often refractory to treatment and continues to be a significant problem in transplantation due to difficulties in establishing a consensus for safe optimal treatments directed against allosensitization and alloantibody production. Humoral responses also greatly contribute to late acute graft losses and the development of chronic rejection. [62] Humoral rejection has been linked to the presence of donor specific antibody and activation of complement resulting in C4d deposits in renal tissue. Therapeutic strategies have been aimed both at removing alloantibodies as well as decreasing alloantibody production by impairing and/or depleting B-cells. [63, 64]

The best known treatment algorithms to treat antibody mediated rejection include combinations of plasma exchange to remove donor-specific antibody, and/or intravenous immunoglobulins and the anti-CD20 monoclonal antibody (rituximab) to suppress donor-specific antibody production. [65, 66] There are no randomized controlled trials powered to show efficacy or safety of potential different combinations of these different therapeutic strategies. Some side effects of plasmapheresis include hypotension, citrate induced hypocalcemia, complications with access placement, and infections due to removal of immunoglobulins. Adverse reactions of IVIG include anaphylactoid reactions, fevers, chills, flushing, myalgias, malaise, headache, nausea, vomiting, dilutional hyponatremia, pseudohyponatremia, hemolysis and neutropenia. See previous section on Rituximab for side effects.

Bortezomib continues to be a promising agent for acute humoral rejection because of its ability to target multiple pathways involved in B-cell activation and antibody production and its direct activity against CD138+ long lived plasma cells that exist in survival niches such as the bone marrow and spleen. [67] These cells, primarily responsible for producing high affinity alloantibody, are not targeted by Rituximab, the current mainstay treatment for humoral rejection. [68, 69] Initial reports on Bortezomib were in patients with AMR that were refractory to traditional anti-humoral therapies, but recent reports show that Bortezomib can be used as

primary therapy for AMR. [70] In terms of its ability to decrease the levels of donor specific antibodies in sensitized patients and patients with AMR, studies have provided mixed results. [71, 72] Part of this may be secondary to differing conditioning regimens that accompany the use of Bortezomib. Another important finding reported by two studies is the differential responses of early versus late AMR after treatment with Bortezomib, with early AMR responding much better than late. [25]

8.3. Treatment of mixed rejection

Rejection may be mixed and have both cellular and humoral components. To date, there are no randomized control studies evaluating different therapies for the treatment of mixed rejection. Case series and small studies suggest that choosing a biologic agent that has activity against both T-cell and B-cell activity would be more favorable. Agents that have broad based activity such as Campath or Bortezomib may be better choices, than T-cell directed agents such as rATG. Plasmapharesis and IVIG may also be added therapies, especially if there is the presence of circulating donor specific antibody. Unfortunately, trials evaluating different combinations of these therapies or head to head comparison of these biologic agents do not exist.

9. Novel immunosuppressive agents

Given substantially decreased rates of acute rejection secondary to potent induction agents and CNI based maintenance regimens, the focus has shifted away from acute rejection to preserving grafts for the long-term. However, many studies are still focused on short term outcomes and there are very few studies looking at which drugs or combinations thereof offer better long term graft function.

Long term graft preservation may be particularly challenging given the nephrotoxic effects of CNIs on allografts. To address this issue, a number of novel agents are undergoing trials currently as a replacement to CNIs. [73] Several biologic agents and fusion proteins have emerged and unfortunately many of these agents have been discarded after preliminary trials due to their toxicity. In addition there are several trials focusing on tolerogenic protocols to avoid use of long term immunosuppression. Table 4 below summarizes the new agents that are currently undergoing clinical trials. Belatacept discussed below, is a newer biologic agent that has been studied the most extensively.

