Transplant Immunosuppression

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Abstract

Advances in our understanding on the mechanisms of the immune response have led to the development of a wide array of drugs that are commonly used for the treatment of autoimmune diseases, cancer, and organ transplantation. Our knowledge of the immune system has also helped to refine target selectivity which has decreased drug side effects. Since the introduction of calcineurin inhibitors, patient and allograft outcomes in the short term are excellent, but despite the increase in the repertoire of drugs, we have not been able to improve long-term outcomes. Goals for the new drugs that are getting developed are not only to maintain the same excellent short-term outcomes, but also to improve the side effect profile, be easy to use and tolerate, and to improve long-term outcomes. This review will present the main pharmacological agents that are currently used in solid organ transplantation, some of the agents that are in the pipeline, and some of the agents that have been left aside despite potential benefits in transplantation.

Keywords

Immunosuppression · Lymphocytes · Complement · Cytokines · Antibodies

Introduction

The first transplant performed in the United States happened in Boston in 1954 between identical twins. The transplant lasted for almost 10 years and demonstrated that transplantation was a feasible option for treatment of end stage renal disease. In the early stages of transplantation, immunosuppression consisted in total body irradiation and corticosteroids and resulted in dismal allograft longevity. In 1960, transplant protocols included azathioprine and steroids, and in 1970 anti-thymocyte globulin and anti-lymphocyte globulin were introduced with change in overall prognosis, but with a patient and allograft survival that would be considered unacceptable for our current standards. The biggest advancement in transplantation up to date was the discovery of cyclosporine in 1980 by Jean Borel. After cyclosporine, graft and patient survival increased dramatically and have continued to improve with the discovery of many other drugs including muromonab or OKT3 in 1985; tacrolimus, mycophenolate, basiliximab, and daclizumab in the 1990s; sirolimus in 1999; belatacept in 2011; and currently the long-acting tacrolimus: Astagraft (FDA approved 2013) and Envarsus (FDA approved 2015). Despite the steady state of drug development in kidney transplantation, as outcomes are much improved, it is more challenging to come up with agents that are both safe and superior to current therapies. Also due to the limited number of transplant complications, it is also unlikely the drugs will be tested in big multicenter trials, and many times transplant physicians will be left with off-label use of drugs that are approved by the FDA for oncology or autoimmune indications. This review will summarize the most common used therapies after kidney transplantation and also will give a brief look at drugs in the development pipeline that are promising.

Classification

Transplant immunosuppression can be classified depending on the cellular target, the phase of the immunological response that they affect, or type of pharmacological agents. The immune response

Table 1 T cell activation signaling

Signal 1	Binding T cell receptor (CD3) to an antigen in the surface of an antigen-presenting cell
Signal 2	Binding of T cell CD28 to CD80/86 in antigen-presenting cell or costimulation signaling
Signal 3	IL2 binding to IL2 receptor in the surface of T cells causing downstream activation of mammalian target of rapamycin (mTOR) pathway, phosphoinositide-3-kinase (PI3K) pathway, and Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT)
Signal 4	Nucleotide synthesis

to an allograft involves not only T cell activation but also B cell activation, and complement activation, and there is a wide array of drugs that act at different levels. The majority of the drugs that are utilized in transplantation block T cell activation and division, a process that involves four major immunological signaling pathways (Table 1). For the purpose of this chapter, immunosuppression agents will be organized as:

1. T cell-directed therapy including agents that target signal 1, signal 2 (costimulation blockage), signal 3 (IL2 inhibition and mTOR inhibitors)
2. Inhibitors of purine or pyrimidine synthesis (antimetabolites)
3. Agents that target cytokines
4. B cell-directed therapy including complement inhibition
5. Agents with multiple cellular targets

T Cell-Directed Therapies that Target Signal 1

Signal 1 in the T cell activation includes the interaction of the T cell receptor (TCR) to the MHC complex in the antigen presenting cells. Anti-TCR therapies include the murine monoclonal antibody muromomab-CD3 also commonly called OKT3 that target specifically the CD3 subunit of the TCR (Ortho Multicenter Transplant Study Group 1985). It was used as a lymphocyte depleting agent for induction but is no longer used.

