Novel Immunosuppression: Small Molecules and Biologics

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Summary: Kidney transplantation today has excellent short-term outcomes that have paralleled the use of new immunosuppressive agents introduced in the 1990s. In addition to reducing acute rejection, the goals for developing new agents is to improve long-term outcome, minimize nephrotoxicity, and reduce infectious, cardiovascular, and malignancy-related complications. Novel small molecules and biological agents currently in clinical development may help to minimize the use of calcineurin inhibitors and steroids. These small molecules include FTY720, a sphingosine phosphate–receptor modulator, FK778, an inhibitor of pyrimidine synthesis, CP-690550, a JAK3 inhibitor, and AEB-071, a protein kinase C inhibitor. The biological agents include drugs targeting interleukin-15, anti-CD40, belatacept (LEA29Y), a second-generation CTLY4Ig that blocks the interaction between CD80/86 and CD28 costimulatory pathways, and efalizumab, a humanized anti-LFA1 monoclonal antibody. These new agents currently in preclinical and clinical trials appear promising and may represent the emergence of novel immunosuppressive agents that can deliver immunosuppression without long-term toxicity.
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Kidney transplantation today has excellent short-term outcomes that have paralleled the use of new immunosuppressive agents introduced in the 1990s. The goal of immunosuppressive therapy is to balance the beneficial effects of reducing acute rejection while minimizing adverse effects from oversuppression including the development of infections and malignancy. Overall, effective immunosuppression that minimizes nephrotoxicity, dyslipidemia, posttransplant diabetes mellitus, hypertension, and cosmetic side effects (which lead to noncompliance) are among the important factors to consider when developing new immunosuppressive agents. In general, combinations of immunosuppressive agents are used to maximize efficacy and minimize the toxicity of each drug, an approach that also is used in new drug development.

SMALL MOLECULES

This article reviews 4 small molecules that are new immunosuppressive drugs (Table 1), each with unique and novel mechanisms of action at different stages of clinical development for use in renal transplantation.

FTY720

FTY720 is a novel immunomodulating agent that has been shown to be effective in experimental models of transplantation and autoimmunity. It is a structural analogue of myriocin, a metabolite of the fungus *Isaria sinclairii*, which has been used in traditional Chinese medicine.

FTY720 has a completely different mechanism of action compared with the immunosuppressive medications currently used in transplant patients. Rather than impairing T- and

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Table 1. Immunosuppressive Drugs in Transplantation: Mechanism of Action and Development Status

Small Molecule	Mechanism of Action	Development Status
FTY720	Agonist to S1P receptor	Discontinued after phase III
FK778	Inhibits pyrimidine	Discontinued after phase II
CP-690550	JAK3 inhibitor	In phase II
AEB-071	PKC inhibitor	In phase II

B-cell activation and function, FTY720 alters the lymphocyte homing patterns by interfering with the exit of lymphocytes from the thymus to the blood and from the tissues of secondary lymphoid organs into efferent lymphatics.[1] The molecular mode of action of FTY720 is thought to involve the down-regulation of chemokine receptors on lymphocytes.[2] After phosphorylation, FTY720 acts as an agonist at the G-protein–coupled sphingosine 1-phosphate (S1P) receptor-1 on thymocytes and lymphocytes, causing aberrant internalization of the receptor. Subsequently, the cells become unresponsive to the serum lipid S1P, and the lymphocytes are unable to egress from lymphoid organs into graft sites or inflamed tissues. By inhibiting lymphocyte infiltration into the allograft, FTY720 causes prolonged lymphopenia. However, FTY720 does not impair memory T-cell activation.

In a phase IIA multicenter study, 208 patients were randomized to receive 4 doses of FTY720, 0.25, 0.5, 1.0, or 2.5 mg, or mycophenolate mofetil (MMF) in combination with cyclosporine and corticosteroids.[3] The incidence of biopsy-proven acute rejection at 3 months was 23.2%, 34.9%, 17.5%, and 9.8%, in patients receiving FTY720 at escalating doses versus 17.1% in patients receiving MMF, with no differences in the incidences of graft loss or death. Side effects in patients treated with FTY720 included transient bradycardia and lymphope-

nia. Therefore, FTY720 at 2.5 mg was found to be as effective as MMF in combination with cyclosporine and corticosteroids for the prevention of acute rejection after renal transplantation.