9.1. Belatacept

Belatacept is a recombinant fusion protein with an extracellular domain that consists of human cytotoxic T lymphocyte antigen-4 (CTLA-4) and the Fc fragment of human IgG. The fusion protein Belatacept (CTLA-4Ig) blocks the interaction of CD80/86 present on antigen presenting cells (APC), with the CD28 receptor expressed on T cells. CD80/86 are costimulatory molecules that are necessary for providing costimulation and full activation of T-cells, a requirement for T-cell cytokine production and expansion. The most exciting feature of CTLA4Ig is its known ability to generate immune tolerance particularly in animal models of

transplantation and autoimmunity. [74, 75] Whether tolerance can be generated in vivo in humans, however remains to be seen.

Agent	Mechanism of action	Clinical Indication	Studies
TOL101	Target ? T-cell receptor Non-depletional Inactivates T-cell	Induction	Phase 2
Sotrastaurin	Proteinkinase C inhibitor Blocks T-cell activation	Maintenance	Studies halted secondary to increased rejection rates
Tofacitinib	Inhibitor of the JAK-STAT pathway. Blocks T-cell activation	Maintenance	Phase 2
ASKP1240	Humanized antibody against CD40 on antigen presenting cells	Maintenance	Phase 1

*References [77-79]

Table 4. Novel Immunosuppressive Agents

Belatacept is a relatively new agent used in human transplantation with the first report of its use in human renal transplantation in 2005. The focus of clinical investigative trials utilizing belatacept was to provide a new effective maintenance regimen that would allow for the avoidance of the renal and metabolic side effects of chronic CNI use. Studies such as the BENEFIT and BENEFIT-EXT trials demonstrate its efficacy as a maintenance agent in place of calcineurin inhibitors. [76] The three year follow up data of BENEFIT where belatacept was compared to cyclosporine concluded that patient and graft survival were comparable with better GFR in the belatacept arm. There was however increased incidence of acute rejection and early post transplant lymphoproliferative disease in the belatacept group (especially in EBV sero negative patients). For this reason, belatacept use is approved only for patients who are EBV seropositive. The cost and long term need for intravenous administration of the drug appear to be major obstacles for wide spread use of belatacept. Nevertheless, it still provides a valuable alternative to long term CNI use.

10. Conclusion

Establishing optimal immunosuppressive regimens involves maintaining a delicate balance between over-immunosuppression which increases infection risk and under-immunosuppression which increases risk of allograft rejection. Use of potent induction agents and maintenance therapies that include CNI has led to dramatic decrease in the incidence of acute rejection episodes in the immediate post transplantation period. However, late allograft loss

and long-term graft survival are problems that persist despite better immunosuppression. Chronic CNI toxicity, humoral rejection and the development of chronic alloreactivity to donor allograft tissue are major contributing factors to late graft loss.

One challenge with current maintenance regimens is the toxicity related to long term CNI use. Steroid avoidance/withdrawal protocols continue to be evaluated and are being implemented successfully at some centers. Rapamune has been studied in several trials as a CNI sparing agent, but has not gained wide acceptance due to its side effect profile. The predominant trend in recent clinical trials is to find a long term alternative agent to replace CNI. Belatacept was recently approved by the FDA for use as maintenance agent and appears to be a promising alternative to long term CNI use. However, the majority of centers lack experience with belatacept and long term outcome data is lacking.

Other challenges include the rising percentage of sensitized patients on the transplant wait list. Strategies to offer transplantation to these highly sensitized recipients include transplantation against a positive cross match donor, paired kidney exchange and aggressive desensitization to lower alloantibody titers. Immunosuppressive protocols aimed at successfully transplanting sensitized recipients continue to be investigated as these patients present a special immunologic challenge. Sensitized patients are at increased risk of developing antibody mediated rejection and earlier graft loss post-transplant. Several new agents like bortezomib and eculizumab are currently being tested in these patients.

Finally, the optimal immunosuppressive strategy would ideally be one which promotes the development of tolerance to alloantigens such that immunosuppression can be withdrawn successfully. The development of tolerance is certainly possible as the literature supports incidental cases of operational tolerance, where recipients are on minimal or no immunosuppression without evidence of allograft rejection. Currently, the majority of patients will require life long immunosuppressive therapy. Basic mechanisms promoting tolerance are being investigated with the hope that new medications or tolerogenic protocols may be implemented in the near future.

