Published in final edited form as:

Transplant Rev (Orlando). 2013 July ; 27(3): 85–89. doi:10.1016/j.trre.2013.04.001.

Tofacitinab in Renal Transplantation

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Abstract

Tofacitinib (tositinib, CP-690,550) is a small molecule inhibitor of Janus associated kinases, primarily JAK3 and JAK2, which inhibits cytokine signaling through the IL-2R γ chain. In this article, we review the mechanism of action of tofacitinib, and pre-clinical and clinical data regarding its use in solid organ transplantation thus far. It is hoped that tofacitinib may form the basis for calcineurin-free immunosuppression, improving renal function while eliminating calcineurin inhibitor renal toxicity. Current studies suggest that tofacitinib is an effective immunosuppressive agent for renal transplantation, but its use in current protocols carries an increased risk of CMV, BK, and EBV viral infection, anemia and leukopenia, and post-transplant lymphoproliferative disorder.

Introduction

Activation of alloreactive T cells and subsequent proliferation in solid organ transplantation requires 3 separate signals: T cell receptor ligation, signaling through costimulatory receptor pathways, and cytokine signaling. (1) Current immunosuppressive regimens in solid organ transplantation are directed at blocking or inhibiting at least one of these pathways, and most successful regimens interfere with TCR signaling after ligation through inhibition of calcineurin mediated signaling.(1–3)

Cytokine signaling during the T cell allo-response generally occurs via the IL-2R γ chain, which participates in signaling for IL-2, IL-4, IL-7, IL-9, IL-10, IL-15, and IL-21.(4, 5) These cytokines strongly influence activated T cell growth, differentiation, and apoptosis. Signaling through the IL-2R γ chain is mediated by a small number of structurally similar kinases, known as the Janus associated kinase (JAK) family.(6) JAKs bind to, and form a complex with, the membrane proximate portion of the IL-2R γ chain. Engagement of the IL-2R γ chain by Type I cytokines triggers a signaling cascade that begins with JAK phosphorylation of the cytokine receptor, facilitating recruitment of a variety of signaling proteins, including those of the STAT family of transcription factors. The STAT proteins then bind to the receptor, are phosphorylated, and translocate to the nucleus where they facilitate transcription of a numerous of T cell activation genes.

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JAK3 is an essential mediator of signaling through the IL-2R γ chain in lymphocytes and NK cells.(7, 8) Jak3 knockout mice and humans with mutations in the Jak3 gene have common variable immune deficiency (CVID).(9–13) CVID is characterized by highly impaired lymphocyte development, reduced numbers of lymphocytes, and markedly reduced peripheral T, B and NK cells with an increased sensitivity to apoptosis.(9–13) Expression of and signaling by JAK3 occurs primarily in lymphocytes and other monocytes that express the IL-2R2R γ chain. Thus, there has been considerable interest in developing inhibitors of JAK3 as potential immunosuppressive agents in solid organ transplantation.(14) In this review, we describe the development of the JAK3 inhibitor tofacitinib in solid organ transplantation, including preclinical and clinical trials.

Tofacitinib

Tofacitinib (tositinib, CP-690,550) is a small molecule (MW=504.49) JAK kinase inhibitor that is potent and selective (Table 1). The Janus kinase family has four members, JAK-1, JAK-2, JAK-3 and TYK2. Tofacitinib has a high affinity for JAK-3 (IC₅₀ = 1 nM) and JAK-2 (IC₅₀ = 20 nM), a lower affinity for JAK-1 (IC₅₀ = 100 nM), and minimal if any activity against TYK2(15). It is hepatically metabolized by the CYP-450 3A4 system. Tofacitinib blocks cytokine signaling by the IL-2R γ chain cytokine receptor and increases susceptibility of T cells, B cells and NK cells to apoptosis. Potential adverse effects from tofacitinib can be predicted from naturally occurring and induced JAK gene mutations, as well as its affinity for the members of the Janus kinase family. JAK1 mutations result in defective signaling for a wide range of cytokines, including those which signal through the IL-2R γ , as well as IL-6, IL-11 and the Class II cytokine receptor family including interferons and as well as IL-10. Phenotypes include severe combined immunodeficiency (SCID) with an increased frequency of common and opportunistic infections in mice and humans seen with both JAK3 and JAK1 mutations, and severely impaired lymphoid development as seen in JAK1 mutations. JAK2 is a signaling mediator for the Type I erythropoietin homodimeric cytokine receptor, and thus some degree of anemia would be expected with tofacitinib use.