The results of another 1-year phase II clinical trial compared FTY720 plus full-dose cyclosporine (FDC) or reduced-dose cyclosporine (RDC) with MMF plus FDC in renal transplant patients also were promising.[4]

Two large, phase III clinical trials compared the safety and efficacy of 5 mg FTY720 plus RDC and 2.5 mg FTY720 plus FDC versus MMF plus FDC.[5,6] Both studies showed that FTY720 plus RDC resulted in a higher rate of acute rejection. Although FTY720 with FDC had comparable efficacy with MMF, there was lower renal function and a higher incidence of macular edema in the FTY720-treated patients. Furthermore, there were safety concerns in the form of significant side effects including transient bradycardia, pulmonary adverse effects, and macular edema. Subsequently, further clinical development of FTY720 in renal transplantation has been halted. However, FTY720 is continued to be studied for the treatment of autoimmune disorders. Recently, in a phase II trial, FTY720 was efficacious in reducing the number of lesions and clinical activity in patients with multiple sclerosis.[7]

FK778

FK778 is an analogue of a metabolite of leflunomide with a shorter half-life, and it belongs to a new class of low-molecular-weight immunosuppressants, the malononitrilamides. FK778 has both immunosuppressive and antiproliferative effects. In animal models, FK778 has been shown to inhibit both T-cell and B-cell functions, and may have a role in preventing not only acute rejection but also chronic allograft dysfunction.[8] FK778 exerts its immunosuppressive effects by inhibiting dihydroorotic acid dehydrogenase, an enzyme important in de novo pyrimidine synthesis, and thereby inhibits cell proliferation.[9] In addition to its immunosuppressive effects, FK778 has been shown in in vitro and in animal studies to have antiviral activity against cytomegalovirus and polyoma virus.

In a phase II, double-blind, clinical trial, 149 adult renal transplant recipients were randomized to 12-week treatment with FK778 at 150 mg or 75 mg with a 600-mg loading dose versus placebo in combination with tacrolimus and corticosteroids.[10] Graft survival at week 16 was 89.7%, 88.8%, and 91.3%, in the high-dose, low-dose, and placebo groups, respectively, and the incidences of acute rejection were 26.5%, 25.9%, and 39.1%, respectively. The most common side effect in the FK778-treated patients was anemia. This study concluded that FK778 was efficacious when used in combination with tacrolimus and corticosteroids, with FK778-treated patients having lower acute rejection rates. Adverse effects included anemia, hypokalemia, symptomatic heart disease, and esophagitis. However, results from an as yet unpublished phase III clinical trial indicated that FK778 did not show clear benefits over current treatment options. Therefore, the further development of FK778 for use in renal transplantation has ceased.

Janus Kinase-3 Inhibitors

Most immunosuppressive medications affect not only cells important to the immune system but also cells that are expressed ubiquitously, thereby causing considerable side effects that lead to morbidity and a diminished quality of life. Therefore, the development of medications that have molecular targets specific to inhibiting the immune response has been at the forefront in creating new immunosuppressive medications.

Janus kinases (JAKs) are cytoplasmic tyrosine kinases that participate in the signaling of a broad range of cell-surface receptors, particularly members of the cytokine-receptor superfamily. Mammals have 4 members of this family: JAK1, JAK2, JAK3, and tyrosine kinase 2.

