REVIEW

Novel immunosuppressive agents in kidney transplantation

Karen L Hardinger, Daniel C Brennan

Karen L Hardinger, Department of Pharmacy Practice and Administration, University of Missouri-Kansas City, Kansas City, MO 64108, United States
Daniel C Brennan, Department of Medicine, Washington University School of Medicine in St. Louis, St. Louis, MO 63110, United States
Author contributions: All authors have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.
Correspondence to: Karen L Hardinger, PharmD, BCPS, Clinical Associate Professor of Pharmacy Practice, Department of Pharmacy Practice and Administration, University of Missouri-Kansas City, 2464 Charlotte Street, Rm 2241, Kansas City, MO 64108, United States. hardingerk@umkc.edu
Telephone: +1-816-2769023   Fax: +1-816-2764751
Received: June 28, 2013   Revised: August 26, 2013
Accepted: October 16, 2013
Published online: December 24, 2013

Abstract

Excellent outcomes have been achieved in the field of renal transplantation. A significant reduction in acute rejection has been attained at many renal transplant centers using contemporary immunosuppressive, consisting of an induction agent, a calcineurin inhibitor, an antiproliferative agent plus or minus a corticosteroid. Despite improvements with these regimens, chronic allograft injury and adverse events still persist. The perfect immunosuppressive regimen would limit or eliminate calcineurin inhibitors and/or corticosteroid toxicity while providing enhanced allograft outcomes. Potential improvements to the calcineurin inhibitor class include a prolonged release tacrolimus formulation and voclosporin, a cyclosporine analog. Belatacept has shown promise as an agent to replace calcineurin inhibitors. A novel, fully-human anti-CD40 monoclonal antibody, ASKP1240, is currently enrolling patients in phase 2 trials with calcineurin minimization and avoidance regimens. Another future goal of transplant immunosuppression is effective and safe treatment of allograft rejection. Novel treatments for antibody mediated rejection include bortezomib and eculizumab. Several investigational agents are no longer being pursed in transplantation including the induction agents, efalizumab and alefacept, and maintenance agents, sotrastaurin and tofacitinib. The purpose of this review is to consolidate the published evidence of the effectiveness and safety of investigational immunosuppressive agents in renal transplant recipients.

Core tip: Many new agents are being studied that may improve outcomes after renal transplantation. Potential improvements to the calcineurin inhibitor class include a recently Food and Drug Administration approved, prolonged release tacrolimus formulation and voclosporin, a cyclosporine analog. A novel, fully-human anti-CD40 monoclonal antibody, ASKP1240, is currently enrolling patients in phase 2 trials with calcineurin minimization and avoidance regimens. Novel treatments for antibody mediated rejection include bortezomib and eculizumab.

Hardinger KL, Brennan DC. Novel immunosuppressive agents in kidney transplantation. *World J Transplant* 2013; 3(4): 68-77 Available from: URL: http://www.wjgnet.com/2220-3230/full/v3/i4/68.htm DOI: http://dx.doi.org/10.5500/wjt.v3.i4.68

INTRODUCTION

Although significant advances in renal transplant immunosuppression have occurred in the past decades, a vital need to improve long-term survival remains. Currently, immunologic causes of early graft failure have become rare, yet late graft loss has remained virtually unchanged. One of the most common causes for graft loss is chronic

Table 1 Summary of investigational and available agents

Generic	Brand	FDA indication	Company
Alefacept[1,2]	Amevive	Treatment of moderate-to-severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	Astellas
Alemtuzumab[2]	Campath	Treatment of B-CLL	Berlex Laboratories
ASKP1240		Not FDA approved	Astellas
Azathioprine	Imuran	Adjunctive therapy in prevention of rejection of kidney transplants; management of active rheumatoid arthritis	Generic manufacturers
Basiliximab	Simulect	Prevention of acute rejection in kidney transplantation	Novartis
Belatacept	Nulojix	Prevention of acute rejection in renal transplant recipients	Bristol-Myers-Squibb
Bortezomib	Velcade	Treatment of multiple myeloma; treatment of relapsed or refractory mantle cell lymphoma	Millenium Pharmaceuticals
Cyclosporine	Neoral	Prevention of acute rejection in renal transplant recipients	Novartis
Eculizumab	Soliris	Treatment of PNH to reduce hemolysis and aHUS	Alexion Pharmaceuticals
Efalizumab[1,2]	Raptiva	Management of moderate to severe chronic plaque psoriasis in adults	Genentech
Everolimus	Afinitor, Zortress	Treatment of advanced renal cell cancer (Afinitor®); treatment of subependymal giant cell astrocytom associated with tuberous sclerosis (Afinitor®); treatment of advanced, metastatic or unresectable pancreatic neuroendocrine tumors (Afinitor®); prophylaxis of organ rejection in patients at low-moderate immunologic risk receiving renal transplants (Zortress®)	Novartis
Mycophenolate Mofetil	Cellcept	Prophylaxis of organ rejection concomitantly with cyclosporine and corticosteroids in patients receiving allogeneic renal cardiac, or hepatic transplants	Genentech
Mycophenolate Sodium	Myfortic	Prophylaxis of organ rejection concomitantly with cyclosporine and corticosteroids in patients receiving allogeneic renal transplantation	Novartis
Horse or Rabbit anti-thymocyte Globulin	Atgam or Thymoglobulin	Treatment of corticosteroid resistant rejection in kidney transplantation	Pfizer/Sanofi
Rituximab	Rituxan	Treatment of CD20-positive non-Hodgkin's lymphomas; Treatment of moderately- to severely-active rheumatoid arthritis in adult patients with inadequate response to one or more TNF antagonists; Treatment of Wegener's granulomatosis; Treatment of microscopic polyangiitis	Genentech
Sirolimus	Rapamune	Prevention of acute rejection in renal transplant recipients	Pfizer
Sotrastaurin, AEB-0711		Not FDA approved	Novartis
Tacrolimus	Prograf	Prevention of acute rejection in renal transplant recipients	Astellas
Tacrolimus Prolonged Release	Astragraf XL	Preventing organ rejection in kidney transplant recipients, as combination therapy with mycophenolate mofetil and corticosteroids, with or without tasiliximab induction	Astellas
Tolfacitinib[1]	Xeljanz	Treatment of moderate to severe rheumatoid arthritis	Pfizer
Voclosporin		Not FDA approved	Isotechnika Pharma

[1]No longer being investigated for transplantation; [2]Withdrawn from United States Market. FDA: Food and Drug Administration; B-CLL: B-cell chronic lymphocytic leukemia; PNH: Paroxysmal nocturnal hemoglobinuria; aHUS: Atypical hemolytic uremic syndrome.

allograft nephropathy. Additionally, significant drug improvements in transplantation have come with the expense of side effects. Many of these adverse events, including new onset diabetes after transplant, dyslipidemia, and hypertension, may contribute to cardiovascular related deaths after transplantation. The ideal immunosuppressive regimen would improve long-term outcomes while minimizing exposure to drug toxicity and infection.

Induction agents are typically antibodies (anti-thymocyte globulins) or interleukin 2 receptor antagonists (basiliximab). Another induction agent, alemtuzumab has been removed from the United States market, but is still available through a special manufacturer program. The five drug classes that currently comprise maintenance regimens may include calcineurin inhibitors (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), antiproliferative agents (azathioprine and mycophenolic acid), costimulation blockers (belatacept) and corticosteroids (Table 1). KDIGO Clinical Practice Guidelines suggest that first-line agents should include

basiliximab induction for low-risk patients and an anti-thymocyte globulin for high-risk patients in conjunction with maintenance immunosuppression including tacrolimus and mycophenolate[1]. Potential improvements to the calcineurin inhibitor class include a prolonged release tacrolimus formulation and voclosporin, a cyclosporine analog (Table 2). A novel, anti CD-40 molecule has completed phase 1 studies.