After the interaction between TCR and MHC, the calcineurin pathway gets activated to enhance T cell transcription of cytokines including IL2 that will promote further T cell activation and division. Cyclosporine (CYA), the first calcineurin inhibitor that was approved in the early 1980s, is a fungal polypeptide composed of 11 amino acids from *Tolypocladium inflatum*. CYA binds to cyclophilin in the cytoplasm and the complex of CYA-cyclophilin inhibits calcineurin, a phosphatase necessary for dephosphorylation of nuclear factor of activated T cells (NFATc). NFATc is a transcription factor required for the synthesis of critical cytokine genes including IL2. CYA when given orally is slowly and incompletely absorbed as it has poor solubility in water and is largely lipophilic. CYA is highly dependent on bile solubility. It was initially marketed as Sandimmune which is an oil-based formulation that was replaced by a micro-emulsion formulation called Neoral. The bioavailability of Neoral was much improved compared to Sandimmune and currently there are multiple generic formulations. There are also intravenous (IV) preparations of CYA that are normally used in a 3:1 ratio when converted from the oral formulation. Calcineurin inhibitors (CNI) have a narrow therapeutic window, and therapeutic drug monitoring (TDM) has been widely embraced with the use of trough levels used as good representation of systemic exposure. Initial doses will depend on the formulation used but recommended through levels during the first 3 months are 200–300 ng/mL and after 3 months 100–200 ng/mL or lower if clinically indicated. CYA is associated with significant side effects that are dose dependent which again makes a case for TDM. CYA has been associated with nephrotoxicity from renal vasoconstriction and upregulation of fibrotic pathways. Nephrotoxicity due to renal vasoconstriction can present acutely and be easily reversible with a dose decrease or more chronically due to progressive interstitial fibrosis and tubular atrophy. CYA also is associated with neurotoxicity including tremors, headache, insomnia, hypertension from impaired Na excretion, hyperuricemia, hyperkalemia from type IV renal tubular acidosis, hypomagnesemia due to downregulation of

magnesium transport proteins, post-transplant diabetes due to beta cell toxicity, gum hyperplasia, hirsutism, and hyperlipidemia. Calcineurin inhibitor use has also been associated with development of thrombotic microangiopathy, and, in many cases, the endothelial damage is just limited to the renal vessels without thrombocytopenia or peripheral schistocytes (Schwimmer et al. 2003).

CYA is metabolized by CYT-P450 system (CYP3A4) and as such it has multiple interactions with drugs that impact the cytochrome activity. Common CYP3A4 inhibitors that will cause a significant increase in CYA drug levels and potentiate toxicity include antibiotics such as clarithromycin, antifungals such as fluconazole, antihypertensive medications such as diltiazem, protease inhibitors such as boceprevir, telaprevir, or ritonavir, and amiodarone. Grapefruit juice is also a potent CYP3A4 inhibitor. On the other hand, CYP3A4 inducers will cause a significant decrease in CYA levels with an increase in rejection risk. CYP3A4 inducers include rifampin and rifabutin, carbamazepine, phenytoin, phenobarbital, efavirenz, and modafinil.

CYA is rarely used in transplantation currently as it has been substituted by tacrolimus. Tacrolimus is a fungal macrolide antibiotic that is chemically not related to cyclosporine, although both drugs have similar mechanism of action. The internal receptor for tacrolimus is the immunophilin FK-binding protein (FK-BP), and the tacrolimus-FKBP complex inhibits calcineurin similarly to CYA. Tacrolimus (FK) is also available in oral and IV formulations with a 3:1 conversion when switched from oral to IV. Immediately post-transplant, FK is dosed at 0.1 mg/kg/day in two divided doses given every 12 h. The goal trough level for the first 3 months is normally 8–12 ng/ml and can be maintained between 5 and 7 ng/ml thereafter. It is also poorly absorbed if given orally and it is mainly excreted in the bile with minimal excretion in the urine. Prograf is the main brand name for tacrolimus although there are currently several generic formulations available. The side effect profile is a little different than CYA. FK still has significant nephrotoxicity similar to CYA but has more pronounced neurological side effects including posterior reversible encephalopathy syndrome. In contrast to CYA, FK is associated with hair loss but no gum hyperplasia. FK is associated with higher rates of post-transplant diabetes than CYA (Johnston et al. 2008). FK is also metabolized by the CYP3A4 with the same drug interactions as CYA.