Tofacitinib in autoimmune disease

Tofacitinib has been used in clinical trials for a number of autoimmune diseases including rheumatoid arthritis(16–21), ulcerative colitis(22), and psoriasis (23, 24). In these studies, patients have shown marked improvement in arthritis and psoriasis functional scores. The major side effects in these trials included increased risk of opportunistic infections, tuberculosis, malignancies, and lymphoma. It is recommended that patients be tested for latent tuberculosis prior to initiating therapy with tofacitinib, and be monitored during prolonged treatment. In addition, tofacitinib treated patients had a higher incidence of hypercholesterolemia, elevated liver function tests, and leukopenia. It was approved in November 2012 by the United States Food and Drug Administration for treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate.

Pre-clinical studies of tofacitinib in solid organ transplantation

The first animal studies of tofacitinib in solid organ transplantation were reported with the discovery of tofacitinib, which included results from an MHC mismatched murine heterotopic cardiac allograft model. Median survival times of tofacitinib treated allografts were greatly improved in a congenic murine heterotopic heart transplants (>60 days versus 8 days in control animals), with an effective concentration where 50% of animals maintained their graft (EC50) of 60 ng/ml. Compared to vehicle treated mice, tofacitinib treated animals had equivalent cellular infiltrates, but greatly inhibited transcript expression of granzyme B,

FasL, RANTES, Mig, and IP-10, many of which are induced by IFN- γ and IL-2R γ -chain signaling.

These studies were extended in the same report using a kidney transplant model in *Macaca fascicularis* monkeys. Animals were dosed with tofacitinib oral gavage twice daily, beginning at the time of transplantation. Dose adjustments were made three times per week based on serum levels. While animals in the control group had a mean allograft survival time (MST) of 6 ± 1 days, animals in the low- and high dose groups had prolonged MSTs of 62 ± 6 and 83 ± 6 days respectively. Transplanted animals also developed modest leukopenia and dose related anemia.

These results were confirmed by the same group in a separate manuscript describing renal transplantation in tofacitinib treated cynomolgus monkeys, with prolonged mean survival times in the tofacitinib group versus the vehicle control treated animals (MST 53 ± 7 days versus 7 ± 1 days respectively). (25) However, all treated animals had low grade rejection when sacrificed at 90 days post-transplant. (25) An additional study of renal transplantation in cynomolgus monkeys receiving a combination of tofacitinib and mycophenolate mofetil (MMF) showed similar results. (26) While mean renal allograft survival times were prolonged (75.2 ± 8.7 days high dose tofacitinib + MMF, 33.3 ± 12.6 days lower dose tofacitinib + MMF versus 23 ± 1 day for MMF alone), all animals had cellular infiltrates consistent with rejection at necropsy 90 days post transplant.

In vivo measurements corroborated previous *in vitro* findings that tofacitinib inhibits IL-2 mediated production of IFN- γ in vivo. *In vivo* dosing of tofacitinib in non-human primates produced reductions of IL-2-enhanced IFN- γ , T-cell surface expression of CD25 and CD71. (27) In addition, transplanted non-human primates also displayed significant reduction of NK cell (90% from baseline) and T-cell numbers whereas CD8 effector memory T-cell populations were unaffected. (25) Tofacitinib was also found to inhibit arterial intimal hyperplasia in a rat aortic allograft model, suggesting a possible inhibitory effect on chronic allograft vasculopathy. (28)

Several animal studies have further defined potential dose dependent side effects of tofacitinib. (29) Cynomolgus monkeys dosed daily with tofacitinib demonstrated reduced numbers of CD8+ T cells and NK cells, while CD4+ T and B cell numbers remained unchanged. (29) The effects were felt to be due to inhibition of IL-15 signaling through the common IL-2R γ -chain, as IL-15 induced CD69 expression was reduced in both NK and CD4+ T cells. (29) When tofacitinib was administered with MMF, dose-dependent anemia and gastrointestinal side effects were observed. (26) The anemia was felt to be due to tofacitinib inhibition of JAK2 signaling in the erythropoietin receptor signaling cascade (30–32), a hypothesis supported by the observation that tofacitinib inhibits proliferation of human polycythemia vera cell lines at clinically relevant concentrations. (33) Thus, animal models predicted anemia and leukopenia as potential side effects of tofacitinib.