Another area for improvement is treatment of humoral rejection. Historically, treatment has been difficult and not well studied. Humoral rejection is typically treated with intravenous immunoglobulin, rituximab and plasmapheresis. Investigational treatments for antibody mediated rejection that will be discussed include bortezomib and eculizumab.

In the past years, several clinical trials have been unsuccessful and therefore many agents are no longer being pursued for transplantation. These agents include two inductions agents, efalizumab and alefacept, and two maintenance agents, sotrastaurin (a protein kinase C in-

Table 2 Non-Food and Drug Administration approved/investigational agents and their mechanism

Drug name	Mechanism of action
Induction	
Efalizumab[1]	Humanized antibody, CD11a/LFA-1
Alefacept[1]	Costimulation inhibitor, CD2 LFA3
Maintenance	
Voclosporin, ISA247	Calcineurin inhibitor
Sotrastaurin, AEB0711	Protein kinase C inhibitor
Tofacitinib, CP-6905501	JAK 3 inhibitor
ASKP1240	Anti-CD40 monoclonal antibody
Treatment of Antibody	
Medicated Rejection	
Bortezomib	Proteasome inhibitor
Eculizumab	Monoclonal antibody, C5 complement protein

[1]No longer being investigated for transplantation.

hibitor) and tofacitinib (a JAK 3 inhibitor). This review article will update a previously published article found in this journal[2] on the effectiveness and safety of novel immunosuppressive agents.

PREVENTATIVE AGENTS

Alternatives to currently available calcineurin inhibitors

Calcineurin inhibitors have revolutionized post-transplantation immunosuppressive regimens by significantly lowering acute rejections rates. Yet, long-term use of these drugs has been associated with the development of chronic allograft nephropathy and adverse events. New immunosuppressive agents that eliminate these issues are needed. Prolonged release tacrolimus (Astragraf XL®, Astellas) has been approved for use in various European countries, Canada and the United States (in July 2013). The expectation is that the products once daily, rather than twice daily, dosing will improve adherence in transplant recipients. Large, randomized, phase 3 studies have compared prolonged release-tacrolimus compared to tacrolimus with similar efficacy and safety outcomes[3,4]. Of note, tacrolimus levels may be slightly lower with prolonged release tacrolimus compared to twice daily tacrolimus patients[5-7], although serum creatinine, creatinine clearance and estimated glomerular filtration rate were very similar. Prolonged release tacrolimus has a non-inferior efficacy profile with convenient daily dosing which is expected to improve patient compliance. Drug cost may influence the widespread use of this product as generic tacrolimus formulations are now available.

A novel calcineurin inhibitor, voclosporin (ISA 247, Isotechnika Pharma, Inc.) is being investigated in solid organ transplant, uveitis, and psoriasis[8-11]. Animal studies demonstrated that voclosporin, a cyclosporine analogue, had a higher affinity and greater *in-vivo* potency[12,13]. PROMISE, a phase 2b trial of low risk renal transplant recipients with immediate allograft function (*n* = 334) compared low (0.4 mg/kg), medium (0.6 mg/kg) and high (0.8 mg/kg) dose voclosporin to tacrolimus (0.05 mg/kg), in combination with a standard immunosup-

pressive regimen (anti-CD25 antibody, mycophenolate mofetil, and corticosteroids). Rejection rates were non-inferior to tacrolimus (11%, 9%, 2 %, and 6% respectively) and renal function was clinically similar (69-72 mL/min) at 6 mo after transplantation[8]. The incidence of new onset diabetes after transplantation was significantly lower in the low dose voclosporin group (1.6% *vs* 16.4% tacrolimus), but not in the medium (5.7%) and high dose (17.7%) arms[8]. The major limitation of this trial was that only low risk patients were studied. Low to medium dose voclosporin may provide adequate immunosuppression with a lower incidence of new onset diabetes after transplantation. A large, phase 3 (*n* = 598) trial is planned for 2013.

Recently, pharmacokinetic data of voclosporin was presented at the American Transplant Congress[14-17]. Researchers have learned that voclosporin should be given on an empty stomach and that dosage adjustment may be needed in severe renal failure (< 30 mL/min) and mild to moderate hepatic impairment[14-16]. Optimal trough concentrations should be targeted between 35-60 ng/mL[17].

Belatacept (Nulojix®, Bristol Myers Squibb) is a second generation co-stimulation blocker (CD80 antagonism) that received Food and Drug Administration (FDA) approval for use in kidney transplantation in June of 2011. Belatacept is contraindicated in patients that are Ebstein-Barr virus seronegative, because of high incidence of post-transplant lymphoproliferative seen in clinical trials[19-22]. Belatacept is administered as a well-tolerated intravenous infusion over 30 min. The recommended dosing is 10 mg/kg administered, prior to transplantation, on day 5, and at the end of weeks 2, 4, 8, and 12, then 5 mg/kg every 4 wk (plus or minus 3 d). The chronic intravenous administration could prove beneficial in increasing patient compliance with less frequent (monthly) infusions. In contrast, it may be perceived as a barrier to patients without social support that cannot readily access an infusion center. Administration and drug costs may also influence prescribing patterns and patient compliance.

Belatacept is the first immunosuppressive to demonstrate a renal benefit over a calcineurin inhibitor based regimen[18-22]. One limitation of the early belatacept trials (BENEFIT and BENEFIT-EXT) was that cyclosporine, a less contemporary immunosuppressive, was utilized[19-22]. In a phase 2, 1 year randomized study, belatacept/mycophenolate mofetil, belatacept/sirolimus and tacrolimus/mycophenolate mofetil, in combination with rabbit antithymocyte globulin and without corticosteroids were compared (*n* = 89)[23]. Acute rejection was highest in the belatacept/mycophenolate mofetil arm, graft loss was lowest in the tacrolimus/mycophenolate arm, and renal function was improved in the belatacept arms.

As an alternative to *de novo* immunosuppression, a conversion trial recently tested the hypothesis that belatacept-based regimens may provide a treatment option in patients already being treated with calcineurin-based maintenance immunosuppression[24]. Patients with stable

graft function (calculated glomerular filtration rate between 35-75 mL/min) were randomized to either switch to belatacept (*n* =84) or continue calcineurin inhibitor treatment (*n* = 89). Despite a higher acute rejection rate in the belatacept group, the relative renal benefit of belatacept was observed in patients switched from either cyclosporine (+7.8 mL/min) or tacrolimus (+8.9 mL/min), and was observed regardless of baseline renal function. Patient survival, graft survival and the overall safety profile was similar between groups.

The impact of belatacept on long-term cardiovascular profiles is yet to be determined. An analysis of the pooled data from the BENEFIT AND BENEFIT-EXT trials showed lower blood pressures, lower non HDL cholesterol, lower triglycerides and less new onset diabetes mellitus after transplanation in the belatacept-treated patients versus the cyclosporine treated patients[25]. Yet, in a post-hoc analysis in patients with pre-existing diabetes from the BENEFIT and BENEFIT-EXT, 12 mo patient survival, graft survival, and renal function were similar between belatacept and cyclosporine treated patients[26]. Further trials are needed to explore the long-term outcomes, the impact of Epstein-Barr virus on post-transplant lymphoproliferative disease, and chronic allograft nephropathy. These trials should include contemporary immunosuppressive regimens.