Voclosporin is a new calcineurin inhibitor that resulted from the addition of an extra carbon molecule at the first amino acid residue of CYA. Voclosporin studies showed more consistent pharmacokinetic and pharmacodynamic responses to the drug than CYA, more potent cyclophilin binding, and faster elimination of metabolites. The pharmacological profile suggests voclosporin can be more potent and less toxic than CYA. Phase II studies in kidney transplantation have shown safety and tolerability as well as efficacy (noninferior to CYA in preventing acute rejection compared to FK with potentially lower incidence of post-transplant diabetes) but there are not currently any phase III trials underway for its use in transplantation (Busque et al. 2011).

Extended Released Tacrolimus Formulations: Recently, extended release formulations of tacrolimus have been approved by the FDA. Astagraf XL, a daily tacrolimus drug, was approved in 2013 followed by Envarsus XR in 2015. The once a day formulation has been touted to facilitate patient adherence, to achieve a more consistent drug exposure, and to improve patient and graft long-term outcomes. There is also a budget-impact model analysis from the United Kingdom that shows significant cost savings over 5 years with conversion to Astagraf from bid dosing (Muduma et al. 2014a, b). Unfortunately, the UK data will be hard to generalize to the USA. The once a day formulations are only currently approved for use in kidney transplantation and there is only minimal data in other organ transplants. Astagraf is not indicated for liver transplant due to data showing increased mortality in female recipients in post-hoc analysis (Astagraf 2015). The package insert of both extended release formulations emphasizes that the medications are not interchangeable or substitutable with the immediate release formulation. Astagraf was studied as de novo immunosuppression (Silva et al. 2007, 2014; Kramer et al. 2010) and conversion (Alloway et al. 2005) from twice

daily formulations. Current recommendations are to convert twice daily tacrolimus dosing to extended release Astagraf in a 1:1 total daily dose base but consider a 20% increase during the first week post-transplantation (Van Hooff et al. 2012).

Phase II and III clinical trials with Envarsus demonstrated 15–30% lower dose requirements than with twice daily dosing in general, and a 15% lower dose in African Americans. Envarsus has 50% more bioavailability than bid tacrolimus so for conversions of twice daily tacrolimus to Envarsus, the twice daily tacrolimus dose should be reduced by 20% (Bunnapradist et al. 2013; Rostaing et al. 2016). The flatter pharmacokinetics seen with Envarsus with lower peak-trough fluctuations is probably the cause of lesser peak-related side effects like tremors, insomnia, and fatigue. Due to the decreased dose requirement, Envarsus presents a more favorable PK profile for patients with CYP3A5.1 considered rapid metabolizers of tacrolimus and highly prevalent in African Americans.