Clinical trials of tofacitinib in solid organ transplantation

Clinical trials of tofacitinib began after animal studies showed the prolongation of graft survival. The central concept was that tofacitinib might allow for calcineurin inhibitor-free immunosuppression, and thus spare renal function from calcineurin inhibitor toxicity. (34) Thus, such trials involved protocols using tofacitinib combined with mycophenolate mofetil or mycophenolic acid, as well as corticosteroids (35–39) and, in one study, anti-lymphocyte antibody induction (35).

An initial phase I dose-escalation study was performed in 28 stable transplant recipients in conjunction with mycophenolate mofetil. (38) Subjects received varying doses of tofacitinib

(placebo, 5, 15 or 30 mg twice per day) in conjunction with MMF. Dose dependent decreases in hemoglobin and NK cells were observed, without any change in CD4+ or CD8+ T cells, and an increase in CD19+ B cells.(38) This finding is interesting as others have reported specific decreases in STAT5 phosphorylation in CD4+ and CD8+ T cells isolated from peripheral blood of renal transplant patients receiving tofacitinib.(40) Viral and bacterial infections were the most common adverse events, but were reported as mild or moderate in severity, and of limited duration. However, viral illnesses in the 30 mg group of tofacitinib were more severe, including CMV infection.(38) No clinical rejections were identified in any of the groups. Overall, serum creatinine remained unchanged, supporting a minimal effect for tofacitinib on renal function. This was similar to other studies which found that tofacitinib had no effect on glomerular filtration rate and effective renal plasma flow in healthy adult volunteers.(41)

The following year brought the report of a prospective, randomized, 12 month pilot study of tacrolimus (n=21) versus tofacitinib, 15 mg (LD; n=20) or 30 (HD; n=20) mg twice per day. (39) All groups received an IL-2R blocking agent for induction, concomitant mycophenolate mofetil, and corticosteroid immunosuppressive therapy. After the initial six months of treatment, tofacitinib doses were reduced to 15 mg twice per day in the HD group, and 10 mg twice per day in the LD group. Treatment groups did not have equivalent demographics. The HD group had a higher proportion of men (80% HD vs 40% LD), deceased donors (35% HD vs. 15% LD), and a longer cold ischemic time (17.5 hours HD versus 9.1 hours LD). The biopsy proven acute rejection rates were low in the tacrolimus group (4%) and in the LD tofacitinib group (5%), but elevated (20%) in the HD group. Rejections in the HD group occurred 1.3–2.1 months after transplantation, and were Banff 97 grade IA, IIA, IIA, and IIB. There was an increased incidence of BK nephropathy in the HD tofacitinib group (20%), resulting in early discontinuation of MMF in this arm of the study. There was also an increased incidence of cytomegalovirus disease in the HD group (21.1%) compared to the LD (16.3%) and the tacrolimus (0%) groups. Overall, clinically significant infections of any type were statistically significant and more frequent at 12 months in the LD (45.7%) and HD (59.3%) groups compared to the tacrolimus group (35.2%). NK cell levels were substantially reduced in both tofacitinib groups and, as in previous studies, there was a trend toward anemia and neutropenia(39). There was also an increased trend towards hypercholesterolemia, hyperlipidemia, and hyperglycemia in the tofacitinib group. Estimated glomerular filtration rates were greater than 70 ml/min among all three groups at 6 and 12 months. The authors concluded that the HD group in this regimen was over-immunosuppressed, and that lipid elevations and an increased incidence of viral infectious complications occurred in the tofacitinib groups.

Based on this pilot study, a larger prospective, randomized, multi-center trial of tofacitinib in *de novo* kidney transplant recipients was conducted.(35) A total of 331 renal transplant recipients enrolled at multiple centers across the world were randomized to one of three treatment arms. The more intensive (MI) arm included tofacitinib at 15 mg twice per day for months 1–6, with a dose reduction from months 7–12. The less intensive (LI) arm received tofacitinib 15 mg twice per day from months 1–3, with a dose reduction in months 4–12. The control arm was treated with cyclosporine to target levels of 125–400 ng/ml during the first three months, and 100–300 ng/ml in months 4–12. All groups received received basiliximab induction (20 mg intravenously given on days 0 and 4), 2 g/day mycophenolate mofetil (MMF) or 1.44 g/day enteric-coated MPA, and corticosteroids. The demographics among all groups were comparable in this study, with approximately 60% deceased donor kidney transplants and 80% male participants in all three groups.