Author details

M. Ghanta, J. Dreier, R. Jacob and I. Lee*

*Address all correspondence to: iris.lee@tuhs.temple.edu

Section of Nephrology, Temple University School of Medicine, Philadelphia, PA, USA

References

[1] Lamb, K. E, & Lodhi, S. Meier-Kriesche HU: Long-term renal allograft survival in the United States: a critical reappraisal. Am J Transplant, , 11, 450-462.

[2] Einecke, G, Sis, B, Reeve, J, Mengel, M, Campbell, P. M, Hidalgo, L. G, & Kaplan, B. Halloran PF: Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant (2009).

[3] Cai, J. Terasaki PI: Induction immunosuppression improves long-term graft and patient outcome in organ transplantation: an analysis of United Network for Organ Sharing registry data. Transplantation, , 90, 1511-1515.

[4] Beiras-fernandez, A, & Thein, E. Hammer C: Induction of immunosuppression with polyclonal antithymocyte globulins: an overview. Exp Clin Transplant (2003).

[5] Zand, M. S, Vo, T, Huggins, J, Felgar, R, Liesveld, J, Pellegrin, T, Bozorgzadeh, A, & Sanz, I. Briggs BJ: Polyclonal rabbit antithymocyte globulin triggers B-cell and plasma cell apoptosis by multiple pathways. Transplantation (2005).

[6] Lopez, M, Clarkson, M. R, Albin, M, Sayegh, M. H, & Najafian, N. A novel mechanism of action for anti-thymocyte globulin: induction of CD4+CD25+Foxp3+ regulatory T cells. J Am Soc Nephrol (2006).

[7] Stock, P. G, Barin, B, Murphy, B, Hanto, D, Diego, J. M, Light, J, Davis, C, Blumberg, E, Simon, D, Subramanian, A, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med, (2004). , 363, 2004-2014.

[8] Trullas, J. C, Cofan, F, Tuset, M, Ricart, M. J, Brunet, M, Cervera, C, Manzardo, C, Lopez-dieguez, M, Oppenheimer, F, Moreno, A, et al. Renal transplantation in HIV-infected patients: (2010). update. Kidney Int, , 79, 825-842.

[9] Kamar, N, Borde, J. S, Sandres-saune, K, Suc, B, Barange, K, Cointault, O, Lavayssiere, L, Durand, D, & Izopet, J. Rostaing L: Induction therapy with either anti-CD25 monoclonal antibodies or rabbit antithymocyte globulins in liver transplantation for hepatitis C. Clin Transplant (2005).

[10] Roth, D, Gaynor, J. J, Reddy, K. R, Ciancio, G, Sageshima, J, Kupin, W, Guerra, G, Chen, L, & Burke, G. W. rd: Effect of kidney transplantation on outcomes among patients with hepatitis C. J Am Soc Nephrol, , 22, 1152-1160.

[11] Noel, C, Abramowicz, D, Durand, D, Mourad, G, Lang, P, Kessler, M, Charpentier, B, Touchard, G, Berthoux, F, Merville, P, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol (2009).

[12] Locke, J. E, Montgomery, R. A, Warren, D. S, & Subramanian, A. Segev DL: Renal transplant in HIV-positive patients: long-term outcomes and risk factors for graft loss. Arch Surg (2009).

[13] Carter, J. T, Melcher, M. L, Carlson, L. L, & Roland, M. E. Stock PG: Thymoglobulin-associated Cd4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. Am J Transplant (2006).

[14] (Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, Holman J: Alemtuzumab induction in renal transplantation. N Engl J Med, 364:1909-1919). 364, 1909-1919.