T Cell-Directed Therapies that Target Signal 2: Costimulation Blockade

Belatacept

The interaction between the antigen presenting cell surface molecule CD80/86 and CD28 from T cells is necessary for effective T cell activation and it is referred as costimulation. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) is a cell surface molecule that is expressed in T cells. Its function is to bind CD80/86 competitively and downregulate the T cell response. Abatacept was the first-generation costimulation blocker composed of Fc fragment of a human IgG1 fused to the extracellular domain of CTLA4. Abatacept is approved for treatment of autoimmune disorders such as adult rheumatoid arthritis and juvenile idiopathic arthritis but it is also used off label for renal disorders such as focal segmental glomerulosclerosis. Abatacept was not effective in preclinical studies of organ transplantation so a second-generation costimulation blocker was then developed for use in transplantation. Belatacept was approved by the FDA in 2011 after 3-year data outcomes were obtained by two phase 3 clinical trials in both standard criteria (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial or BENEFIT trial (Vincenti et al. 2010, 2012a)) and expanded criteria kidney recipients (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial–Extended Criteria Donors or BENEFIT-EXT trial (Durrbach et al. 2010; Pestana et al. 2012)) that used low intensity and high intensity belatacept arm versus CYA maintenance. Belatacept is not approved for liver or any other organ transplant except kidney. The population included in the BENEFIT trial was mainly Caucasian with a really low representation of African Americans/Blacks, and less than $<15\%$ of patients in every arm had PRA $>20\%$, so we can conclude it was mainly a low immunological risk population. The BENEFIT trial that included standard criteria deceased donors and living donors demonstrated lower rates of graft loss and death in the low-intensity belatacept group compared to cyclosporine (CYA) despite higher rates of rejection even after extended follow-up (up to 7 years now (Vincenti et al. 2016)). Belatacept was used in combination with basiliximab induction, mycophenolate mofetil, and glucocorticoids for maintenance immunosuppression. Belatacept use was associated with higher rates of post-transplant lymphoproliferative disorder (PTLD) especially in Epstein Barr virus (EBV) naïve patients or patients that used lymphocyte depletion agents for induction, and its current indication is restricted to EBV positive patients. The BENEFIT-EXT trial that included extended criteria deceased donors showed similar patient and graft survival between the belatacept and CYA arms but lower measured glomerular filtration rates. There were also similar rates of rejection, infections, and malignancies between the treatment groups and again higher rates of PTLD in EBV naïve patients. Currently the bigger barriers for belatacept use are its increased cost, the need for IV infusion, and the lack of comparison trials with tacrolimus. A recent retrospective trial that used registry

data compared 1 year clinical data between kidney recipients treated with tacrolimus alone, belatacept alone, and tacrolimus plus belatacept at discharge from kidney transplantation (Wen et al. 2016). The rates of 1-year patient and graft loss in the two belatacept regimens were not different from those in the tacrolimus-alone group with significantly higher rejection rates in any of the belatacept groups compared to tacrolimus group. Rejection rates were higher in patients with high PRA that did not receive lymphocyte depleting agents for induction. Also recipients that would have been eligible for BENEFIT-EXT had higher renal function at 1 year in the belatacept arms. More studies that compare tacrolimus with belatacept protocols are needed but it will be reasonable to consider regimens that use belatacept and low dose tacrolimus with lymphocyte depletion agents in patients with high immunological risk. Currently, there are more than 40 clinical trials in renal transplantation that are using belatecept in different regimens that will help to shed light on how to combine this drug for different recipient needs.

Anti-CD40 (ASKP1240)

The interaction between CD40L (CD154) in activated T cells to CD40 in antigen presenting cells is a key stage in costimulation blockage as it upregulates CD80/86 in the antigen presenting cells. ASKP1240 is a fully human monoclonal IgG4 antibody to CD40 that is currently under development for use in kidney transplantation in either a CNI free-regimen or a CNI minimization regimen (Okimura et al. 2014; Harland et al. 2015).

T Cell-Directed Therapies that Target Signal 3, IL-2, and mTOR Pathway

After activation of signal 1 and 2, IL2 and other cytokines are released from the T lymphocyte. IL2 binds to IL2R or CD25 in the T cell causing downstream activation of phosphoinositide-3-kinase (PI3K) pathway and Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT) and eventually activate the mammalian target of rapamycin (mTOR) pathway. Upregulation of these pathways will allow the T cell to proliferate and expand peptide-specific effector T cells.

IL-2 Receptor Antagonists (Basiliximab)

Basiliximab is a humanized antibody towards CD25 (α-subunit chain of IL-2 receptor on activated lymphocytes). The term humanized means that Basiliximab is a chimeric human-mouse IgG with 25% of the IgG molecule being from murine origin and 75% from human origin. Basiliximab blocks IL-2 stimulated T cell replication. It is used intravenously in two divided doses (intraoperative and day 4 post-transplantation) to prevent transplant rejection as part of induction protocols in low immunological risk patients. In general, it is well tolerated with mainly GI side effects.

