Efficacy and safety of a tofacitinib-based immunosuppressive regimen after kidney transplantation: results from a long-term extension trial

Stephan Busque
Flavio G. Vincenti
Helio Tedesco Silva
Philip J. O'Connell
Atsushi Yoshida

Henry Ford Health System, AYOSHID1@hfhs.org

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/surgery_articles

Recommended Citation
Busque S, Vincenti FG, Tedesco Silva H, O'Connell PJ, Yoshida A, Friedewald JJ, Steinberg SM, Budde K, Broeders EN, Kim YS, Hahn CM, Li H, and Chan G. Efficacy and safety of a tofacitinib-based immunosuppressive regimen after kidney transplantation: Results from a long-term extension trial. Transplant Direct 2018;4(9):e380.
Authors
Stephan Busque, Flavio G. Vincenti, Helio Tedesco Silva, Philip J. O'Connell, Atsushi Yoshida, John J. Friedewald, Steven M. Steinberg, Klemens Budde, Ermine N. Broeders, Yon-Su Kim, Carolyn M. Hahn, Huihua Li, and Gary Chan

This article is available at Henry Ford Health System Scholarly Commons: https://scholarlycommons.henryford.com/surgery_articles/78
Efficacy and Safety of a Tofacitinib-based Immunosuppressive Regimen After Kidney Transplantation: Results From a Long-term Extension Trial

Stephan Busque, MD, MSc, FRCSC,¹ Flavio G. Vincenti, MD,² Helio Tedesco Silva, MD,³ Philip J. O’Connell, MD,⁴ Atsushi Yoshida, MD,⁵ John J. Friedewald, MD,⁶ Steven M. Steinberg, MD,⁷ Klemens Budde, MD,⁸ Emine N. Broeders, MD,⁹ Yon Su Kim, MD,¹⁰ Carolyn M. Hahn, BA,¹¹ Huihua Li, MS,¹¹ and Gary Chan, PharmD¹²

Background. Tofacitinib is an oral Janus kinase inhibitor. This open-label, long-term extension (LTE) study (NCT00658359) evaluated long-term tofacitinib treatment in stable kidney transplant recipients (n = 178) posttransplant. Methods. Patients who completed 12 months of cyclosporine (CsA) or tofacitinib treatment in the phase IIb parent study (NCT00483756) were enrolled into this LTE study, evaluating long-term tofacitinib treatment over months 12 to 72 posttransplant. Patients were analyzed by tofacitinib less-intensive (LI) or more-intensive (MI) regimens received in the parent study. For both groups, tofacitinib dose was reduced from 10 to 5 mg twice daily by 6 months into the LTE. Patients were followed up through month 72 posttransplant, with a focus on month 36 results. Results. Tofacitinib demonstrated similar 36-month patient and graft survival rates to CsA. Biopsy-proven acute rejection rates at month 36 were 11.2% for CsA, versus 10.0% and 7.4% (both P < 0.05) for tofacitinib LI and MI, respectively. Least squares mean estimated glomerular filtration rates were 9 to 15 mL/min per 1.73 m² higher for tofacitinib versus CsA at month 36. The proportions of patients with grade 2/3 interstitial fibrosis and tubular atrophy in month 36 protocol biopsies were 20.0% for LI and 18.2% for MI (both P > 0.05) versus 33.3% for CsA. Kaplan-Meier cumulative serious infection rates at month 36 were numerically higher for tofacitinib LI (43.9%; P = 0.45) and significantly higher for MI (55.9%; P < 0.05) versus CsA (37.1%). Conclusions. Long-term tofacitinib continued to be effective in preventing renal allograft acute rejection and preserving renal function. However, long-term tofacitinib and mycophenolic acid product combination was associated with persistent serious infection risk.