A fully human anti-CD40 monoclonal antibody, ASKP1240 (Astellas®), has shown promise in phase 1 studies[27-29]. The first human, phase 1 study of healthy subjects (*n* = 12) demonstrated that the antibody was safe and well-tolerated[28]. Subsequently, a phase 1b trial, was performed in *de novo* kidney transplant recipients that received a single intravenous dose of 50 mg (*n* = 10), 100 mg (*n* = 9), 200 mg (*n* = 10), 500 mg (*n* = 9) or placebo (*n* = 8), no induction and standard maintenance immunosuppression per each center's protocol[26]. ASKP1240 exhibited non-linear pharmacokinetics and was well tolerated at all doses. Acute rejection occurred in 3 patients in the 50 mg arm, 3 patients in the 500 mg arm and 1 patient in the placebo arm. The incidence of infection was not dose dependent. A phase 2 trial will compare the efficacy of ASKP1240 with calcineurin avoidance (basiliximab induction, ASKP1240, mycophenolate mofetil, and steroids) to the standard of care immunosuppressive regimen (basiliximab induction + tacrolimus + mycophenolate mofetil + steroids). In addition, the study will compare the efficacy of calcineurin inhibitor minimization-mycophenolate mofetil avoidance (basiliximab induction, ASKP1240, tacrolimus and steroids) to the standard of care immunosuppressive regimen.

TREATMENT OF ANTIBODY MEDIATED REJECTION

Antibody mediated rejection is an important cause of acute and chronic graft failure. Acute and chronic antibody mediated rejections are difficult to treat, because they are typically less responsive to conventional anti-

rejection therapy. Treatment regimens for acute antibody mediated rejection may include one or more of the following: plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab[30-38], although these regimens are not well-studied. A recent meta-analysis of over 10000 citations on treatment of antibody-mediated rejection concluded that data describing these treatments are of low or very low quality[34]. The first, prospective, randomized study comparing these strategies (plasmapheresis/IVIG/rituximab *vs* IVIG alone) demonstrated improved graft survival in the combination group[38]. Little guidance is given by the KDIGO Clinical Practice Guidelines, they suggest treating antibody-mediated acute rejection with one or more of the following alternatives with or without corticosteroids: plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; lymphocyte-depleting antibody (Grade 2C Recommendation)[1]. Two investigational treatments for antibody mediated rejection include bortezomib and eculizumab.

Bortezomib (Velcade®, Millenium Pharmaceuticals) has been used for treatment of acute antibody mediated rejection, although it is approved for multiple myeloma in the United States (2010). It inhibits the degradation of cell-cycle regulatory proteins resulting in cell-cycle death *via* apoptosis. Bortezomib is metabolized via the cytochrome P450 system, a major substrate of 2C19 and 3A4 and inhibitor of 2C19, and therefore several drug interactions may occur including ketoconazole, clopidogrel, and grapefruit juice. Adverse events associated with bortezomib may include neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, constipation (up to 50%), peripheral neuropathy (up to 30%), hypotension, QT prolongation, heart failure, pneumonitis and pneumonia. One case series of 52 transplant patients treated for antibody mediated rejection or desensitization reported bortezomib associated toxicity to be low, most commonly reported as manageable anemia or peripheral neuropathy[39]. Dosing of bortezomib is 1.3 mg/m^2 on days 1, 4, 8, 11. No adjustments are necessary for renal impairment, but the dosage should be reduced by one-half for moderate to severe hepatic impairment.

Case series have reported the use of bortezomib to remove HLA antibodies in live-donor transplant recipients with HLA alloantibodies[40,41] and to treat antibody and cell-mediated acute rejection[42-51]. Few comparative trials have been performed. One German, historical control study of 10 bortezomib-treated patients (4 doses of 1.3 mg/m^2) *vs* 9 rituximab-treated patients (one fixed dose of 500 mg) with antibody mediated rejection showed improved survival in the bortezomib treated group with an 18 mo graft survival of 60% *vs* 11% in the rituximab group[52]. All patients received plasmapheresis and intravenous immune globulin (30 g). Randomized trials are needed to determine the influence of bortezomib on antibody removal.

Eculizumab (Soliris®, Alexion Pharmaceuticals) is a humanized monoclonal IgG antibody that binds to complement protein C5 and blocks the activation of terminal complement. It is FDA approved for paroxysmal

Table 3 Clinical trials

Agent	Identifier	Study name	Start date
ASKP1240	NCT01780844	A Study to Assess the Efficacy and Safety of ASKP1240 in de Novo Kidney Transplant Recipients	February 2013
Voclosporin	NCT01586845	Safety and Efficacy Study of Voclosporin and Tacrolimus in Transplantation	March 2013
Prolonged Release Tacrolimus	NCT01294020	Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted From Prograf® to Advagraf®	May 2011
Bortezomib	NCT01873157	Bortezomib in Late Antibody-mediated Kidney Transplant Rejection (BORTEJECT)	October 2013
	NCT01349595	Impact of Proteasome Inhibition on Anti-Donor HLA Antibody Production After Kidney Transplantation	December 2011
	NCT01842074	Desensitization With Bortezomib Before a Living Kidney Donation (VELDON)	January 2013
	NCT01502267	Desensitization Protocol for Highly Sensitized Patients on the Waiting List for Kidney Transplant	January 2010
	NCT00722722	The Impact of Velcade on Antibody Secreting Cells in Sensitized Renal Allograft Candidates	June 2008
Eculizumab	NCT01349595	Impact of Proteasome Inhibition on Anti-Donor HLA Antibody Production After Kidney Transplantation	December 2011
	NCT01327573	Eculizumab Therapy for Chronic Complement-Mediated Injury in Kidney Transplantation	March 2011
	NCT01095887	Eculizumab Added to Conventional Treatment in the Prevention of Antibody-mediated Rejection in ABO Blood Group Incompatible Living Donor Kidney Transplantation (ABOi)	March 2010
	NCT01403389	A Study of the Activity of Eculizumab for Prevention of Delayed Graft Function In Deceased Donor Kidney Transplant	August 2011
	NCT01567085	Safety and Efficacy Of Eculizumab In The Prevention Of Antibody Mediated Rejection (AMR) In Sensitized Recipients Of A Kidney Transplant From A Deceased Donor	May 2012
	NCT01106027	Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Deceased Donor Kidney Transplant	March 2010
	NCT01399593	Safety and Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Requiring Desensitization	September 2011

nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. The most common side effects are headache, nausea, fatigue, back pain, cough and nasopharyngitis. Fatal immune hemolytic anemia following allogeneic stem cell transplantation has been reported[53]. Vaccination with meningococcal vaccine at least 2 wk prior to initiation of treatment with continued long-term prophylaxis is recommended. Eculizumab should not be used in patients with serious infections.

Case studies in renal transplant recipients have reported successful treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathy with eculizumab[54-66]. Eculizumab has also been successful in reducing antibodies in a highly sensitized patient with positive crossmatches prior to live donor transplant[67] and in prevention of antibody mediated rejection in a case series of patients with donor specific antibodies and positive flow cytometry cross-matches ($n = 4$)[68]. In a larger case-control study, patients with donor specific antibodies who received pre-transplant plasmapheresis and post-transplant eculizumab were compared to historical controls[69]. At a median follow up of 12 mo for the eculizumab group, antibody mediated rejection occurred in 7.7 % (2/26) in the eculizumab group compared to 41% (21/51) in the control group ($P < 0.01$). One-year protocol biopsy revealed transplant glomerulopathy in 6.7% (1/15) eculizumab-treated recipients and in 35.7% (15/42) of control patients ($P = 0.044$). Eculizumab use has also been described in an ABO-incompatible deceased-donor kidney and pancreas transplant with a severe antibody-mediated rejection[70,71].