[15] Vo, A. A, Lukovsky, M, Toyoda, M, Wang, J, Reinsmoen, N. L, Lai, C. H, Peng, A, & Villicana, R. Jordan SC: Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med (2008).

[16] Takagi, T, Ishida, H, Shirakawa, H, & Shimizu, T. Tanabe K: Evaluation of low-dose rituximab induction therapy in living related kidney transplantation. Transplantation, , 89, 1466-1470.

[17] Clatworthy, M. R, Watson, C. J, Plotnek, G, Bardsley, V, Chaudhry, A. N, & Bradley, J. A. Smith KG: B-cell-depleting induction therapy and acute cellular rejection. N Engl J Med (2009).

[18] (Stegall MD, Diwan T, Raghavaiah S, Cornell LD, Burns J, Dean PG, Cosio FG, Gandhi MJ, Kremers W, Gloor JM: Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant, 11:2405-2413). 11, 2405-2413.

[19] Perry, D. K, Burns, J. M, Pollinger, H. S, Amiot, B. P, Gloor, J. M, & Gores, G. J. Stegall MD: Proteasome inhibition causes apoptosis of normal human plasma cells preventing alloantibody production. Am J Transplant (2009).

[20] Wu J: On the role of proteasomes in cell biology and proteasome inhibition as a novel frontier in the development of immunosuppressants. (2002). *Am J Transplant*.

[21] Wang, X, Luo, H, Chen, H, & Duguid, W. Wu J: Role of proteasomes in T cell activation and proliferation. J Immunol (1998).

[22] Everly, M. J, Everly, J. J, Susskind, B, Brailey, P, Arend, L. J, Alloway, R. R, Roy-chaudhury, P, Govil, A, Mogilishetty, G, Rike, A. H, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation (2008).

[23] Idica, A, Kaneku, H, Everly, M. J, Trivedi, H. L, Feroz, A, Vanikar, A. V, Shankar, V, Trivedi, V. B, Modi, P. R, Khemchandani, S. I, et al. Elimination of post-transplant donor-specific HLA antibodies with bortezomib. Clin Transpl (2008). , 2008, 229-239.

[24] Lee, I, Constantinescu, S, Gillespie, A, Swami, A, Birkenbach, M, Leech, S, Silva, P, Karachristos, A, & Daller, J. A. Sifontis NM: Bortezomib as therapy for mixed humoral and cellular rejection: should it be first line? Clin Transpl (2009). , 2009, 425-429.

[25] Lee, I, Constantinescu, S, Gillespie, A, Rao, S, Silva, P, Birkenbach, M, Leech, S, Karachristos, A, & Daller, J. A. Sifontis NM: Targeting alloantibody production with bortezomib: does it make more sense? Clin Transpl:, 397-403.

[26] Madsen, K, Friis, U. G, Gooch, J. L, Hansen, P. B, Holmgaard, L, & Skott, O. Jensen BL: Inhibition of calcineurin phosphatase promotes exocytosis of renin from juxtaglomerular cells. Kidney Int, , 77, 110-117.

[27] Khanna, A. K, Cairns, V. R, & Becker, C. G. Hosenpud JD: Transforming growth factor (TGF)-beta mimics and anti-TGF-beta antibody abrogates the in vivo effects of cyclosporine: demonstration of a direct role of TGF-beta in immunosuppression and nephrotoxicity of cyclosporine. Transplantation (1999).

[28] Wu, Q, Marescaux, C, Wolff, V, Jeung, M. Y, Kessler, R, & Lauer, V. Chen Y: Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. Eur Neurol, , 64, 169-177.

[29] Meier-kriesche, H. U, Steffen, B. J, Hochberg, A. M, Gordon, R. D, Liebman, M. N, & Morris, J. A. Kaplan B: Mycophenolate mofetil versus azathioprine therapy is associated with a significant protection against long-term renal allograft function deterioration. Transplantation (2003).