(Transplantation Direct 2018;4: e380; doi: 10.1097/TXD.0000000000000819. Published online 8 August, 2018.)
Chronic allograft nephropathy, histologically described as kidney allograft interstitial fibrosis and tubular atrophy (IFTA), is understood to be driven by multiple factors, including immune injury, ischemia reperfusion, donor disease, and immunosuppressive drug toxicity. The extent to which calcineurin inhibitors (CNI) contribute to allograft IFTA over the long term has been disputed. Nevertheless, concern over potential nephrotoxic and deleterious metabolic effects of CNI has prompted interest in CNI minimization and avoidance of immunosuppressive regimens. Although some CNI-sparing regimens have achieved improvement in renal function, there was suboptimal prevention of acute allograft rejection. Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Phase II studies in kidney transplant recipients showed that a CNI-free regimen using tofacitinib was effective in preventing acute allograft rejection, improving renal function, and reducing chronic allograft histologic injury, and was associated with a lower risk of developing diabetes in the 6- to 12-month period posttransplant. However, these studies demonstrated an increased risk of serious infections and posttransplant lymphoproliferative disease (PTLD), although it has subsequently been demonstrated that these risks were associated with higher tofacitinib exposure. Whether the clinical benefits and risks persist during long-term treatment with tofacitinib in kidney transplant patients is unknown.

De novo kidney transplant recipients who completed 12 months of treatment in a phase IIb study comparing tofacitinib with cyclosporine (CsA) (NCT00483756) were eligible to participate in a long-term extension (LTE) study and were followed up for an additional 5 years. Here, we report data from this LTE study describing the long-term efficacy and safety of tofacitinib in stable kidney transplant recipients.

MATERIALS AND METHODS

Patients

Patients were 18 to 70 years of age and were recipients of primary renal allografts from deceased donors or human leukocyte antigen-mismatched living donors. Patients must have completed 12 months of treatment with tofacitinib or CsA in A3921030 (NCT00483756). All patients provided written, informed consent. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. The final protocol, amendments, and informed consent documentation were reviewed and approved by the institutional review boards and independent ethics committees of the investigational centers. All patients provided written, informed consent.

Efficacy and Safety: Objectives and Endpoints

The objective of this LTE study was to evaluate the long-term efficacy and safety of tofacitinib in stable kidney transplant recipients. Efficacy outcomes included: patient and allograft survival rates, incidence of first biopsy-proven acute rejection (BPAR) and IFTA (as determined by a blinded central pathologist), incidence of treated clinical acute rejection (episodes were diagnosed by the study site, and patients received antirejection treatment), and glomerular filtration rate (GFR). Allograft biopsy and GFR measured using iohexol were required at month 36. Safety endpoints included: adverse events (AEs), serious AEs (SAEs), serious infections, malignancies, PTLD, polyomavirus-associated nephropathy (PVAN), new-onset diabetes mellitus (NODM), and herpes zoster virus (HZV) infections. Laboratory evaluations included: hemoglobin (Hgb) levels, white blood cell (WBC) count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and the proportions of patients with Epstein-Barr virus (EBV) and BK virus (BKV).

Statistical Analysis

Efficacy and safety analyses were based on the full analysis set, which included all patients who received 1 dose or more of study treatment in the LTE study. Kaplan-Meier (KM) curves were fitted for time-to-event data for: patient and allograft survival, serious infections, HZV infection, BPAR, treated clinical acute rejection, PVAN, and NODM. Kaplan-Meier rate differences were compared between tofacitinib doses and active comparators, based on the Wald test, at each time point. Although KM analysis was applied to all data available through month 72, interpretation of the data is limited after month 36, owing to the decreasing number of patients in the tofacitinib group (partly as a result from the parent study— tofacitinib less intensive (LI) and more intensive (MI)—for analysis. Mycophenolic acid (MPA) products were continued through month 72 posttransplant. Corticosteroids could be discontinued after month 12 at the investigator’s discretion.

Reported clinical outcomes in tofacitinib-treated patients primarily reflected experience in patients maintained on tofacitinib 5 mg BID after months 12 to 18 posttransplant, with background MPA products and corticosteroids. A protocol amendment was implemented to discontinue patients with above-median exposure (AME) of tofacitinib, due to potential association with PTLD. Patients with AME exposure within the first 6 months posttransplant were discontinued. After discontinuation, patients were followed up for 12 months, including a follow-up evaluation 2 months (+14 days) after the last tofacitinib dose. Additional follow-up visits (or a minimum of a telephone call) were arranged every 3 months for 12 months after the last dose of tofacitinib, to determine new-onset serious infections, malignancy, graft loss, or death.