Eculizumab 600 mg weekly for six doses with plasmapheresis has also been successful in reversing refractory, early (mean time 6.5 d), acute antibody mediated rejection in four transplant recipients[72]. Mean follow up time is 6.4 ± 5.7 mo, and while antibodies persisted in the majority of the patients, the allografts are functioning and infectious complications have not occurred. Successful use of eculizumab has also been reported in two patients with antibody mediated rejection associated with thrombotic microangiopathy[73] and three patients with resistant antibody mediated rejection[74,75].

Despite the small sample size and lack of randomized controls, these studies are encouraging, and although larger studies and long-term follow-up are needed, bortezomib and eculizumab may play a major role in acute antibody mediated therapy in the future. Their role in transplant desensitization may be better elucidated as more clinical data and well-designed clinical trials become available. Current and future trials of bortezomib and eculizumab are listed in Table 3[76].

AGENTS NO LONGER BEING INVESTIGATED

Efalizumab (Raptiva®, Genentech) works an immunosuppressant by binding to the CD11a subunit of lymphocyte function-associated antigen 1 (LFA-1) and inhibiting white blood cell migration. This once weekly intramus-

cular injection was indicated for the treatment of chronic moderate-to-severe plaque psoriasis, but has been associated with an increased risk for progressive multifocal leukoencephalopathy (PML) and was withdrawn from the market in April of 2009[77]. Likewise, clinical trials in renal transplant recipients have not been successful due to higher rates of lymphoproliferative disease[78].

Alefacept (Amevive®, Astellas Pharmaceuticals) is a CD2-LFA3 co-stimulation inhibitor[79,80], was an intramuscular injection indicated for treatment of moderate-to-severe chronic plaque psoriasis. Alefacept was voluntarily withdrawn from the market by Astellas Pharmaceuticals in December of 2011 due to "business needs"[81]. Prior to the discontinuation, alefacept was being developed for use in conjunction with tacrolimus, mycophenolate mofetil and steroids in renal transplantation. In a phase 2, *de novo* study of adult kidney transplant patients alefacept (*vs* placebo) resulted in similar survival and rejection rates, however the incidence of malignancy was higher in the alefacept arm[82].

Sotrastaurin (AEB071, Novartis), a protein kinase inhibitor, initially proved to have a good tolerability profile with few adverse effects[83]. Sotrastaurin development has been halted due high rejection rates (up to 40%) in *de novo* transplant recipients despite promising results with renal function and a low toxicity profile[83-87].

Tofacitinib (Xeljanz®, Tofacitinib CP-690550, Pfizer Inc.), is a kinase inhibitor with immunosuppressant properties that was FDA approved for moderate to severe rheumatoid arthritis in November of 2012. Tofacitinib is a small molecule agent which exhibits selective inhibition for the JAKs, thus inactivating the JAK/STAT dependent IL-2 induced T-cell proliferation.

Tofacitinib was being studied as a drug to be used in place of calcineurin inhibitors along with other antimetabolite agents in two phase 2 clinical trials. In a small, initial, clinical study on *de novo* kidney allograft recipients comparing a tofacitinib regimen at 15 mg twice daily (CP15) and 30 mg twice daily (CP30) with tacrolimus, researchers reported the 6-mo biopsy-proven acute rejection rates to be 1 of 20, 4 of 20 and 1 of 21 for CP15, CP30 and tacrolimus groups respectively and concluded the 15 mg *bid* regimen to be similar to the tacrolimus regimen[88]. All patients received interleukin-2 receptor antagonist induction, mycophenolic acid and corticosteroids. In a subsequent, larger phase-2 trial (*n* = 331), a standard cyclosporine regimen was compared with a 15 mg twice daily regimen of tofacitinib which is subsequently switched to 10 mg twice daily after 3 mo (less-intensive) and another 15 mg twice daily regimen of tofacitinib which is switched to 10 mg twice daily after 6 mo (more-intensive)[89]. The biopsy proven acute rejection at 6 mo with the low-dose group (11%) was lower than the more-intensity or cyclosporine groups (7% and 9%, respectively). In terms of glomerular filtration rate at 12 mo, the tofacitinib groups (less-intensity: 65 mL/min and more-intensity: 65 mL/min) showed a significant difference in preservation of renal function compared to the cyclosporine group (54 mL/min). In this study, there

was a lower incidence of chronic allograft nephropathy in the more intense and less intense groups (25% and 24% respectively) compared to the cyclosporine group (48%).

The smaller clinical study reported a high incidence of BK virus in the CP30 group (4/20) and a higher 6 mo rate of CMV disease (4/20) compared to CP15 and tacrolimus (2/20 and 0/20 respectively)[88]. Some other common abnormalities noted with this agent were trends towards higher lipid elevations, anemia and neutropenia during the first 6 mo of the treatment when the mycophenolate mofetil dose was high. In the larger, phase 2 trial, there were fewer cases of new-onset diabetes in the more-intense and less-intense groups (9.9% and 9.3% respectively) compared to cyclosporine (20.8%)[89]. The rate of serious infections, BK virus nephritis, post-transplant lymphoproliferative disorder and CMV disease was higher in the tofacitinib groups. The overall findings of the phase 2 studies suggest that tofacitinib is effective in preventing acute rejection and chronic allograft nephropathy, although this was achieved at the expense of hematological toxicity and over-immunosuppression when used in combination with mycophenolate mofetil. Although research has shown that safety may be improved by concentration-controlled dosing[90], tofacitinib development has been discontinued.

CONCLUSION

Induction agents are typically antibodies (anti-thymocyte globulins) or interleukin 2 receptor antagonists (basiliximab). Alemtuzumab has been removed from the United States market, but is available through the manufacturer through a special program. Many questions remain surrounding the use of potent induction agents including whether or not the use is associated with infection and malignancy, if the use is cost-effective, and if there is a true graft survival benefit. Due to poor clinical outcomes, induction investigational agents including, efalizumab and alefacept, are no longer being studied. Maintenance immunosuppressives may show some promise with future novel agents. Prolonged release tacrolimus provides once daily dosing of this product and hopefully will simplify a complex post-transplant immunosuppressive regimen. It is unknown if the perceived benefits will outweigh the cost of this product. Voclosporin, a cyclosporine analog, has not shown superior efficacy outcomes, but perhaps improvement in the safety profile (namely new-onset diabetes after transplant) will secure its place in transplant immunotherapy as the phase 3 trials are underway. ASKP, an anti-CD40 antibody, has successfully completed phase 1 studies and phase 2 trials are ongoing. Although belatacept has shown promise, two other investigational maintenance agents, sotrastaurin and tolfacitinib, will not be studied further in transplantation.

Treatment regimens for acute humoral rejection may include one or more of the following: plasmapheresis, intravenous immunoglobulin, and rituximab. Investigations of bortezomib and eculizumab have been hindered by small, non-randomized trials. Although results are

encouraging, larger studies and long-term follow-up is ongoing.

At this point in time, there are very few immunosuppressants in clinical trials. Although some investigational agents have shown promise, tailoring available agents may need to be the short-term focus for transplant recipients. Hopefully, modifying exist regimens and approval of investigational agents will satisfy the ultimate goal of transplantation to improve long-term survival without toxicity or infection.