The primary endpoints of this Phase IIb study were the incidence of biopsy proven rejection at 6 months, and measured glomerular filtration rates at 12 months.(35) Patient and graft

survival was similar among all treatment groups.(35) The incidence of clinical biopsy proven rejection was similar among the MI, LI and CSA groups (11%, 7%, and 9% respectively), and lower serum exposure to tofacitinib was associated with rejection episodes. In addition, measured glomerular filtration rates were higher for the MI and LI groups (65 ml/min for both) compared to the cyclosporine group (54 ml/min; $p<0.01$). Most strikingly, the tofacitinib groups had a much lower incidence of chronic allograft nephropathy by renal biopsy (25% MI, 24% LI vs. 48% CSA). However, complications and side effects were also, more common the tofacitinib groups. There was a higher rate of BK virus infection (14% MI, 18% LI, 6% CSA), CMV disease (44.5%, 37%, vs 25%), and anemia (46%, 40%, vs. 26%). Post-transplant lymphoproliferative disease was also more common in the tofacitinib groups. Impaired fasting glucose or new onset diabetes mellitus were less frequent in the tofacitinib groups compared to the cyclosporine controls.

Overall, this Phase IIb study demonstrated that tofacitinib provided similar protection to cyclosporine for the incidence of acute rejection, with improved renal function and chronic allograft glomerular changes at 12 months.(35) Compared to the cyclosporine control group, both tofacitinib treatment groups were associated with an increased incidence of CMV and EBV infection, a higher incidence of anemia, and an reduced incidence of post-transplant diabetes mellitus. Of most concern was the increased incidence of post-transplant lymphoproliferative disease in the tofacitinib groups.(35) The study concluded that while the regimens provide similar outcomes with respect to rejection, and improved allograft function with reduced levels of chronic allograft nephropathy, over-immunosuppression and increased infectious complications were still an issue. One possible factor appeared to be the lack of a pharmacokinetic interaction between MPA and tofacitinib, resulting in higher MPA exposure in the tofacitinib groups than in the cyclosporine group.

Future protocols and considerations

Chronic renal toxicity of calcinurin inhibitors toxicity has plagued renal and non-renal solid organ transplantation since the introduction of cyclosporine and tacrolimus, even as these agents has greatly reduced the incidence of acute cellular allograft rejection.(42) Tofacitinib holds promise as a transplant immunosuppressant agent that may facilitate calcineurin inhibitor-free immunosuppression, without the deleterious renal side effects of CNIs.(35) The results of current clinical trials are encouraging, although a tofacitinib-based immunosuppression protocol with a lower risk of infectious side effects, specifically viral infections, still needs to be developed.

Despite the initial high rejection rates in prior animal studies, the Phase IIb clinical trial of tofacitinib showed rejection rates at 6 and 12 months comparable to the cyclosporine-based immunosuppression control group.(35) Renal function in the tofacitinib treated groups in currently published studies is better than calcineurin inhibitor-based controlled regimens. The incidence of post-transplant diabetes is similarly improved in tofacitinib treatment groups compared to CNI based immunosuppression.

Anemia and leukopenia are an issue in the long-term clinical use of tofacitinib. Post-renal transplant anemia is itself common, with a multitude of causes. Further suppression of JAK2 signaling from the EPO receptor by tofacitinib may aggravate this problem. It is not yet clear, however, if this will be a clinically significant issue or whether use of synthetic erythropoietin at high levels would be able to overcome tofacitinib induced anemia. Similarly, tofacitinib induced lymphopaenia may be a significant clinical issue, increasing the risk of infectious complications. This may also be a limiting factor in the use of tofacitinib in liver transplant recipients, where leukopenia is common but a calcineurin inhibitor-free immunosuppressive regimen would be desirable to spare renal function.