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. The final protocol, amendments, and informed consent documentation were reviewed and approved by the institutional review boards and independent ethics committees of the investigational centers. All patients provided written, informed consent.
of discontinuations required by the protocol amendment); in-
text discussion of results therefore focuses on month 36 data.

Estimated GFR (eGFR) was calculated using the modification
diet in renal disease (MDRD) formula, with last observation
carried forward (LOCF) and an imputation of death and graft
loss as zero eGFR. For continuous data collected over time, a lin-
ear mixed-effects model with repeated measures was used. The
model included treatment, visit, and treatment-by-visit interac-
tion as fixed effects, and baseline (as appropriate) as covariates.

Binary variables were analyzed using large sample approx-
imation or exact methods for endpoints with sparse cells.

**Exploratory Exposure Analysis**

As a post hoc exploratory analysis, patients receiving
tofacitinib LI or MI regimens were recategorized, according
to their pharmacokinetic exposure, into below-median ex-
posure (BME) or AME, within 6 months posttransplant. This
enabled investigation of the relationship between tofacitinib
concentrations and both efficacy and safety endpoints. In
each evaluable tofacitinib-treated patient, available 2-hour
postdose concentrations (C2) over the first 6 months post-
transplant were normalized by dose and a median C2 was
calculated. Following this, the median C2 (for each individ-
ual patient) was adjusted for the dose and weighted for the
duration of treatment with the particular dose.\textsuperscript{19} For ex-
posure analysis, the total number of patients available for eval-
uation over time for groups CsA, BME, and AME, respectively,
were as follows: baseline, \(n = 64, 62,\) and 50; month 12,
\(n = 64, 62,\) and 50; month 36, \(n = 52, 45,\) and 0; and month
72, \(n = 31, 27,\) and 0.
RESULTS

Patient Demographics and Baseline Characteristics

A total of 178 patients were enrolled and treated, of whom 119 patients discontinued; patient disposition is shown in Figure 2. A summary of patient demographics and baseline characteristics at the time of transplantation is shown in Table 1. Baseline characteristics were generally similar among the treatment groups. The median treatment duration for patients was 66.1 months (range, 12.4-72.9) for the CsA group, 53.7 months (range, 12.1-74.9) for the tofacitinib LI group, and 28.4 months (range, 12.3-73.8) for the tofacitinib MI group.

Efficacy Outcomes

Patient and Allograft Survival

Among patients who entered this LTE study, KM estimates showed no significant differences in patient survival and death-censored allograft survival (to month 36) for either of the tofacitinib groups versus CsA (Table 2).

First BPAR

Before study entry at month 12, first BPAR was reported in 4, 6, and 3 patients in the CsA, tofacitinib LI, and tofacitinib MI groups, respectively. From month 12 posttransplant through month 72, first BPAR was reported in 4 patients in the CsA group and in 1 patient in the tofacitinib MI group; no patients in the tofacitinib LI group experienced BPAR. At month 36, KM estimates were 11.2% for CsA versus 10.0% (P = 0.83) and 7.4% (P = 0.48) for tofacitinib LI and MI, respectively (Table 2). Although BPAR events continued to accumulate in the CsA group after month 12, the difference versus tofacitinib did not reach statistical significance (Figure 3). For tofacitinib exposure-based analysis, through months 12 to 72 first BPAR was reported in 1 patient in the BME group and in no patients in the AME group. For patients with BME at month 36, KM estimates for first BPAR were 11.3% (P = 0.98) versus 11.2% for CsA.

Treated Clinical Acute Rejection

Treated clinical acute rejection was reported in 9, 4, and 5 patients in the CsA, tofacitinib LI, and tofacitinib MI groups, respectively, in the parent study. From month 12 through month 72, additional treated clinical acute rejection was reported in 9, 3, and 1 patients in the CsA, tofacitinib LI, and tofacitinib MI groups, respectively. At month 36, the KM rates of clinical acute rejection were 11.7% (P = 0.07) and 11.1% (P = 0.06) for tofacitinib LI and MI, respectively, versus 23.9% for CsA (Table 2).

Rates of IFTA

Only 61 of 178 enrolled patients completed the protocol-required allograft biopsy at month 36, and 44 patients showed findings consistent with IFTA. Most IFTA cases were classified as mild (grade 1). The proportions of patients with grade 2/3 IFTA in month 36 protocol biopsies were 20.0% for tofacitinib LI and 18.2% for tofacitinib MI versus 32.0% for CsA.