REFERENCES

1 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

2 **Kalluri HV**, Hardinger KL. The current state of renal transplant immunosuppression: present and future. *World J Transplant* 2012; **2**: 51-68 [DOI: 10.5500/wjt.v2.i4.51]

3 **Silva HT**, Yang HC, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, Dhadda S, Holman J, Fitzsimmons W, First MR. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *Am J Transplant* 2007; **7**: 595-608 [PMID: 17217442 DOI: 10.1111/j.1600-6143.2007.01661.x]

4 **Krämer BK**, Charpentier B, Bäckman L, Silva HT, Mondragon-Ramirez G, Cassuto-Viguier E, Mourad G, Sola R, Rigotti P, Mirete JO. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. *Am J Transplant* 2010; **10**: 2632-2643 [PMID: 20840480 DOI: 10.1111/j.1600-6143.2010.03256.x]

5 **Jelassi ML**, Lefeuvre S, Karras A, Moulonguet L, Billaud EM. Therapeutic drug monitoring in de novo kidney transplant receiving the modified-release once-daily tacrolimus. *Transplant Proc* 2011; **43**: 491-494 [PMID: 21440742 DOI: 10.1016/j.transproceed.2011.01.043]

6 **Hougardy JM**, Broeders N, Kianda M, Massart A, Madhoun P, Le Moine A, Hoang AD, Mikhalski D, Wissing KM, Abramowicz D. Conversion from Prograf to Advagraf among kidney transplant recipients results in sustained decrease in tacrolimus exposure. *Transplantation* 2011; **91**: 566-569 [PMID: 21192316 DOI: 10.1097/TP.0b013e3182098ff0]

7 **Kitada H**, Okabe Y, Nishiki T, Miura Y, Kurihara K, Terasaka S, Kawanami S, Tuchimoto A, Masutani K, Tanaka M. One-year follow-up of treatment with once-daily tacrolimus in de novo renal transplant. *Exp Clin Transplant* 2012; **10**: 561-567 [PMID: 23082898 DOI: 10.6002/ect.2012.0087]

8 **Busque S**, Cantarovich M, Mulgaonkar S, Gaston R, Gaber AO, Mayo PR, Ling S, Huizinga RB, Meier-Kriesche HU. The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *Am J Transplant* 2011; **11**: 2675-2684 [PMID: 21943027 DOI: 10.1111/j.1600-6143.2011.03763.x]

9 **Naidoo P**, Rambiritch V. Voclosporin (ISA247) for plaque psoriasis. *Lancet* 2008; **372**: 888-889; author reply 889 [PMID: 18790303 DOI: 10.1016/S0140-6736(08)61391-4]

10 **Papp K**, Bissonnette R, Rosoph L, Wasel N, Lynde CW, Searles G, Shear NH, Huizinga RB, Maksymowych WP. Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371**: 1337-1342 [PMID: 18424323 DOI: 10.1016/S0140-6736(08)60593-0]

11 **Bissonnette R**, Papp K, Poulin Y, Lauzon G, Aspeslet L, Huizinga R, Mayo P, Foster RT, Yatscoff RW, Maksymowych WP. A randomized, multicenter, double-blind, placebo-controlled phase 2 trial of ISA247 in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2006; **54**: 472-478 [PMID: 16488299 DOI: 10.1016/j.jaad.2005.10.061]

12 **Kuglstatter A**, Mueller F, Kusznir E, Gsell B, Stihle M, Thoma R, Benz J, Aspeslet L, Freitag D, Hennig M. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E-ISA247 (voclosporin). *Acta Crystallogr D Biol Crystallogr* 2011; **67**: 119-123 [PMID: 21245533 DOI: 10.1107/S0907444910051905]

13 **Gregory CR**, Kyles AE, Bernsteen L, Wagner GS, Tarantal AF, Christe KL, Brignolo L, Spinner A, Griffey SM, Paniagua RT, Hubble RW, Borie DC, Morris RE. Compared with cyclosporine, ISATX247 significantly prolongs renal-allograft survival in a nonhuman primate model. *Transplantation* 2004; **78**: 681-685 [PMID: 15371668 DOI: 10.1097/01.TP.0000131950.75697.71]

14 **Aspeslet L**, Freitag D, Huizinga R, Mayo P, Ling S, Foster R. The pharmacokinetics of voclosporin (VCS) in renal impairment. *Am J Transpl* 2013; **13** Suppl 5: abstr B1020

15 **Aspeslet L**, Freitag D, Huizinga R, Mayo P, Ling S, Foster R. The effects of hepatic impairment on single and multiple oral dose pharmacokinetics of voclosporin (VCS). *Am J Transpl* 2013; **13** Suppl 5: abstr B1033

16 **Aspeslet L**, Freitag D, Huizinga R, Mayo P, Ling S, Foster R. The effects of high fat breakfast, low fat breakfast or fasting on the absorption of voclosporin (VCS). *Am J Transpl* 2013; **13** Suppl 5: abstr B1032

17 **Alloway R**, Bloom R, Gaston R, Goggins M, Mayo P, Busque S. A comparison of voclosporin and tacrolimus 1 year outcomes as predicted by PKPD in the PROMISE trial. *Am J Transpl* 2013; **13** Suppl 5: abstr B1018

18 **Vincenti F**, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G, Lang P, Grinyo J, Halloran PF, Solez K, Hagerty D, Levy E, Zhou W, Natarajan K, Charpentier B. Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353**: 770-781 [PMID: 16120857 DOI: 10.1056/NEJMoa050085]

19 **Vincenti F**, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, Massari P, Mondragon-Ramirez GA, Agarwal M, Di Russo G, Lin CS, Garg P, Larsen CP. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010; **10**: 535-546 [PMID: 20415897 DOI: 10.1111/j.1600-6143.2009.03005.x]

20 **Larsen CP**, Grinyó J, Medina-Pestana J, Vanrenterghem Y, Vincenti F, Breshahan B, Campistol JM, Florman S, Rial Mdel C, Kamar N, Block A, Di Russo G, Lin CS, Garg P, Charpentier B. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation* 2010; **90**: 1528-1535 [PMID: 21076381 DOI: 10.1097/TP.0b013e3181ff87cd]

21 **Durrbach A**, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, Rial Mdel C, Florman S, Block A, Di Russo G, Xing J, Garg P, Grinyó J. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant* 2010; **10**: 547-557 [PMID: 20415898 DOI: 10.1111/j.1600-6143.2010.03016.x]

22 **Florman S**, Becker T, Bresnahan B, Chevaile-Ramos A, DeCarvalho D, Muehlbacher F, O'Connell P, Duan T, Agarwal M, Larsen C. Three year outcomes by donor type in phase III studies of belatacept vs cyclosporine in kidney transplantation (BENEFIT & BENEFIT-EXT). *Am J Transplant* 2011; **11** Suppl S2: abstract 229

23 **Ferguson R**, Grinyó J, Vincenti F, Kaufman DB, Woodle ES, Marder BA, Citterio F, Marks WH, Agarwal M, Wu D, Dong Y, Garg P. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant* 2011; **11**: 66-76 [PMID: 21114656

DOI: 10.1111/j.1600-6143.2010.03338.x]

24 **Rostaing L**, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, del Carmen Rial M, Steinberg S, Vincenti F, Shi R, Di Russo G, Thomas D, Grinyó J. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. *Clin J Am Soc Nephrol* 2011; **6**: 430-439 [PMID: 21051752 DOI: 10.2215/CJN.05840710]

25 **Vanrenterghem Y**, Bresnahan B, Campistol J, Durrbach A, Grinyó J, Neumayer HH, Lang P, Larsen CP, Mancilla-Urrea E, Pestana JM, Block A, Duan T, Glicklich A, Gujrathi S, Vincenti F. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation* 2011; **91**: 976-983 [PMID: 21372756 DOI: 10.1097/TP.0b013e31820c10eb]