[30] Hale, M. D, Nicholls, A. J, Bullingham, R. E, Hene, R, Hoitsma, A, Squifflet, J. P, Weimar, W, & Vanrenterghem, Y. Van de Woude FJ, Verpooten GA: The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther (1998).

[31] Van Gelder, T, Hilbrands, L. B, Vanrenterghem, Y, Weimar, W, De Fijter, J. W, Squifflet, J. P, Hene, R. J, Verpooten, G. A, Navarro, M. T, Hale, M. D, & Nicholls, A. J. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. Transplantation (1999).

[32] Le Meur YBuchler M, Thierry A, Caillard S, Villemain F, Lavaud S, Etienne I, Westeel PF, Hurault de Ligny B, Rostaing L, et al: Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant (2007).

[33] Coscia, L. A, Constantinescu, S, Moritz, M. J, Frank, A. M, Ramirez, C. B, Maley, W. R, Doria, C, & Mcgrory, C. H. Armenti VT: Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl:, 65-85.

[34] Cooper, M, Deering, K. L, Slakey, D. P, Harshaw, Q, Arcona, S, Mccann, E. L, & Rasetto, F. A. Florman SS: Comparing outcomes associated with dose manipulations of enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients. Transplantation (2009).

[35] Euvrard, S, Morelon, E, Rostaing, L, Goffin, E, Brocard, A, Tromme, I, & Broeders, N. del Marmol V, Chatelet V, Dompmartin A, et al: Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med, , 367, 329-339.

[36] Dormond, O, & Madsen, J. C. Briscoe DM: The effects of mTOR-Akt interactions on anti-apoptotic signaling in vascular endothelial cells. J Biol Chem (2007).

[37] Dogan, E, & Ghanta, M. Tanriover B: Collapsing glomerulopathy in a renal transplant recipient: potential molecular mechanisms. Ann Transplant, , 16, 113-116.

[38] (Biancone L, Bussolati B, Mazzucco G, Barreca A, Gallo E, Rossetti M, Messina M, Nuschak B, Fop F, Medica D, et al: Loss of nephrin expression in glomeruli of kidney-transplanted patients under m-TOR inhibitor therapy. Am J Transplant, 10:2270-2278). 10, 2270-2278.

[39] Stallone, G, Infante, B, Pontrelli, P, Gigante, M, Montemurno, E, Loverre, A, Rossini, M, Schena, F. P, & Grandaliano, G. Gesualdo L: Sirolimus and proteinuria in renal transplant patients: evidence for a dose-dependent effect on slit diaphragm-associated proteins. Transplantation, , 91, 997-1004.

[40] Coombes, J. D, Mreich, E, & Liddle, C. Rangan GK: Rapamycin worsens renal function and intratubular cast formation in protein overload nephropathy. Kidney Int (2005).

[41] Reynolds, J. C, Agodoa, L. Y, & Yuan, C. M. Abbott KC: Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis (2003).

[42] Lebranchu, Y, Thierry, A, Toupance, O, Westeel, P. F, Etienne, I, Thervet, E, Moulin, B, & Frouget, T. Le Meur Y, Glotz D, et al: Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. Am J Transplant (2009).

[43] Glotz, D, Charpentier, B, Abramovicz, D, Lang, P, Rostaing, L, Rifle, G, Vanrenterghem, Y, Berthoux, F, Bourbigot, B, Delahousse, M, et al. Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation, , 89, 1511-1517.

[44] Ekberg, H, Tedesco-silva, H, Demirbas, A, Vitko, S, Nashan, B, Gurkan, A, Margreiter, R, Hugo, C, Grinyo, J. M, Frei, U, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med (2007).

[45] Mctaggart, R. A, Tomlanovich, S, Bostrom, A, & Roberts, J. P. Feng S: Comparison of outcomes after delayed graft function: sirolimus-based versus other calcineurin-inhibitor sparing induction immunosuppression regimens. Transplantation (2004).