Compared with other members of the JAK family, JAK3 has special features that make it attractive as a potential target for immunosuppression (Fig. 1). First, JAK3 has a restricted tissue distribution and is found primarily on hematopoietic cells. Second, JAK3 associates specifically with the common gamma (cγ) chain of the interleukin-2 (IL-2) receptor, which is shared by tissue receptors for IL-4, IL-7, IL-9, IL-15, and IL-21.[11] Moreover, mice and human beings with the genetic absence or mutation of JAK3 express defects in lymphoid cell develop-
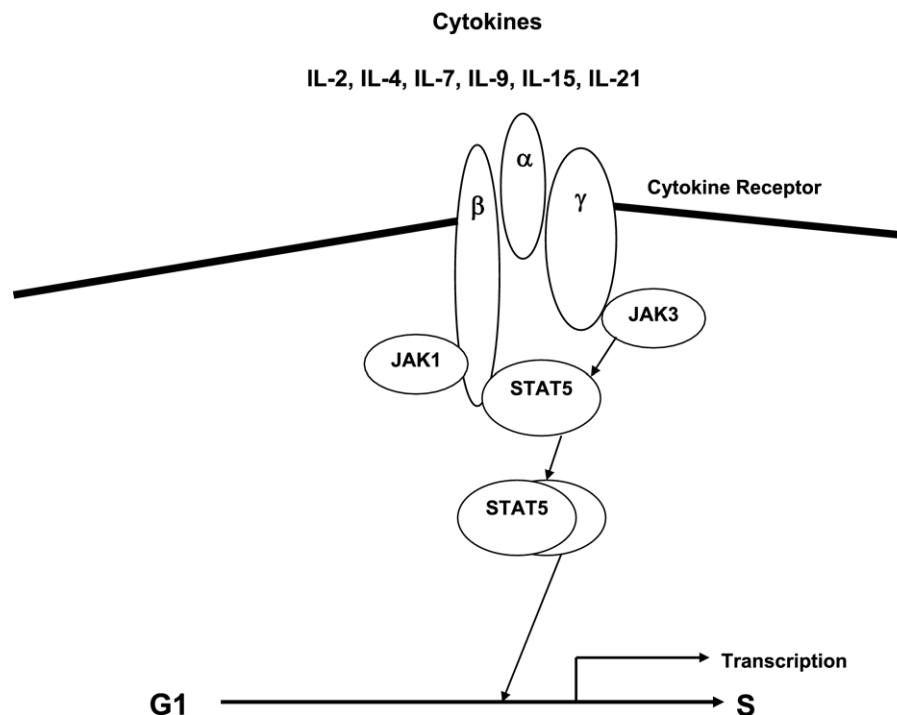

Figure 1. Site of action of the JAK3 inhibitors.

ment that give rise to a severe combined immunodeficiency syndrome phenotype.[12]

The first studies indicating that blocking the cγ chain of cytokine receptors can lead to long-term allograft survival were reported in mice receiving allogeneic islets in the presence of monoclonal anti-cγ receptor antibodies.[13] These mice accepted the allografts as a result of apoptosis of activated T cells.

Several oral JAK3 inhibitors have shown benefit in animal models of transplantation.[14] CP-690550, one of the JAK3 inhibitors, has shown improved renal allograft survival in nonhuman primate studies. In a study performed in 22 nonhuman primates, animals were administered CP-690550 versus vehicle by oral gavage twice daily, dosed to produce various levels of exposure with median 12-hour trough levels ranging from 1 to 147 ng/mL.[15] The animals with the highest CP-690550 trough levels had the best results, with survival times ranging from 83.2 ± 6.3 days for the highest level of exposure to 18.8 ± 6.3 days for the lowest level of exposure. The main side effect in the high-exposure animals was anemia.

In a follow-up, combination-therapy study performed in 11 nonhuman primates, animals were treated with CP-690550 and MMF by oral gavage twice daily versus MMF alone to target either high or low levels of exposure similar to the dosing regimen in the first study.[16] The mean survival time was 23 ± 1 days in animals treated with MMF alone versus 75.2 ± 8.7 days in animals receiving CP-690550 plus MMF. In addition, the animals receiving combination therapy with the highest CP-690550 trough levels had a significantly better survival rate. Based on these 2 preclinical studies in nonhuman primates, CP-690550 improved graft survival and thus has the potential to be an effective immunosuppressive agent in human beings.

A phase II trial studying the safety and efficacy of CP-690550 in recipients of primary renal transplants is in progress. Patients are randomized to 1 or 2 dose levels of CP-690550 plus MMF and corticosteroids versus tacrolimus, MMF, and corticosteroids. The results of this study will better determine the role for JAK3 inhibitors in renal transplantation.

AEB-071

AEB-071 (AEB) is a novel, oral, low-molecular-weight compound that effectively blocks early T-cell activation by selectively inhibiting protein kinase C (PKC). PKCs are important mediators of immune intracellular signaling, including activation of T and B cells.[17] The PKC member PKCθ is largely restricted to T lymphocytes and mediates activation of the transcription factors activator protein-1 and nuclear factor κB, leading to downstream IL-2 production.

AEB exerts its immunosuppressive effect by inhibiting the classic and novel PKC isoforms, and, thereby, blocking early T-cell activation. In vitro studies showed that AEB inhibited classic and novel PKC isoforms and blocked T-cell activation and IL-2 production with minimal effect on nuclear factor of activated T-cells (NF-AT) and cytokine and growth factor–induced cell proliferation.[18,19] Thus, AEB has a mechanism that can block T-cell activation that is independent from that of calcineurin inhibitors; however, the true nephrotoxic effect of AEB is yet to be determined.