Sirolimus and Everolimus

Sirolimus is macrolide antibiotic from *S. hygroscopicus* from Easter Island. It binds to FKBP and the formed complex binds to mTOR (mammalian target of rapamycin). The mTOR pathway leads to cell cycle progression from G1 to S phase and proliferation in response to cytokine stimulation, including but not limited to IL-2. Sirolimus was approved for its use in kidney transplantation in 1999 with the hope that it would improve long-term transplant outcomes due to the lack of nephrotoxicity. Everolimus is a metabolite of sirolimus with shorter half-life than the parent compound. De novo use of sirolimus was found to be difficult due to the increased rates of wound dehiscence, urinomas and seromas, as well as prolonged delayed graft function and increased rejection. Further systematic reviews also showed increased mortality (Knoll et al. 2014). Sirolimus then was used concomitantly following conversion from CYA. Initial studies showed a significantly higher eGFR in the sirolimus group at 12 months post-transplant

(Budde et al. 2011) but the same data were not reproduced in later studies (Weir et al. 2011; Flechner et al. 2011). Also when the conversion from a CNI to sirolimus was done more than 6 months post-transplant, only patients with higher GFRs and that did not have proteinuria benefitted in the long run (Schena et al. 2009).

Besides the limited efficacy, mTOR inhibitors are associated with significant toxicity which limits further its widespread use. Hyperlipidemia, proteinuria, mouth ulcers, pneumonitis, interstitial lung disease, sodium retention, thrombocytopenia, and an increased renal toxicity with calcineurin inhibitors when used concomitantly are some of the main side effects observed besides the well-known wound healing, and delayed graft function issues. Sirolimus has also been associated with cases of thrombotic microangiopathy and post-transplant diabetes. Despite the significant side effects, sirolimus has been associated with decreased risk of skin cancers (Euvrard et al. 2012), and it is possible that sirolimus has antitumor effects in other cancers.

Currently the use of sirolimus is mainly in patients with CNI toxicity, in patients with malignancies and with PTLD.

Janus Kinase Inhibition (Tofacitinib)

Tofacitinib (tositinib, CP-690,550) is a Janus associated kinases inhibitor (JAK3 and JAK2), which inhibits cytokine signaling through the IL-2Rγ chain. It has been used in different trials in kidney transplantation as an alternative to CNI. Initial enthusiasm with this small molecule (phase IIb trial showed similar rates of acute rejection when compared to cyclosporine, with better renal function and chronic allograft changes at 12 months) has been tainted by an increased rate of infections in patients treated with tofacitinib, specifically cytomegalovirus, BK virus, and also increased rates of PTLD (Vincenti et al. 2012b). Currently, the pursuit of the transplantation indication has been abandoned by the pharmaceutical company as tofacitinib has been successful for the treatment of rheumatoid arthritis and the company is focused on other autoimmune disease indications.

Inhibitors of Purine or Pyrimidine Synthesis (Antimetabolites)

Azathioprine (AZA)

AZA is a derivative of mercaptopurine. It was the first immunosuppressant used in transplantation in conjunction with steroids. Initially AZA gets metabolized in the liver to 6-mercaptopurine (6-MP) and thanks to hypoxanthine-guanine phosphoribosyltransferase (HGPRT) 6-mercaptopurine is converted to 6-mercaptopurine nucleotide, and ultimately to thioinosinic acid, a nucleotide analog. The metabolites incorporate into replicating DNA, halting replication, as well as blocking the pathway for purine synthesis. AZA strongly affects proliferating cells, such as the T cells and B cells of the immune system. 6-MP can also be inactivated by two enzymes, thiopurine s-methyltransferase (TPMT) and xanthine oxidase (XO), to nontoxic metabolites. Allopurinol inhibits xanthine oxidase, thus promoting AZA toxicity by increasing its bioavailability fivefold. There are also different polymorphisms of the TPMT gene that will result in different enzyme activity. Up to 10% of the general population may present with reduced TMPT activity with 0.3% of the population presenting a real enzyme deficiency (Mcleod and Siva 2002). There are more than 25 variant alleles described with different clinical relevance. Four variant alleles account for >95% of reduced TPMT activity: TPMT*2 (238G>C), TPMT*3A (460G>A and 719A>G), TPMT*3B (460G>A), and TPMT*3C (719A>G). Wild type TPMT1* homozygotes have normal enzyme activity. Patients with TPMT deficiency treated with standard doses of AZA or 6-MP are at significantly increased risk of side effects. TPMT genotyping can identify patients who are at an increased risk for developing AZA toxicity and is easily available in commercial labs. AZA can be used either orally or IV with a 1:1 conversion. AZA is widely distributed but does not cross the blood brain barrier and is excreted primarily in urine. Usual maintenance doses range from 1–3 mg/kg in one or two divided doses.