[46] Mjornstedt, L, & Sorensen, S. S. von Zur Muhlen B, Jespersen B, Hansen JM, Bistrup C, Andersson H, Gustafsson B, Undset LH, Fagertun H, et al: Improved Renal Function After Early Conversion From a Calcineurin Inhibitor to Everolimus: a Randomized Trial in Kidney Transplantation. Am J Transplant.

[47] Goodwin, W. E, & Mims, M. M. Kaufman JJ: Human renal transplantation III. Technical problems encountered in six cases of kidney homotransplantation. Trans Am Assoc Genitourin Surg (1962).

[48] Starzl, T. E, & Marchioro, T. L. Waddell WR: The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance. Surg Gynecol Obstet (1963).

[49] Mcgeown, M. G, Douglas, J. F, Brown, W. A, Donaldson, R. A, Kennedy, J. A, Loughridge, W. G, & Mehta, S. Hill CM: Low dose steroid from the day following renal transplantation. Proc Eur Dial Transplant Assoc (1979).

[50] Josephson, M. A, Gillen, D, Javaid, B, Kadambi, P, Meehan, S, Foster, P, Harland, R, Thistlethwaite, R. J, Garfinkel, M, Atwood, W, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation (2006).

[51] Williams, J. W, Javaid, B, Kadambi, P. V, Gillen, D, Harland, R, Thistlewaite, J. R, Garfinkel, M, Foster, P, Atwood, W, Millis, J. M, et al. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med (2005).

[52] Kasiske, B. L, Chakkera, H. A, Louis, T. A, & Ma, J. Z. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol (2000).

[53] Pascual, J, Quereda, C, & Zamora, J. Hernandez D: Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. Transplantation (2004).

[54] Knight, S. R. Morris PJ: Steroid avoidance or withdrawal in renal transplantation. Transplantation, 91:e25; author reply e, 26-27.

[55] (Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R: Meta-analysis of calcineurin-inhibitor-sparing regimens in kidney transplantation. J Am Soc Nephrol, 22:2107-2118). 22, 2107-2118.

[56] Rush, D, Nickerson, P, Gough, J, Mckenna, R, Grimm, P, Cheang, M, Trpkov, K, & Solez, K. Jeffery J: Beneficial effects of treatment of early subclinical rejection: a randomized study. J Am Soc Nephrol (1998).

[57] Rush, D. N, Karpinski, M. E, Nickerson, P, Dancea, S, & Birk, P. Jeffery JR: Does subclinical rejection contribute to chronic rejection in renal transplant patients? Clin Transplant (1999).

[58] Kurtkoti, J, Sakhuja, V, Sud, K, Minz, M, Nada, R, Kohli, H. S, Gupta, K. L, & Joshi, K. Jha V: The utility of and 3-month protocol biopsies on renal allograft function: a randomized controlled study. Am J Transplant (2008). , 1.

[59] Joosten, S. A, Sijpkens, Y. W, & Van Kooten, C. Paul LC: Chronic renal allograft rejection: pathophysiologic considerations. Kidney Int (2005).

[60] Mengel, M, Chapman, J. R, Cosio, F. G, Cavaille-coll, M. W, Haller, H, Halloran, P. F, Kirk, A. D, Mihatsch, M. J, Nankivell, B. J, Racusen, L. C, et al. Protocol biopsies in renal transplantation: insights into patient management and pathogenesis. Am J Transplant (2007).

[61] Webster, A. C, Pankhurst, T, Rinaldi, F, & Chapman, J. R. Craig JC: Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systematic review of randomized trial data. Transplantation (2006).

[62] Bartel, G, Regele, H, Wahrmann, M, Huttary, N, Exner, M, & Horl, W. H. Bohmig GA: Posttransplant HLA alloreactivity in stable kidney transplant recipients-incidences and impact on long-term allograft outcomes. Am J Transplant (2008).

[63] Terasaki, P. I. Ozawa M: Predicting kidney graft failure by HLA antibodies: a prospective trial. Am J Transplant (2004).