26 **Rostaing L**, Neumayer HH, Reyes-Acevedo R, Bresnahan B, Florman S, Vitko S, Heifets M, Xing J, Thomas D, Vincenti F. Belatacept-versus cyclosporine-based immunosuppression in renal transplant recipients with pre-existing diabetes. *Clin J Am Soc Nephrol* 2011; **6**: 2696-2704 [PMID: 21921152 DOI: 10.2215/CJN.00270111]

27 **Oura T**, Yamashita K, Suzuki T, Fukumori D, Watanabe M, Hirokata G, Wakayama K, Taniguchi M, Shimamura T, Miura T, Okimura K, Maeta K, Haga H, Kubota K, Shimizu A, Sakai F, Furukawa H, Todo S. Long-term hepatic allograft acceptance based on CD40 blockade by ASKP1240 in non-human primates. *Am J Transplant* 2012; **12**: 1740-1754 [DOI: 10.1111/j.1600-6143.2012.04014.x]

28 **Goldwater R**, Keirns J, Blahunka P, First R, Sawamoto T, Zhang W, Kowalski D, Kaibara A, Holman J. A phase 1, randomized ascending single-dose study of antagonist anti-human CD40 ASKP1240 in healthy subjects. *Am J Transplant* 2013; **13**: 1040-1046 [PMID: 23356210 DOI: 10.1111/ajt.12082.]

29 **Vincenti F**, Yang H, Klintmalm G, Steinberg S, Wang L, Zhang W, Conkle A, Blahunka P, First R, Holman J. Clinical Outcomes in a Phase 1b, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Single-Dose Study of ASKP1240 in De Novo Kidney Transplantation. *Am J Transpl* 2013; **13** Suppl 5: abstr 181

30 **Jordan SC**, Vo AA, Tyan D, Nast CC, Toyoda M. Current approaches to treatment of antibody-mediated rejection. *Pediatr Transplant* 2005; **9**: 408-415 [PMID: 15910400 DOI: 10.1111/j.1399-3046.2005.00363.x]

31 **Rocha PN**, Butterly DW, Greenberg A, Reddan DN, Tuttle-Newhall J, Collins BH, Kuo PC, Reinsmoen N, Fields T, Howell DN, Smith SR. Beneficial effect of plasmapheresis and intravenous immunoglobulin on renal allograft survival of patients with acute humoral rejection. *Transplantation* 2003; **75**: 1490-1495 [PMID: 12792502 DOI: 10.1097/01.TP.0000060252.57111.AC]

32 **Becker YT**, Becker BN, Pirsch JD, Sollinger HW. Rituximab as treatment for refractory kidney transplant rejection. *Am J Transplant* 2004; **4**: 996-1001 [PMID: 15147435 DOI: 10.1111/j.1600-6143.2004.00454.x]

33 **Montgomery R**, Simpkins C, Zachary A. Anti-CD20 rescue therapy for kidneys undergoing antibody-mediated rejection. *Am J Transplant* 2004; **4**: abstract 258

34 **Locke JE**, Zachary AA, Haas M, Melancon JK, Warren DS, Simpkins CE, Segev DL, Montgomery RA. The utility of splenectomy as rescue treatment for severe acute antibody mediated rejection. *Am J Transplant* 2007; **7**: 842-846 [PMID: 17391127 DOI: 10.1111/j.1600-6143.2006.01709.x]

35 **Faguer S**, Kamar N, Guilbeaud-Frugier C, Fort M, Modesto A, Mari A, Ribes D, Cointault O, Lavayssière L, Guitard J, Durand D, Rostaing L. Rituximab therapy for acute humoral rejection after kidney transplantation. *Transplantation* 2007; **83**: 1277-1280 [PMID: 17496547 DOI: 10.1097/01.tp.0000261113.30757.d1]

36 **Blume OR**, Yost SE, Kaplan B. Antibody-mediated rejection: pathogenesis, prevention, treatment, and outcomes. *J Transplant* 2012; **2012**: 201754 [PMID: 22545199 DOI: 10.1155/2012/201754]

37 **Roberts DM**, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation* 2012; **94**: 775-783 [PMID: 23032865]

38 **Lefaucheur C**, Nochy D, Andrade J, Verine J, Gautreau C, Charron D, Hill GS, Glotz D, Suberbielle-Boissel C. Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. *Am J Transplant* 2009; **9**: 1099-1107 [PMID: 19422335 DOI: 10.1111/j.1600-6143.2009.02591.x]

39 **Schmidt N**, Alloway RR, Walsh RC, Sadaka B, Shields AR, Girnita AL, Hanseman DJ, Woodle ES. Prospective evaluation of the toxicity profile of proteasome inhibitor-based therapy in renal transplant candidates and recipients. *Transplantation* 2012; **94**: 352-361 [PMID: 22836132 DOI: 10.1097/TP.0b013e318257acf6]

40 **Trivedi HL**, Terasaki PI, Feroz A, Everly MJ, Vanikar AV, Shankar V, Trivedi VB, Kaneku H, Idica AK, Modi PR, Khemchandani SI, Dave SD. Abrogation of anti-HLA antibodies via proteasome inhibition. *Transplantation* 2009; **87**: 1555-1561 [PMID: 19461494 DOI: 10.1097/TP.0b013e3181a4b91b]

41 **Everly MJ**, Terasaki PI, Hopfield J, Trivedi HL, Kaneku H. Protective immunity remains intact after antibody removal by means of proteasome inhibition. *Transplantation* 2010; **90**: 1493-1498 [PMID: 21042236 DOI: 10.1097/TP.0b013e3181ff87b1]

42 **Everly MJ**, Everly JJ, Susskind B, Brailey P, Arend LJ, Alloway RR, Roy-Chaudhury P, Govil A, Mogilishetty G, Rike AH, Cardi M, Wadih G, Tevar A, Woodle ES. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation* 2008; **86**: 1754-1761 [PMID: 19104417 DOI: 10.1097/TP.0b013e318190af83]

43 **Flechner SM**, Fatica R, Askar M, Stephany BR, Poggio E, Koo A, Banning S, Chiesa-Vottero A, Srinivas T. The role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. *Transplantation* 2010; **90**: 1486-1492 [PMID: 21042239 DOI: 10.1097/TP.0b013e3181fdd9b0]

44 **Walsh RC**, Everly JJ, Brailey P, Rike AH, Arend LJ, Mogilishetty G, Govil A, Roy-Chaudhury P, Alloway RR, Woodle ES. Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. *Transplantation* 2010; **89**: 277-284 [PMID: 20145517 DOI: 10.1097/TP.0b013e3181c6ff8d]

45 **Sberro-Soussan R**, Zuber J, Suberbielle-Boissel C, Candon S, Martinez F, Snanoudj R, Rabant M, Pallet N, Nochy D, Anglicheau D, Leruez M, Loupy A, Thervet E, Hermine O, Legendre C. Bortezomib as the sole post-renal transplantation desensitization agent does not decrease donor-specific anti-HLA antibodies. *Am J Transplant* 2010; **10**: 681-686 [PMID: 20121729 DOI: 10.1111/j.1600-6143.2009.02968.x]

46 **Nigos JG**, Arora S, Nath P, Hussain SM, Marcus RJ, Ko TY, Sureshkumar KK. Treatment of antibody-mediated rejection in kidney transplant recipients: a single-center experience with a bortezomib-based regimen. *Exp Clin Transplant* 2012; **10**: 609-613 [PMID: 23216567 DOI: 10.6002/ect.2012.0131]