The main side effects of AZA are leukopenia, bone marrow depression, macrocytosis,

gastrointestinal toxicity and less likely, liver toxicity. Blood counts should be monitored during AZA treatment.

Mycophenolate Mofetil (MMF)

MMF is a semisynthetic derivative of mycophenolic acid (MPA) from penicillium molds. MMF blocks the proliferation of T and B cells by inhibiting inosine monophosphate dehydrogenase (IMP), an enzyme that is crucial for purine synthesis. MMF was approved in the 1990s for use in kidney transplantation after three large randomized studies showed its improved efficacy over AZA in combination with CYA and steroids (European Mycophenolate Mofetil Cooperative Study Group 1995; The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group 1996; Sollinger 1995).

MMF can be given orally and IV with a 1:1 conversion rate. MMF is converted to the active form MPA by esterases in the stomach, small intestine, and other tissue including the liver. MPA is extensively bound to plasma proteins and is metabolized in the liver by glucuronidation, and excreted in urine as glucuronide conjugate (MPAG). Some MPAG gets deconjugated in the gut and enters the enterohepatic circulation adding to the active drug pool.

MMF absorption is reduced by CYA as CYA inhibits the biliary secretion of MPA glucuronide (MPAG) through multidrug resistance protein 2 transporter, resulting in decreased MPA reabsorption during enterohepatic recirculation. Dose of MMF should be adjusted accordingly when patients are switched from tacrolimus to CYA. Usual doses range from 1500 mg to 2000 mg divided in two daily doses.

MPA main toxicity is gastrointestinal including nausea, vomiting, and diarrhea, in up to 10% of the patients. Abdominal pain, leukopenia, and neutropenia are also common. An enteric-coated formulation of mycophenolate sodium or myfortic was developed to decrease the upper gastrointestinal side effects (nausea and vomiting). Enteric-coated formulations have similar efficacy than MMF with some studies showing marked decrease in gastrointestinal side effects (Salvadori et al. 2004; Bolin et al. 2007; Chan et al. 2006). For conversion of MMF to enteric-coated formulations, 250 mg of MMF are considered equivalent to 180 mg of the enteric-coated formulation.

MPA is contraindicated during pregnancy as it is associated with increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, including external ear and facial abnormalities including cleft lip and palate. MMF has also been associated with anomalies of the distal limbs, heart, esophagus, kidney, and nervous system.

Therapeutic drug monitoring is not widely used for MMF as trough levels do not correlate well with total exposure of the drug and AUC measurements are cumbersome to do. Also studies that looked at fixed and concentration controlled doses of MMF have not consistently shown improved outcomes in the therapeutic drug monitoring groups (Gaston et al. 2009).

Agents that Target Cytokines

Corticosteroids

Steroids have always been part of the backbone for immunosuppression for renal transplantation. Steroids affect the immune system through several mechanisms but mainly by decreasing the production of cytokines (IL-1, IL-2, interferon, TNFα). Inhibition of cytokines then suppresses T-cell helper function, decreases T lymphocyte proliferation (IL-2), facilitates eosinophil apoptosis (IL-5), and inhibits antigen processing by macrophages (IL-1 and TNFα). Steroids have little effect on neutrophil function or beta cell function.

Corticosteroids are potent immunosuppressive and anti-inflammatory agents but are associated with a myriad of metabolic side effects including adrenal suppression, osteoporosis, hypercholesterolemia, hyperglycemia, hypertension, and cataracts.

Corticosteroid withdrawal protocols have been studied in randomized controlled trials and discontinuation of steroids 7 days post-transplantation has not been associated with detrimental

outcomes at 12 months post-transplantation when used in conjunction with thymoglobulin induction and tacrolimus and MMF maintenance (Woodle et al. 2010).