Suppression of NK cells may also have long-term implications for other non-hematologic malignancy rates in tofacitinib treated patients.(43)

The biggest hurdle for tofacitinib-based immunosuppression protocols at present appears to be the increased incidence of post-transplant lymphoproliferative disorder (PTLD), CMV and BK virus infections. With respect to PTLD, cytokine signaling through the IL-2R γ chain is a key component of the CD4 and CD8 T cell response against EBV, the initiating agent of PTLD.(44, 45) Transformation of EBV infected lymphocytes, generally B cells, results first in a polyclonal EBV+ lymphoproliferative disease that can then transform into a monoclonal lymphoma.(46, 47) Risk factors for PTLD include primary EBV infection in immunosuppressed transplant recipients who are EBV seronegative at the time of transplant.(46, 48) The increased incidence of PTLD in tofacitinib treated animals and patients is interesting in that activation of JAK3 plays a role in EBV transformation of lymphocytes, and one might think that blocking JAK3 activation with tofacitinib could reduce the risk of PTLD.(49) The EBV latent membrane protein LMP1 induces STAT3 phosphorylation through the JAK3 and ERK pathways, and constitutive activation of the JAK/STAT pathway is thought to play a role in EBV pathogenesis.(50, 51) The pre-clinical and clinical trial data, however, suggests that JAK3 suppression does not prevent EBV induced PTLD, and that the effects of tofacitinib immunosuppression on EBV immune responses via EBV-specific CD4 and CD8 T cells are likely to be more important in PTLD development. It remains to be seen if future protocols can reduce this risk, and maintain the low incidence of acute and chronic renal allograft rejection.

In the interim, it seems prudent to frequently monitor patients receiving tofacitinib immunosuppression in solid organ transplantation for EBV using molecular diagnostics, along with BK virus and CMV. Monitoring for tuberculosis is mandatory for patients receiving tofacitinib for rheumatoid arthritis, and PPD screening with ongoing monitoring should be adopted for tofacitinib based protocols in solid organ transplantation. Other considerations may include reduced dose mycophenolate mofetil or mycophenolic acid dosing, and avoiding the use of polyclonal anti-lymphocyte induction agents with tofacitinib. Similar concerns exist with respect to CMV and BK virus infection rates and tofacitinib based immunosuppression under current protocols. Lower dose tofacitinib regimens, and prophylaxis with valgancyclovir, resulted in a lower incidence of CMV in the Phase IIb study.(35) In addition, rates of BK nephropathy appeared statistically similar in the Phase IIb study over 12 months, although it remains to be seen what the long term incidence will be. Similar monitoring and precautions regarding over-immunosuppression may reduce the risk of CMV and BKV infections as well.

Finally, it does not appear that there are clinically approved tests to monitor tofacitinib levels. Development and implementation of such testing in solid organ transplantation would be desirable for several reasons. Tofacitinib is metabolized by the CYP-P450 3A4 system, and interactions with common inhibitors and inducers of CY P450 3A4 have the potential to alter immunosuppressive efficacy and the risk of infectious side effects. Regular monitoring of tofacitinib levels would also be desirable as protocols develop in solid organ transplantation to better judge the extent of immunosuppression, and the potential association of levels with other side effects. Given the natural genetic variation in CY P450 3A4 activity across individuals, tailoring long-term dosing of such a potent immunosuppressant with pharmacokinetic monitoring would be prudent.

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Table 1

			Inhibitors			
	Receptor	Associated Kinase(s)	JAK1	JAK2	JAK3	Tyk2
Type I Receptors	IL-12R, IL-23R	JAK2 Tyk2	–	+	–	+
	IL-2R, IL-4R, IL7R, IL-9R, IL15R, IL-21R	JAK1 JAK3	+	–	+	–
	IL-6R, IL-11R, OSMR, LIFR	JAK1 JAK2 Tyk2	+	+	–	+
	IL-3R, IL5R, GM-CSFR,	JAK2	–	+	–	–
	EPOR, TOPR, G-CSFR, GHR, PRLR	JAK2	–	+	–	–
Type II Receptors	IFN α , IFN β , IFN γ , IL-10R, IL-19R, IL-20R, IL-22R, IL-24 R, IL-29R	JAK1 JAK2 Tyk2	+	+	–	+
	Immune Cell Types Affected by JAK Inhibitor		Th1 Th2 CD8 NK Bc Pc MAC Dc	Th1 CD8 NK Bc Pc MAC Dc Eryth Gran	Th1 Th2 CD8 NK Bc	Pre-Bc Bc Pc MAC Dc