TABLE 1

Demographics and baseline characteristics at the time of transplantation

|                | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|----------------|-------------|------------------------|-------------------------|
| **Recipient information** |             |                        |                         |
| Sex, n (%)     |             |                        |                         |
| Male           | 44 (68.8)   | 41 (68.3)              | 40 (74.1)               |
| Age: mean (SD), y | 46.4 (12.7) | 45.7 (12.6)            | 48.5 (10.9)             |
| Race, n (%)    |             |                        |                         |
| White          | 46 (71.9)   | 45 (75.0)              | 34 (63.0)               |
| Black          | 8 (12.5)    | 7 (11.7)               | 7 (13.0)                |
| Asian          | 5 (7.8)     | 6 (10.0)               | 9 (16.7)                |
| Other          | 5 (7.8)     | 2 (3.3)                | 4 (7.4)                 |
| PRA level ≤30%, n (%) | 64 (100.0) | 60 (100.0)             | 54 (100.0)              |
| **Donor information** |             |                        |                         |
| Living, n (%)  | 22 (34.4)   | 23 (38.3)              | 17 (31.5)               |
| Deceased, n (%)| 42 (65.6)   | 37 (61.7)              | 37 (68.5)               |
| Age: mean (SD), y | 41.0 (13.3) | 39.4 (14.9)            | 39.4 (13.0)             |

Demographics and baseline characteristics for both recipients and donors are shown, from the full analysis set, and are based on the parent study (A3921050; NCT00483756) of the LTE study (A3921050; NCT00658359). In the parent study, patients with PRA levels >30% were excluded. N, total number of patients per treatment group; n, number of patients; SD, standard deviation; PRA, panel-reactive antibody.
Any IFTA grade, n (%) 23 (76.7) 13 (65.0) 8 (72.7)

Figure 3. KM estimates of BPAR by dose groups. BPAR was defined as acute/active cellular rejection as interpreted by the central blinded pathologist, according to the Banff 97 working classification. Data are based on all biopsies (including for-cause and protocol biopsies). Data in graphs show the first occurrence of BPAR. Data presented are from the full analysis set for the parent study (A3921030; NCT00483756), months 0 to 12, and the LTE study (A3921050; NCT00658359), months 12 to 72.

Glomerular Filtration Rate

Only 13 patients in the tofacitinib MI group completed measured GFR at month 36 versus 30 patients in the tofacitinib LI group and 39 patients in the CsA group. Although least squares means (LSM) of measured GFR were numerically higher at month 36 for the tofacitinib LI and MI groups (76.9 mL/min [P = 0.07] and 75.9 mL/min [P = 0.2], respectively) versus CsA (67.6 mL/min), the differences were not statistically significant. However, LSM of MDRD-estimated eGFR (LOCF plus imputation) were numerically higher in the tofacitinib groups versus CsA at all visits, reaching statistical significance at month 15 through month 36 for tofacitinib MI and at month 15 through month 72 for tofacitinib LI (P < 0.0001 to P < 0.05; Figure 4). At month 36, LSM eGFRs were approximately 9 to 15 mL/min per 1.73 m² higher in the tofacitinib groups versus CsA. Least squares means eGFRs were generally maintained through 72 months, with values approximately 10 to 15 mL/min per 1.73 m² higher in the tofacitinib groups versus CsA at month 72. For patients with BME at month 15 through month 72 and was approximately 13 mL/min per 1.73 m² higher than CsA at month 72.

Safety Outcomes

Adverse Events

Adverse events were reported in 96.9%, 96.7%, and 98.1% of the CsA, tofacitinib LI, and tofacitinib MI groups, respectively (Table 4). The most common types of AE were infections. The most common AE terms for tofacitinib LI and MI were HZV infection (23.3% and 13.0% vs CsA 7.8%) and upper respiratory tract infection (18.3% and 24.1% vs CsA 10.9%) (Table 4). Broadly similar proportions of patients among treatment groups discontinued due to AEs for CsA (18.8%), tofacitinib LI (10.0%), and tofacitinib MI (18.5%). The most common types of SAEs for patients receiving tofacitinib were infections (35.0% for LI and 25.9% for MI versus 28.1% for CsA). The most common individual SAE terms for the tofacitinib LI group were kidney transplant rejection, pneumonia, BK viral nephropathy, and urinary tract infection (all 5%), whereas sepsis was the most common (5.6%) for the tofacitinib MI group.