Tocilizumab

Tocilizumab is a first-in-class humanized monoclonal antibody with specificity for IL-6R. Tocilizumab binds to both soluble and membrane-bound forms of IL6 receptor. It is approved by the FDA for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. IL6 contributes to CD8 T cell and B cell differentiation. Recently, a phase I/II trial of tocilizumab as a desensitization agent has been published. The trial included highly sensitized patients who failed desensitization with intravenous immunoglobulin and rituximab (ClinicalTrials.gov identifier NCT01594424) (Vo et al. 2015). This first study of tocilizumab in human kidney transplants demonstrates that the drug has a good safety profile and encouraging efficacy. Larger trials will be necessary to assess efficacy end points.

B Cell-Directed Therapy

Rituximab

Rituximab is a chimeric monoclonal antibody againts CD20 (70% human and 30% murine). Rituximab binds to CD20 on B cells and mediates B-cell lysis through multiple mechanisms, including complement-dependent cytotoxicity, growth arrest, and apoptosis. Rituximab causes a profound and long-lasting B cell depletion that can be maintained up to 6–9 months. Rituximab use in kidney transplantation has been focused in the treatment of antibody mediated rejection (Sautenet et al. 2016), induction therapy (Macklin et al. 2015; Cheungpasitporn et al. 2015), and for desensitization protocols (Vo et al. 2008; Kahwaji et al. 2016). No randomized trials have been published that support efficacy of rituximab in any of its current off-label uses. Side effects are mainly related to infusion reactions (fever, chills, rash, urticaria, hypotension, bronchospasm, acute respiratory distress syndrome) and also infection reactivations such as hepatitis B and C and progressive multifocal leukoencephalopathy due to reactivation of JC virus.

Anti CD20 therapies that are more humanized (ocrelizumab) or fully humanized (ofatumumab) have been developed but its use in transplantation has not been studied.

Bortezomib

Bortezomib is a proteasome inhibitor that was approved in 2003 by the FDA for treatment of multiple myeloma. Proteasome inhibition causes inhibition of the cell cycle and apoptosis in plasma cells. In renal transplantation it has been mainly used to treat antibody mediated rejection (Cicora et al. 2013; Gupta et al. 2014) and also as part of desensitization protocols (Shah et al. 2015). The studies where bortezomib has been used have been small and with conflicting results, but bortezomib may have some role in the treatment in early antibody mediated rejection (Walsh et al. 2012). The role in desensitization protocols is still unclear. Recent data has shown that bortezomib is able to decrease HLA antibodies for up to 10 months (Woodle et al. 2015), although other cohorts were only able to show a modest reduction of HLA antibodies after an intensive course of treatment and with more side effects (Moreno Gonzales et al. 2016). The main side effect of bortezomib is peripheral neuropathy, although gastrointestinal side effects and cytopenias are also common. In general, bortezomib is well tolerated.

Complement Inhibition: Eculizumab

Eculizumab is a humanized monoclonal antibody to C5 that effectively inhibits its cleavage to C5a and C5b. Because C5a is a neutrophil chemoattractant and because C5b is required to form the C5b-9 membrane attack complex, inhibition of this enzymatic step results in blockade of pro-inflammatory, pro-thrombotic, and lytic functions of complement. Approved for its use in paroxysmal nocturnal hemoglobinuria, and atypical

hemolytic-uremic syndrome (HUS), its use in renal transplantation has been in the setting of antibody mediated rejection (Stegall et al. 2011) and in desensitization protocols. The main risk of eculizumab is infection from encapsulated organisms, and vaccination to Neisseria, Pneumococcus, and Haemophilus is required before its use.

Immunosuppressive Agents with Multiple Cellular Targets

Polyclonal Antithymocyte Globulin (ATG)

Antibody to lymphocyte antigens have been created in different ways. Immunization of rabbits (Thymoglobulin) or horses (Atgam) to human thymocytes or immunization of rabbits to lymphocytes from a Jurkat T cell leukemia line (Fresenius antithymocyte globulin) results in polyclonal antibodies after purification of IgG fraction from the serum. These polyclonal antibodies are directed to multiple T cell epitopes and bind to the surface of circulating T lymphocytes making them susceptible to phagocytosis in the liver and spleen, to complement-derived cytolysis, and to apoptosis. The result is profound lymphopenia and impaired T-cell responses and cellular immunity. Even though thymocytes were used as the main antigenic stimulus, many other cells of the immune system will share same epitopes and that is why ATG will also have some effects in B cells, neutrophils, and monocytes. They are used mainly as IV preparations for transplant induction and to treat allograft rejection and the dose is usually 5 mg/kg divided over 4–5 days. Side effects include cytokine release syndrome or serum sickness reactions (including fever, chills, flu-like syndrome, hypotension, pulmonary edema), and anaphylaxis. They are also associated occasionally with significant thrombocytopenia.