In healthy volunteers, AEB reduced intracellular IL-2 production and had similar antiproliferative activity to MMF.[20] In a 2-week, multiple-dose, pharmacokinetic study of 24 healthy volunteers, AEB showed linear pharmocokinetics across the range of 25 to 200 mg.[21] Trough concentrations correlated with area under the curve (AUC) as well as a dose-response correlation with soluble IL-2–receptor concentrations, indicating modulation of the T-cell pathway.

Initial preclinical studies reported that AEB prolonged renal allograft survival in nonhuman primates as monotherapy or at nontherapeutic doses in combination with cyclosporine.[22] Furthermore, AEB in combination with everolimus, mycophenolic acid sodium salt, or FTY720 at subtherapeutic doses resulted in prolonged graft survival, implicating a possible role for AEB as a replacement for calcineurin inhibitors.[23,24] Two phase II clinical trials are currently enrolling patients.

THE NEW BIOLOGICS

Traditional biologics have been introduced in transplantation as short-term induction therapy

Table 2. Biologic Agents in the Transplant Pipeline

Antibody	Pharmaceutical/ Biotechnology	Status
Belatacept	Bristol-Myers (Princeton, NJ)	Phase III trial
Efalizumab	Xoma (Berkeley, CA)-Genentech (South San Francisco, CA)	Phase II
Mutant IL-15/Fc	Roche (Basel, Switzerland)	Preclinical
Anti-CD40	Bristol-Myers	Preclinical
	Novartis (East Hanover, NJ)	Preclinical
	Astellas (Deerfield, IL)	Preclinical

to reorient the host immune system at the time of antigen presentation (ie, transplantation).[25] These agents have included a variety of polyclonal agents (most recently Thymoglobulin [Genzyme, Cambridge, MA]) and the monoclonal antibodies, OKT3, the new anti–IL-2–receptor antibodies, and alemtuzumab (used off-label in transplantation).[26]

The new generation of biologic agents are being developed for chronic therapy with the purpose of displacing maintenance therapy with oral drugs such as the calcineurin inhibitors and corticosteroids.[27] Table 2 lists the new biologic agents, their targets, and their development status. Currently, only one agent, belatacept (LEA29Y), is in phase III trials. However, it is likely that several additional biologic agents will advance to the clinic within the next 5 years.[28] Although the costimulatory pathway is emerging as an important therapeutic area for immunosuppression therapy, other promising targets include IL-15 and adhesion molecules.[29,30]

Therapies Targeting IL-15

IL-15 is a cytokine with similar biologic activity to that of IL-2.[29,31,32] Although IL-2 results in activation-induced cell death, IL-15 promotes antiapoptosis signals. IL-15 is produced by monocyte-macrophage lineage and by epithelial and renal tubule cells, but not by T cells. Its role in rejection is suggested by the finding of increased levels of IL-15 expression in rejecting allografts.[33] Although IL-15 shares the β and common γ class of the IL-2 receptor, it has a distinct α receptor. Several inhibitors of the IL-15 pathway are likely to be developed for transplantation including direct blockers of IL-15 or the IL-15 α receptor. A potentially attractive use of anti–IL-15 therapy is in conjunction with anti–IL-2 in a calcineurin-free regimen with antiproliferative agents as maintenance therapy.

Anti-CD40

The CD154-CD40 pathway, originally described in the activation of B cells, also has an important role in T-cell activation. The first clinical effort to block costimulation in renal transplantation was attempted with a monoclonal antibody to CD154.[34] After the impressive results of Hu5C8 (a humanized anti-CD154) in nonhuman primates, a phase I study was undertaken with chronic intermittent administration of Hu5C8 in combination with a short course of steroids (2 weeks) and MMF in a calcineurin inhibitor–free regimen.[35] However, the trial was halted after the occurrence of several thromboembolic events.[36] This complication is not epitope-specific because other antibodies to CD154 were associated with similar thrombotic complications. Thus, direct targeting of CD154 will not likely be pursued. However, antibodies against CD40 may prove to be a safer alternative to block the CD40-CD154 pathway.