At study entry (month 12), serious infection rates were similar in the CsA (26.6%) and tofacitinib LI groups (25.0%), but were numerically higher for tofacitinib MI (38.9%; P = 0.15 vs CsA). Kaplan-Meier estimates of serious infection rates increased over time in each group and were significantly higher for tofacitinib MI versus CsA from month 24 through month 36 (range, P = 0.02-0.05). At month 36, KM estimates were numerically higher for tofacitinib LI (43.9%; P = 0.45) and significantly higher for tofacitinib MI (55.9%; P < 0.05) versus CsA (37.1%; Figure 5).

Exposure-based analysis comparing rates of serious infections in the AME and BME tofacitinib groups showed numerically higher rates for AME (44.0%) versus CsA (26.6%) and BME (22.6%) at month 12. Similar to the dose-based analysis, the KM serious infection rate increased in all groups over time after month 12. At the last evaluable time point for the AME group (month 30), the cumulative serious infection rate (53.1%, P = 0.04) was significantly higher versus CsA.

TABLE 3

Proportion of patients with IFTA by severity grades in the protocol-required allograft biopsy at month 36

| IFTA grade at month 36 (protocol-required biopsies) | CsA (n = 30) | Tofacitinib LI (n = 20) | Tofacitinib MI (n = 11) |
|---|---|---|---|
| Any IFTA grade, n (%) | 23 (76.7) | 13 (65.0) | 8 (72.7) |
| Grade 0 | 7 (23.3) | 7 (35.0) | 3 (27.3) |
| Grade 1 | 13 (43.3) | 9 (45.0) | 6 (54.5) |
| Grade 2 | 8 (26.7) | 4 (20.0) | 0 (0.0) |
| Grade 3 | 2 (6.7) | 0 (0.0) | 2 (18.2) |
### Safety outcomes through month 72

| AE Category | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|-------------|--------------|-------------------------|-------------------------|
| **AEs**     |              |                         |                         |
| Patients with AEs, n (%) | 62 (96.9) | 58 (96.7) | 53 (98.1) |
| Most common AEs by SOC, n (%) | | | |
| Infections and infestations | 41 (64.1) | 47 (78.3) | 41 (75.9) |
| Gastrointestinal disorders | 36 (56.3) | 33 (55.0) | 17 (31.5) |
| Patients with SAEs, n (%) | 40 (62.5) | 32 (53.3) | 31 (57.4) |
| **Infections** |              |                         |                         |
| Patients with PTLD, n | 0 | 0 | 2 |
| **Viral tests** |              |                         |                         |
| EBV copies/500 ng DNA by PCR, n (%) | 19 (61.3) | 4 (23.5) | 5 (45.5) |
| **Laboratory data** |              |                         |                         |
| WBC count, mean, K/mm³ (SD) | 114.2 (26.9) | 112.0 (46.4) | 94.3 (21.1) |
| HDL cholesterol, mean, mg/dL (SD) | 50.7 (13.1) | 58.6 (24.6) | 55.6 (15.6) |
| Triglycerides, mean, mg/dL (SD) | 142.4 (74.4) | 172.2 (100.5) | 150.9 (86.7) |

### Use of erythropoiesis-stimulating agents, n (%) | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|----------------|--------------|-------------------------|-------------------------|
| ALT, IU/L, >3.0 x ULN, n (%) | 1 (1.6) | 2 (3.3) | 4 (7.4) |
| AST, IU/L, >3.0 x ULN, n (%) | 1 (1.6) | 1 (1.7) | 1 (1.9) |

### Liver function tests

| Liver function tests | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|----------------------|--------------|-------------------------|-------------------------|
| ALT, IU/L, >3.0 x ULN, n (%) | 1 (1.6) | 2 (3.3) | 4 (7.4) |
| AST, IU/L, >3.0 x ULN, n (%) | 1 (1.6) | 1 (1.7) | 1 (1.9) |