[64] Everly, M. J, Everly, J. J, Arend, L. J, Brailey, P, Susskind, B, Govil, A, Rike, A, Roy-chaudhury, P, Mogilishetty, G, Alloway, R. R, et al. Reducing de novo donor-specific antibody levels during acute rejection diminishes renal allograft loss. Am J Transplant (2009).

[65] Lehrich, R. W, Rocha, P. N, Reinsmoen, N, Greenberg, A, Butterly, D. W, & Howell, D. N. Smith SR: Intravenous immunoglobulin and plasmapheresis in acute humoral rejection: experience in renal allograft transplantation. Hum Immunol (2005).

[66] Levine, M. H. Abt PL: Treatment options and strategies for antibody mediated rejection after renal transplantation. Semin Immunol, , 24, 136-142.

[67] Ellyard, J. I, Avery, D. T, Phan, T. G, Hare, N. J, & Hodgkin, P. D. Tangye SG: Antigen-selected, immunoglobulin-secreting cells persist in human spleen and bone marrow. Blood (2004).

[68] Ramos, E. J, Pollinger, H. S, Stegall, M. D, Gloor, J. M, & Dogan, A. Grande JP: The effect of desensitization protocols on human splenic B-cell populations in vivo. Am J Transplant (2007).

[69] Faguer, S, Kamar, N, Guilbeaud-frugier, C, Fort, M, Modesto, A, Mari, A, Ribes, D, Cointault, O, Lavayssiere, L, Guitard, J, et al. Rituximab therapy for acute humoral rejection after kidney transplantation. Transplantation (2007).

[70] Everly, M. J. A summary of bortezomib use in transplantation across 29 centers. Clin Transpl (2009). , 2009, 323-337.

[71] Trivedi, H. L, Terasaki, P. I, Feroz, A, Everly, M. J, Vanikar, A. V, Shankar, V, Trivedi, V. B, Kaneku, H, Idica, A. K, Modi, P. R, et al. Abrogation of anti-HLA antibodies via proteasome inhibition. Transplantation (2009).

[72] Sberro-soussan, R, Zuber, J, Suberbielle-boissel, C, Candon, S, Martinez, F, Snanoudj, R, Rabant, M, Pallet, N, Nochy, D, Anglicheau, D, et al. Bortezomib as the sole post-

renal transplantation desensitization agent does not decrease donor-specific anti-HLA antibodies. Am J Transplant, , 10, 681-686.

[73] Webber, A, & Hirose, R. Vincenti F: Novel strategies in immunosuppression: issues in perspective. Transplantation, , 91, 1057-1064.

[74] Martin, S. T, & Tichy, E. M. Gabardi S: Belatacept: a novel biologic for maintenance immunosuppression after renal transplantation. Pharmacotherapy, , 31, 394-407.

[75] Sayegh MH: FinallyCTLA4Ig graduates to the clinic. J Clin Invest (1999).

[76] Vincenti, F, Charpentier, B, Vanrenterghem, Y, Rostaing, L, Bresnahan, B, Darji, P, Massari, P, Mondragon-ramirez, G. A, & Agarwal, M. Di Russo G, et al: A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant, , 10, 535-546.

[77] Vincenti, F. Tedesco Silva H, Busque S, O'Connell P, Friedewald J, Cibrik D, Budde K, Yoshida A, Cohney S, Weimar W, et al: Randomized Phase 2b Trial of Tofacitinib (CP-690,550) in De Novo Kidney Transplant Patients: Efficacy, Renal Function and Safety at 1 Year. Am J Transplant.

[78] Oura, T, Yamashita, K, Suzuki, T, Fukumori, D, Watanabe, M, Hirokata, G, Wakayama, K, Taniguchi, M, Shimamura, T, Miura, T, et al. Long-Term Hepatic Allograft Acceptance Based on CD40 Blockade by ASKP1240 in Nonhuman Primates. Am J Transplant, , 12, 1740-1754.

IntechOpen