COSTIMULATION BLOCKADE

The underlying concept behind costimulation blockade is the notion that to fully stimulate and activate a T cell, at least 2 signals from an antigen-presenting cell are required: (1) stimulation of the T-cell receptor by a major histocompatibility complex molecule–antigenic peptide complex and (2) stimulation of costimulatory molecules, the receptor CD28, by ligands CD80 and CD86 on antigen-presenting cells.[37] In fact, if a T cell receives a signal through the T-cell receptor without signal 2, functional inactivation or deletion of that T cell
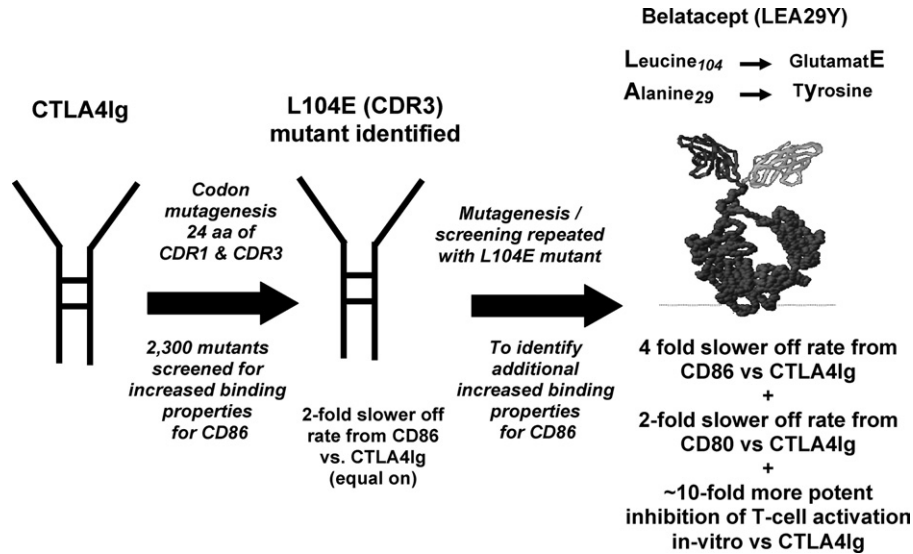
Figure 2. The development of belatacept.

results. Several ligands and receptors within the costimulation pathway currently are being targeted with monoclonal antibodies and/or receptor fusion proteins. The only biologic currently in clinical development in transplantation is belatacept, a second-generation CTLA4Ig.[38]

CTLA4Ig is a fusion protein that consists of the extracellular domain of CTLA4 fused with the Fc portion of human immunoglobulin. Belatacept (previously referred to as *LEA29Y*) is a second-generation CTLA4Ig (extracellular domain of CTLA4 and Ig G1 Fc domain) with an increase in binding avidity to CD80 (2-fold) and CD86 (4-fold), and approximately 10-fold more effectiveness in vitro than CTLA4Ig on a per-dose basis in inhibiting T-cell effector functions (Fig. 2).[38] In a phase II study, 218 primary renal transplant patients were randomized to 3 treatment groups. Groups 1 and 2 were treated with two different regimens of belatacept, either a more intense or less intense, basiliximab (20 mg day 0 and day 4), MMF 2 g, and conventional steroid therapy. Patients randomized to group 3 served as controls and were treated with a standard regimen consisting of basiliximab (20 mg at day 0 and day 4), cyclosporine, MMF, and steroids.[39] The acute rejection rate was comparable between those patients treated with belatacept and cyclosporine. However, at 12 months, belatacept-treated patients had a significantly higher measured glomerular filtra-

tion rate and lower chronic allograft nephropathy on kidney biopsy than cyclosporine-treated patients. Furthermore, belatacept-treated patients had more favorable metabolic and cardiovascular profiles.

Currently belatacept is in phase III trials in transplant recipients receiving kidneys from expanded-criteria donors or standard donors (deceased or living). These 2 trials should provide more definitive information concerning the safety and efficacy of belatacept. In the interim, more than 70 patients in the phase II trials continue to receive administration of belatacept at 4- or 8-week intervals (follow-up period, 36-60 mo). A more innovative study that is supported by the Immune Tolerance Network will evaluate the effectiveness of a regimen consisting of belatacept and sirolimus in recipients of kidneys from living donors. In this trial, drug withdrawal will be attempted and patients who are deemed to have become tolerant will be withdrawn from both sirolimus and belatacept.

Other biologics that target the costimulation pathways also are being investigated. Efazilumab, a humanized anti-lymphocyte function-associated antigen-1 (LFA1), has been used in a phase I/II trial in renal transplantation and is being investigated in several investigator-initiated trials in kidney and islet transplantation. Preclinical trials are ongoing with nonagonist

anti-CD28 and anti-inducible T-cell costimulator (ICOS).

CONCLUSIONS

In conclusion, chronic protein therapies similar to the belatacept regimen used in current clinical trials may represent an emerging and novel paradigm of delivering immunosuppression without the toxicities of current drugs.

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