### Serum lipids

| Serum lipids | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|--------------|--------------|-------------------------|-------------------------|
| LDL cholesterol, >3.0 x ULN, n (%) | 112.0 (46.4) | 94.3 (21.1) | 112.0 (46.4) |
| HDL cholesterol, >3.0 x ULN, n (%) | 58.6 (24.6) | 55.6 (15.6) | 58.6 (24.6) |
| Triglycerides, >3.0 x ULN, n (%) | 150.9 (86.7) | 150.9 (86.7) | 150.9 (86.7) |

### Concomitant medication use at any time during the study

| Concomitant medication use at any time during the study | CsA (n = 64) | Tofacitinib LI (n = 60) | Tofacitinib MI (n = 54) |
|--------------------------------------------------------|--------------|-------------------------|-------------------------|
| Filgrastim or pegfilgrastim use, n (%) | 0 (0.0) | 1 (1.7) | 1 (1.9) |

### Continued next column
Laboratory Data

A summary of laboratory data is included in Table 4. There was a higher proportion of patients receiving CsA who at any time in the study experienced mild anemia (nadir Hgb ≥8.0 and ≤9.9 g/dL; 12.5%) compared with the tofacitinib groups (1.7-3.7%). Moderate to severe anemia (nadir Hgb levels <8 g/dL) was reported in 1 patient (1.6%) receiving CsA and in 1 patient (1.7%) receiving tofacitinib LI. Concomitant use of erythropoiesis-stimulating agents was reported in 3 patients (5.6%) in the tofacitinib MI group. Mean platelet counts, WBC, and ANC were generally similar across the treatment groups. The proportions of patients with ANC less than 1000/mm³ were as follows: CsA, 1.6%; tofacitinib LI, 1.7%; and tofacitinib MI, 1.9%. Concomitant use of filgrastim or pegfilgrastim was reported in 1 (1.7%) patient receiving tofacitinib LI and in 1 (1.9%) patient receiving tofacitinib MI. At month 72, mean ALC was higher for the treatment groups receiving these medications; there was no statistically significant difference among the treatment groups at month 36, with KM rates of 1.7% for tofacitinib LI and 1.6% versus 4.8% for CsA. For the BME group, rates of serious HZV infections were 1.6% versus 4.8% for CsA.

From month 12 through month 72, 6 (9.4%), 6 (10.0%), and 8 (14.8%) patients reported malignancy in the CsA, tofacitinib LI, and tofacitinib MI groups, respectively (Table 4). Of the 31 malignancy events recorded, most (22/31) were nonmelanoma skin cancer (basal cell or squamous cell skin cancer).

Two patients in the tofacitinib MI group developed PTLD after month 12. Both patients, and the 3 patients in parent study A3921030 who experienced PTLD, belonged to the AME group. No additional cases of PTLD were observed after introduction of the protocol amendment that required discontinuation of 43 AME patients. Among the patients who were discontinued from tofacitinib, no PTLD cases were reported during 12 months of postdose follow-up. At month 36, KM analysis showed significantly lower rates of NODM for tofacitinib LI (14.2%; P = 0.006) and numerically lower rates for tofacitinib MI (28.1%; P = 0.37) versus CsA (37.7%) (Table 4). Three cases of BK viral nephropathy occurred in patients receiving tofacitinib LI.

DISCUSSION

Tofacitinib is an oral JAK inhibitor that targets inflammation by reducing proinflammatory cytokine signaling and production and has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Tofacitinib has been evaluated as a substitute for CNIs for rejection prophylaxis in de novo kidney transplantation. The objectives of the phase II LTE study described here were to evaluate the long-term efficacy and safety of tofacitinib.

The results of this LTE study suggest that tofacitinib treatment beyond the first 12 months posttransplant continued to be effective in preventing acute allograft rejection, with few cases of late-onset BPARs, and cumulative rates of BPAR and treated clinical acute rejection no higher than CsA at month 36. A low risk of mortality and graft loss was also observed in all treatment groups. In the exploratory analysis by tofacitinib exposure, similar efficacy to CsA at month 36 was also demonstrated in the patients with lower tofacitinib drug exposure (BME).

