Novel immunosuppressive agents in kidney transplantation

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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. 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. Several investigational agents are no longer being pursued in transplantation including the induction agents, efalizumab and alefacept, and maintenance agents, sostraurin 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.

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Key words: Review; Immunosuppression; Investigational agents; Renal/kidney transplant

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.


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
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 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 induction 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

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Humanized antibody, CD11a/LFA-1</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Costimulation inhibitor, CD2 LFA3</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Calcineurin inhibitor</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Protein kinase C inhibitor</td>
</tr>
<tr>
<td>Voclosporin, ISA247</td>
<td>Anti-CD4 monoclonal antibody</td>
</tr>
<tr>
<td>Sotrastaurin, AEB0771</td>
<td>JAK 3 inhibitor</td>
</tr>
<tr>
<td>Tofacitinib, CT-6905501</td>
<td>Interleukin-27 inhibitor</td>
</tr>
<tr>
<td>ASKP1240</td>
<td>Anti-CD28 monoclonal antibody</td>
</tr>
<tr>
<td>Treatment of Antibody</td>
<td>Calcineurin inhibitor</td>
</tr>
<tr>
<td>Medicated Rejection</td>
<td>Protein kinase C inhibitor</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Monoclonal antibody, C5 complement protein</td>
</tr>
</tbody>
</table>

*No longer being investigated for transplantation.

**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[1-8]. Of note, tacrolimus levels may be slightly lower with prolonged-release tacrolimus compared to twice daily tacrolimus patients[8-7], 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, Isotechinka 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] compared to tacrolimus[14-16]. 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 immunosuppressive 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[17]. 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[18]. 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[19,20]. 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[19-22]. Optimal trough concentrations should be targeted between 35-60 ng/mL[22].

Belatacept (Nulojix®, Bristol Myers Squibb) is a second generation co-stimulation blocker (CD80 antagonist) that received Food and Drug Administration (FDA) approval for use in kidney transplantation in June of 2011. Belatacept is contraindicated in patients that are EBV virus seronegative, because of high incidence of post-transplant lymphoproliferative seen in clinical trials[19-20]. 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[18-22]. 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 transplantation in the belatacept-treated patients versus the cyclosporine treated patients[26]. 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[29]. 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[30-33], 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[30]. 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)[31]. 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[35]. Dosing of bortezomib is 1.3 mg/m² on days 1, 4, 8 and 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[36,37] and to treat antibody and cell-mediated acute rejection[38,39]. Few comparative trials have been performed. One German, historical control study of 10 bortezomib-treated patients (4 doses of 1.3 mg/m²) 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[32]. 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**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Identifier</th>
<th>Study name</th>
<th>Start date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASKP1240</td>
<td>NCT01780844</td>
<td>A Study to Assess the Efficacy and Safety of ASKP1240 in de Novo Kidney Transplant Recipients</td>
<td>February 2013</td>
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<tr>
<td>Eculizumab Prolonged Release</td>
<td>NCT01368645</td>
<td>Safety and Efficacy Study of Eculizumab and Tacrolimus in Transplantation</td>
<td>March 2013</td>
</tr>
<tr>
<td>Tacrolimus Bortezomib</td>
<td>NCT01294020</td>
<td>Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft</td>
<td>May 2011</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>NCT01873157</td>
<td>Bortezomib in Late Antibody-mediated Kidney Transplant Rejection (BORTEJECT)</td>
<td>October 2013</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01349595</td>
<td>Impact of Proteasome Inhibition on Anti-Donor HLA Antibody Production After Kidney Transplantation</td>
<td>December 2011</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01582074</td>
<td>Desensitization With Bortezomib Before a Living Kidney Donation (VELDON)</td>
<td>January 2013</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01502267</td>
<td>Desensitization Protocol for Highly Sensitized Patients on the Waiting List for Kidney Transplant</td>
<td>January 2010</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT00722722</td>
<td>The Impact of Velcade on Antibody Secreting Cells in Sensitized Renal Allograft Candidates</td>
<td>June 2008</td>
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<tr>
<td>Eculizumab</td>
<td>NCT01349595</td>
<td>Impact of Proteasome Inhibition on Anti-Donor HLA Antibody Production After Kidney Transplantation</td>
<td>December 2011</td>
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<tr>
<td>Eculizumab</td>
<td>NCT01327573</td>
<td>Eculizumab Therapy for Chronic Complement-Mediated Injury in Kidney Transplantation</td>
<td>March 2011</td>
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<tr>
<td>Eculizumab</td>
<td>NCT01403389</td>
<td>A Study of the Activity of Eculizumab for Prevention of Delayed Graft Function In Deceased Donor Kidney Transplant</td>
<td>August 2011</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01567085</td>
<td>Safety and Efficacy Of Eculizumab In The Prevention Of Antibody Mediated Rejection (AMR) In Sensitized Recipients Of A Kidney Transplant From A Deceased Donor</td>
<td>May 2012</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01106027</td>
<td>Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Deceased Donor Kidney Transplant</td>
<td>March 2010</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>NCT01399593</td>
<td>Safety and Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Requiring Desensitization</td>
<td>September 2011</td>
</tr>
</tbody>
</table>

**Table 4 Immunologic complications**

- ABO blood group incompatibility
- Rejection
- Antibody-mediated rejection
- Microangiopathy
- Nocturnal hemoglobinuria
- Atypical hemolytic uremic syndrome
- Nausea, fatigue, back pain, cough and nasopharyngitis
- Meningococcal vaccine

**Table 5 Agents no longer being investigated**

- Efalizumab (Raptiva®, Genentech) works on 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-
ular 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[7]. 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].

Sotrastraurin (AEB071, Novartis), a protein kinase inhibitor, initially proved to have a good tolerability profile with few adverse effects[83,84]. Sotrastraurin 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[83,84].

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 anti-metabolite 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[85]. 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)[86]. 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)[87]. 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%)[88]. 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[89], 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, sotrastraurin 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 ecuclizumab 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.

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