47 **Tzvetanov I**, Spaggiari M, Joseph J, Jeon H, Thielke J, Oberholzer J, Benedetti E. The use of bortezomib as a rescue treatment for acute antibody-mediated rejection: report of three cases and review of literature. *Transplant Proc* 2012; **44**: 2971-2975 [PMID: 23195008 DOI: 10.1016/j.transproceed.2012.02.037]

48 **Gheith O**, Al-Otaibi T, Nampoory N, Halim M, Nair P, Saied

T, Al-Waheeb S, Muzeirei I, Ibraheim M. Effective therapy for acute antibody-mediated rejection with mild chronic changes: case report and review of the literature. *Exp Clin Transplant* 2012; **10**: 406-409 [PMID: 22746156 DOI: 10.6002/ect.2011.0153]

49   **Sureshkumar KK**, Hussain SM, Marcus RJ, Ko TY, Khan AS, Tom K, Vivas CA, Parris G, Jasnosz KM, Thai NL. Proteasome inhibition with bortezomib: an effective therapy for severe antibody mediated rejection after renal transplantation. *Clin Nephrol* 2012; **77**: 246-253 [PMID: 22377258]

50   **Hardinger KL**, Murillo D. The influence of bortezomib on donor specific antibody reduction in patients with antibody mediated rejection. *Clin Transpl* 2011: 401-408 [PMID: 22755438]

51   **Westphal S**, Hansson S, Stelin G, Holgersson J, Mjörnstedt L, Friman S. Successful treatment of severe ABO antibody-mediated rejection using bortezomib: a case report. *Transplant Proc* 2013; **45**: 1213-1215 [PMID: 23622662 DOI: 10.1016/j.transproceed.2012.10.013]

52   **Waiser J**, Budde K, Schütz M, Liefeldt L, Rudolph B, Schönemann C, Neumayer HH, Lachmann N. Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. *Nephrol Dial Transplant* 2012; **27**: 1246-1251 [PMID: 21852274 DOI: 10.1093/ndt/gfr465]

53   **Rovira J**, Cid J, Gutiérrez-García G, Pereira A, Fernández-Avilés F, Rosiñol L, Martínez C, Carreras E, Urbano A, Rovira M, Lozano M. Fatal immune hemolytic anemia following allogeneic stem cell transplantation: report of 2 cases and review of literature. *Transfus Med Rev* 2013; **27**: 166-170 [PMID: 23562007 DOI: 10.1016/j.tmrv.2013.02.004]

54   **Roumenina LT**, Loirat C, Dragon-Durey MA, Halbwachs-Mecarelli L, Sautes-Fridman C, Fremeaux-Bacchi V. Alternative complement pathway assessment in patients with atypical HUS. *J Immunol Methods* 2011; **365**: 8-26 [PMID: 21215749 DOI: 10.1016/j.jim.2010.12.020]

55   **Châtelet V**, Lobbedez T, Frémeaux-Bacchi V, Ficheux M, Ryckelynck JP, Hurault de Ligny B. Eculizumab: safety and efficacy after 17 months of treatment in a renal transplant patient with recurrent atypical hemolytic-uremic syndrome: case report. *Transplant Proc* 2010; **42**: 4353-4355 [PMID: 21168697 DOI: 10.1016/j.transproceed.2010.09.125]

56   **Al-Akash SI**, Almond PS, Savell VH, Gharaybeh SI, Hogue C. Eculizumab induces long-term remission in recurrent post-transplant HUS associated with C3 gene mutation. *Pediatr Nephrol* 2011; **26**: 613-619 [PMID: 21125405 DOI: 10.1007/s00467-010-1708-6]

57   **Kavanagh D**, Richards A, Goodship T, Jalanko H. Transplantation in atypical hemolytic uremic syndrome. *Semin Thromb Hemost* 2010; **36**: 653-659 [PMID: 20865642 DOI: 10.1055/s-0030-1262887]

58   **Zimmerhackl LB**, Hofer J, Cortina G, Mark W, Würzner R, Jungraithmayr TC, Khursigara G, Kliche KO, Radauer W. Prophylactic eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. *N Engl J Med* 2010; **362**: 1746-1748 [PMID: 20445192 DOI: 10.1056/NEJMc1001060]

59   **Peffault de Latour R**, Xhaard A, Fremeaux-Bacchi V, Coppo P, Fischer AM, Helley D, Socié G. Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy. *Br J Haematol* 2013; **161**: 279-280 [PMID: 23294015 DOI: 10.1111/bjh.12202]

60   **Xie L**, Nester CM, Reed AI, Zhang Y, Smith RJ, Thomas CP. Tailored eculizumab therapy in the management of complement factor H-mediated atypical hemolytic uremic syndrome in an adult kidney transplant recipient: a case report. *Transplant Proc* 2012; **44**: 3037-3040 [PMID: 23195022 DOI: 10.1016/j.transproceed.2012.07.141]

61   **Zuber J**, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, Heyne N, Ardissino G, Chatelet V, Noël LH,

Hourmant M, Niaudet P, Frémeaux-Bacchi V, Rondeau E, Legendre C, Loirat C; French Study Group for Atypical HUS. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *Am J Transplant* 2012; **12**: 3337-3354

62   **Alachkar N**, Bagnasco SM, Montgomery RA. Eculizumab for the treatment of two recurrences of atypical hemolytic uremic syndrome in a kidney allograft. *Transpl Int* 2012; **25**: e93-e95 [PMID: 22591029 DOI: 10.1111/j.1432-2277.2012.01497.x]

63   **Krid S**, Roumenina LT, Beury D, Charbit M, Boyer O, Frémeaux-Bacchi V, Niaudet P. Renal transplantation under prophylactic eculizumab in atypical hemolytic uremic syndrome with CFH/CFHR1 hybrid protein. *Am J Transplant* 2012; **12**: 1938-1944 [PMID: 22494769 DOI: 10.1111/j.1600-6143.2012.04051.x]

64   **Wilson CH**, Brown AL, White SA, Goodship TH, Sheerin NS, Manas DM. Successful treatment of de novo posttransplant thrombotic microangiopathy with eculizumab. *Transplantation* 2011; **92**: e42-e43 [PMID: 21989273 DOI: 10.1097/TP.0b013e318230c0bd]

65   **Hadaya K**, Ferrari-Lacraz S, Fumeaux D, Boehlen F, Toso C, Moll S, Martin PY, Villard J. Eculizumab in acute recurrence of thrombotic microangiopathy after renal transplantation. *Am J Transplant* 2011; **11**: 2523-2527 [DOI: 10.1111/j.1600-6143.2011.03696.x]

66   **Chandran S**, Baxter-Lowe L, Olson JL, Tomlanovich SJ, Webber A. Eculizumab for the treatment of de novo thrombotic microangiopathy post simultaneous pancreas-kidney transplantation--a case report. *Transplant Proc* 2011; **43**: 2097-2101 [PMID: 21693335 DOI: 10.1016/j.transproceed.2011.02.064]

67   **Lonze BE**, Dagher NN, Simpkins CE, Locke JE, Singer AL, Segev DL, Zachary AA, Montgomery RA. Eculizumab, bortezomib and kidney paired donation facilitate transplantation of a highly sensitized patient without vascular access. *Am J Transplant* 2010; **10**: 2154-2160 [PMID: 20636451 DOI: 10.1111/j.1600-6143.2010.03191.x]

68   **Cohney SJ**, Hughes P, Rosemary M, Walker RG, Cantwell L, Vanhardeveld E, et al. C5 inhibition with eculizumab to prevent antibody mediated rejection (AbMR) in patients with donor specific anti-HLA antibody (DSAb) and a positive cross match. *Am J Transplant* 2011; **11** Suppl S2: abstr 1557