Tofacitinib LI continued to demonstrate a significantly higher MDRD-calculated eGFR than CsA at every time point after month 12, with tofacitinib groups having eGFR 9 to 15 mL/min per 1.73 m² higher than CsA at month 36, and values approximately 10 to 15 mL/min/1.73 m² higher at month 72. The BME tofacitinib group also showed significantly higher MDRD-calculated eGFR than CsA for months 15 to 72 in the exploratory analysis. These allograft function findings were similar to those of the recent phase III BENEFIT study investigating long-term outcomes for kidney transplant recipients receiving a CNI-free regimen including belatacept versus CsA. Similarly, the ZEUS study comparing long-term efficacy of everolimus with CsA showed sustained, although more modest, improvements in eGFR up to 5 years posttransplantation. However, both the BENEFIT and ZEUS studies reported significantly higher initial rates of acute rejection versus the CsA arm.

Unfortunately, the small number of patients who underwent protocol biopsy at month 36 precluded adequate assessment of the rate of progression and severity of IFTA over time. The patients in this study were not evaluated for the development of donor-specific antibodies, thus preventing the assessment of an immunologic contribution to IFTA progression.

Similar rates of AEs were reported for the tofacitinib groups versus CsA. The most common types of AEs were infections and gastrointestinal disorders. Rates of serious infections increased in all treatment groups over time after month 12, such that the cumulative rates of serious infections during month 24 through month 36 were numerically higher for tofacitinib LI and significantly higher for tofacitinib MI versus CsA. In the parent study, 12-month serious infection rates were reported to be 25.3% for CsA, 37.0% for tofacitinib LI, and 44.5% for tofacitinib MI, whereas the cumulative rates of serious infections reported here at month 36 were 37.1% for CsA, 43.9% for tofacitinib LI, and 55.9% for tofacitinib MI, suggesting that the magnitude of the risk relative to CsA persisted. Although the proportion

Kaplan-Meier estimates of HZV infection rate increased over time. At month 36, rates were numerically higher in both tofacitinib groups (LI, 22.6%; P = 0.23; MI, 20.7%; P = 0.38) versus CsA (14.5%), although they did not reach significance. For serious HZV infections, although rates also increased over time, no significant differences were observed among the treatment groups at month 36, with KM rates of 1.7% for tofacitinib LI and 5.6% for tofacitinib MI versus 4.8% for CsA. For the BME group, rates of serious HZV infections were 1.6% versus 4.8% for CsA.

Over time. At month 36, rates were numerically higher in both tofacitinib groups (LI, 22.6%; P = 0.23; MI, 20.7%; P = 0.38) versus CsA (14.5%), although they did not reach significance. For serious HZV infections, although rates also increased over time, no significant differences were observed among the treatment groups at month 36, with KM rates of 1.7% for tofacitinib LI and 5.6% for tofacitinib MI versus 4.8% for CsA. For the BME group, rates of serious HZV infections were 1.6% versus 4.8% for CsA.
of patients with serious infections continued to increase over time in all treatment groups in this LTE study, among the tofacitinib-treated patients, the increase in the risk of serious infection appeared to slow over time with dose reduction. Specifically, in the first 12 months, when the tofacitinib-treated patients received 10 to 15 mg BID, serious infection rates were 25.0% and 38.9%, respectively, for the LI and MI patients who entered this LTE study. Between months 24 and 36, when all tofacitinib-treated patients received 5 mg BID, the cumulative rates of serious infection only increased by approximately 5% to 10% in the LI and MI groups.

Exposure-based analysis suggested that the risk of serious infection could be related to tofacitinib exposure, with the AME group having a statistically higher cumulative rate of serious infections versus CsA at the last evaluable time point (month 30) (53.1% vs 33.4%, P = 0.04). In contrast, the BME group maintained a generally similar cumulative serious infection rate versus CsA at month 36 (45.8% vs 37.1%), though serious infection risk increased with time in all treatment groups. These findings suggest that a risk of serious infection persists with long-term tofacitinib and CsA treatment.

Consistent with previous preliminary exposure-based analyses,19 there was an increased risk of developing PTLD in the tofacitinib AME group, which included all 5 patients with PTLD. As further confirmation, after implementation of a protocol amendment requiring discontinuation of all remaining AME patients, no additional cases of PTLD were reported.