Panlymphocyte Depleting Agents

Alemtuzumab is a humanized monoclonal antibody that targets CD52, present in T and B cells, most monocytes, macrophages, and natural killer cells, causing cell lysis and prolonged cell depletion (up to 6–12 months). Alemtuzumab has been used mainly as an induction agent. Since 2012 alemtuzumab is not available commercially as the manufacturer removed the drug from the market in preparation for relabeling change for its use in multiple sclerosis. Consequently, its use is currently greatly diminished. Its main side effect is profound and prolonged lymphopenia with increased risk for infection including CMV and PTLD. Alemtuzumab is a humanized antibody and infusion reactions are also possible.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is a pool of immunoglobulins purified from multiple donors that contains unselected IgG antibodies with the same subclass distribution as the normal serum. It was initially developed for use in humoral immune-deficiencies as a monthly infusion but has been used widely in other autoimmune and inflammatory diseases. The mechanism of action of pooled immunoglobulins includes modulation of B and T cell responses as well as anti-inflammatory and inhibition of cell growth. IVIG can be used in low doses (100 mg/kg) in acute antibody rejection protocols in combination with plasmapheresis, or at high doses up to 2 g/kg for a maximum of 140 g in a single administration in transplant desensitization protocols (Jordan et al. 2011). The main side effects of IVIG include infusion reactions with fever, chills, nausea, vomiting, hypotension, flushing, and the older formulation were also associated with acute kidney injury secondary to osmotic injury. There is also the possibility of anaphylactic reactions in patients with IgA deficiency that can produce anti-IgA antibodies. In general IVIG is considered more as an immunemodulator agent versus immunosuppressant agent.

Other Agents in the Pipeline

IdeS is an enzyme purified from *Streptococcus pyogenes* that degrades immunoglobulin G

(IgG). It cleaves all the IgG human subclasses preventing IgG-mediated antibody-dependent cellular cytotoxicity and complement-mediated injury. Recent data showed good safety in normal human subjects (Winstedt et al. 2015). This finding could be very important in the prevention and treatment of antibody-mediated rejection. Studies of this agent are now underway in Sweden and the United States (ClinicalTrials.gov identifier NCT02426684).

The success with belatacept has shown that blockage of the costimulation signal is an effective target for transplant immunosuppression giving grounds to the development anti-CD28 antibodies. Selective blockade of CD28 allows CTLA4 and PD-L1 to bind to CD80/CD86 and activate the inhibitory pathways resulting in added immunosuppression effects on T cells. In contrast to CTLA4 Ig or belatacept, anti-CD28 antibodies may have less of an adverse effect on T regulatory cells that require signaling through CTLA4 for optimal function (Vanhove et al. 2003). There are currently two anti-CD28 antibodies in preclinical development (FR104 from Effimune (Poirier et al. 2015) and BMS-931699 from Bristol Myers Squibb).

Conclusion

Multiple new agents have emerged in the past 10 years that are still under investigation in different combinations and compared with the cornerstone of maintenance immunosuppression treatment that is based in tacrolimus and mycophenolate mofetil. Immunosuppression for solid organ transplants will likely continue to expand in the incoming years as drug development within the oncology and autoimmune disease arena can frequently be extrapolated to the transplant population. Short-term and long-term transplant outcomes have to be weighed against the risk of infection and malignancy. The main future challenge will be to demonstrate that the new drugs are superior to tacrolimus and mycophenolate mofetil combinations which would allow CNI substitution and the possibility of better long-term outcomes.

Cross-References

- ▶ Immunology of Kidney Transplantation
- ▶ Medical Complications After Kidney Transplantation: Early
- ▶ Medical Complications After Kidney Transplantation: Late

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