69   **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* 2011; **11**: 2405-2413 [DOI: 10.1111/j.1600-6143.2011.03757.x]

70   **Biglarnia AR**, Nilsson B, Nilsson T, von Zur-Mühlen B, Wagner M, Berne C, Wanders A, Magnusson A, Tufveson G. Prompt reversal of a severe complement activation by eculizumab in a patient undergoing intentional ABO-incompatible pancreas and kidney transplantation. *Transpl Int* 2011; **24**: e61-e66 [PMID: 21696455 DOI: 10.1111/j.1432-2277.2011.01290.x]

71   **Stewart ZA**, Collins TE, Schlueter AJ, Raife TI, Holanda DG, Nair R, Reed AI, Thomas CP. Case report: Eculizumab rescue of severe accelerated antibody-mediated rejection after ABO-incompatible kidney transplant. *Transplant Proc* 2012; **44**: 3033-3036 [DOI: 10.1016/j.transproceed.2012.03.053]

72   **Galliford J**, Lawrence C, Willicombe M, Chan K, Roufosse C, McLean A, Cairns T, Cook HT. Reversal of refractory acute antibody mediated rejection with eculizumab. *Am J Transplant* 2011; **11** Suppl S2: abstr 1098

73   **González-Roncero F**, Suñer M, Bernal G, Cabello V, Toro M, Pereira P, Angel Gentil M. Eculizumab treatment of acute antibody-mediated rejection in renal transplantation: case reports. *Transplant Proc* 2012; **44**: 2690-2694 [PMID: 23146495 DOI: 10.1016/j.transproceed.2012.09.038]

74   **Kocak B**, Arpali E, Demiralp E, Yelken B, Karatas C, Gorcin S, Gorgulu N, Uzunalan M, Turkmen A, Kalayoglu M.

Eculizumab for salvage treatment of refractory antibody-mediated rejection in kidney transplant patients: case reports. *Transplant Proc* 2013; **45**: 1022-1025 [DOI: 10.1016/j.transproceed.2013.02.062]

75   **Locke JE**, Magro CM, Singer AL, Segev DL, Haas M, Hillel AT, King KE, Kraus E, Lees LM, Melancon JK, Stewart ZA, Warren DS, Zachary AA, Montgomery RA.The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. *Am J Transplant* 2009; **9**: 231-235 [DOI: 10.1111/j.1600-6143.2008.02451.x]

76   ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-2013

77   Genentech, Inc. (2009-04-08). "Genentech Announces Voluntary Withdrawal of Raptiva from the U.S. Market". Press release. Available from: URL: http://www.drugs.com/news/genentech-announces-voluntary-raptiva-u-s-market-17125.html

78   **Vincenti F**, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH, Butt K, Laskow D, Slakey DP, Lorber MI, Garg JP, Garovoy M. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. *Am J Transplant* 2007; **7**: 1770-1777 [PMID: 17564637 DOI: 10.1111/j.1600-6143.2007.01845.x]

79   **Bashir SJ**, Maibach HI. Alefacept (Biogen). *Curr Opin Investig Drugs* 2001; **2**: 631-634 [PMID: 11569937]

80   **Weaver TA**, Charafeddine AH, Agarwal A, Turner AP, Russell M, Leopardi FV, Kampen RL, Stempora L, Song M, Larsen CP, Kirk AD. Alefacept promotes co-stimulation blockade based allograft survival in nonhuman primates. *Nat Med* 2009; **15**: 746-749 [PMID: 19584865 DOI: 10.1038/nm.1993]

81   Astellas. (2009-12-15). "Voluntary US Market Discontinuation of Amevive (alefacept)". Press release. Available from: URL: http://www.amevive.com/. Retrieved June 6, 2013

82   **Rostaing L**, Charpentier B, Glyda M, Rigotti P, Hettich F, Franks B, Houbiers JG, First R, Holman JM. Alefacept Combined With Tacrolimus, Mycophenolate Mofetil and Steroids in De Novo Kidney Transplantation: A Randomized Controlled Trial. *Am J Transplant* 2013; **13**: 1724-1733 [PMID: 23730730 DOI: 10.1111/ajt.12303]

83   **Budde K**, Sommerer C, Becker T, Asderakis A, Pietruck F, Grinyo JM, Rigotti P, Dantal J, Ng J, Barten MJ, Weber M. Sotrastaurin, a novel small molecule inhibiting protein kinase C: first clinical results in renal-transplant recipients. *Am J Transplant* 2010; **10**: 571-581 [PMID: 20121745 DOI: 10.1111/j.1600-6143.2009.02980.x]

84   Transplantation: Development of sotrastaurin halted in kidney transplantation. *Nat Rev Nephrol* 2013 May 28; Epub ahead of print [DOI: 10.1038/nrneph.2013.87]

85   **Friman S**, Arns W, Nashan B, Vincenti F, Banas B, Budde K, Cibrik D, Chan L, Klempnauer J, Mulgaonkar S, Nicholson M, Wahlberg J, Wissing KM, Abrams K, Witte S, Woodle ES. Sotrastaurin, a novel small molecule inhibiting protein-kinase C: randomized phase II study in renal transplant recipients. *Am J Transplant* 2011; **11**: 1444-1455 [PMID: 21564523 DOI: 10.1111/j.1600-6143.2011.03538.x]

86   **Tedesco-Silva H**, Kho MM, Hartmann A, Vitko S, Russ G, Rostaing L, Budde K, Campistol JM, Eris J, Krishnan I, Gopalakrishnan U, Klupp J. Sotrastaurin in calcineurin inhibitor-free regimen using everolimus in de novo kidney transplant recipients. *Am J Transplant* 2013; **13**: 1757-1768 [PMID: 23659755 DOI: 10.1111/ajt.12255]

87   **Russ GR**, Tedesco-Silva H, Kuypers DR, Cohney S, Langer RM, Witzke O, Eris J, Sommerer C, von Zur-Mühlen B, Woodle ES, Gill J, Ng J, Klupp J, Chodoff L, Budde K. Efficacy of sotrastaurin plus tacrolimus after de novo kidney transplantation: randomized, phase II trial results. *Am J Transplant* 2013; **13**: 1746-1756 [PMID: 23668931 DOI: 10.1111/ajt.12251]

88   **Busque S**, Leventhal J, Brennan DC, Steinberg S, Klintmalm G, Shah T, Mulgaonkar S, Bromberg JS, Vincenti F, Hariharan S, Slakey D, Peddi VR, Fisher RA, Lawendy N, Wang C, Chan G. Calcineurin-inhibitor-free immunosuppression based on the JAK inhibitor CP-690,550: a pilot study in de novo kidney allograft recipients. *Am J Transplant* 2009; **9**: 1936-1945 [PMID: 19660021 DOI: 10.1111/j.1600-6143.2009.02720.x]

89   **Vincenti F**, Tedesco Silva H, Busque S, O'Connell P, Friedewald J, Cibrik D, Budde K, Yoshida A, Cohney S, Weimar W, Kim YS, Lawendy N, Lan SP, Kudlacz E, Krishnaswami S, Chan G. 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* 2012; **12**: 2446-2456 [PMID: 22682022 DOI: 10.1111/j.1600-6143.2012.04127.x]

90   **Busque S**, Vincenti F, Tedesco Silva H, O'Connell P, Tortorici M, Lawendy N, Wang N, Chan G. Adverse events of over-immunosuppression are dependent on tofacitinib exposure in kidney transplant (KT) patients. *Am J Transpl* 2013; **13** Suppl 5: abstr 182