There were higher cumulative rates of hematologic SAEs (eg, neutropenia/leukopenia or anemia) in the tofacitinib groups versus CsA at month 36. However, most of these hematologic SAEs occurred within the first 12 months posttransplant. In the parent study, lower MPA clearance was observed in patients receiving tofacitinib versus patients receiving CsA,20 which may have contributed to the higher rate of hematologic SAEs in the first 12 months. Mycophenolic acid area under the curve was not determined due to insufficient pharmacokinetic data. The extent to which concomitant MPA administration contributed to infection or hematologic risks of long-term tofacitinib treatment is unknown.

This is the first study to report long-term data on kidney transplant recipients treated with a JAK inhibitor. Nonetheless, our evaluation had several limitations. The implementation of the protocol amendment to discontinue patients with tofacitinib AME decreased patient numbers in the tofacitinib groups by approximately 50% across the tofacitinib groups. The lack of additional transplant studies with tofacitinib also likely prompted investigators and patients to discontinue from this study. The decrease in participating patients over time reduced the statistical power to assess the long-term safety profile of tofacitinib and introduced an imbalance in patient numbers between tofacitinib and CsA groups, confounding between-group comparisons. The use of CsA was also a limitation, preventing the comparison of tofacitinib with the current standard of care (tacrolimus). Also, only clinically stable patients who completed the parent study were eligible for enrollment in the LTE study, potentially resulting in a selection bias. The objective of this LTE study was to evaluate the clinical outcomes of long-term tofacitinib treatment, with an emphasis on events occurring after the first 12 months posttransplant. Although the use of KM analysis allowed assessment of the cumulative event rate through month 72, patient withdrawals that occurred at earlier time points and were censored could present a different risk profile to that presented for patients that remained in the study, which would violate the noninformative censoring assumption required by the KM analysis.

The findings from this LTE phase II study showed that long-term tofacitinib treatment continued to be effective in preventing acute rejection of renal allografts and preserving renal function. The current data confirmed an increased risk of PTLD associated with higher exposure of tofacitinib, as no other cases developed after discontinuation of the AME group. Long-term treatment with tofacitinib with MPA products was also associated with a persistent risk of serious infections. The long-term risk-benefit of a CNI-free regimen based on tofacitinib in kidney transplant patients has yet to be conclusively determined.

ACKNOWLEDGMENTS

The authors would like to thank the study investigators, research coordinators, patients, and study teams. Medical writing support, under the guidance of the authors, was provided by Rebecca Douglas, PhD, at CMC CONNECT, a division of Complete Medical Communications Ltd, Macclesfield, UK and was funded by Pfizer Inc, New York, NY in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med. 2015;163:461-464).

REFERENCES

1. Li X, Zhuang S. Recent advances in renal interstitial fibrosis and tubular atrophy after kidney transplantation. Fibrogenesis Tissue Repair. 2014;7:15.
2. Boor P, Flogoje J. Renal allograft fibrosis: biology and therapeutic targets. Am J Transplant. 2015;15:883–896.
3. Narkivelil B, PNG CH, O’Connell PJ, et al. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: comparison of cyclosporine and tacrolimus eras. Transplantation. 2016;100:1723–1731.
4. Chapman JR. Chronic calcineurin inhibitor use is nephrotoxic. Clin Pharmacol Ther. 2011;90:207–209.
5. Barnould J, Staack O, Halleck F, et al. The need for minimization strategies: current problems of immunosuppression. Transpl Int. 2015;28:891–900.
6. Nanniss M, Kluyvers DR, Sanwal M. Calcineurin inhibitor nephrotoxicity. Curr J Am Soc Nephrol. 2009;4:481–508.
7. Almeida C, Silveira MR, de Araújo VE, et al. Safety of immunosuppressive drugs used as maintenance therapy in kidney transplantation: a systematic review and meta-analysis. Pharmaceuticals (Basel). 2013;6:1170–1194.
8. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. Am J Transplant. 2009;9:1876–1885.
9. Ekberg H, Grinyó J, Nashan B, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. Am J Transplant. 2007;7:560–570.
10. Roostai L, Vincenti F, Grinyó J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant. 2013;13:2875–2883.
11. Vincenti F, Roostai L, Grinyó J, et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med. 2016;374:333–343.
12. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357:2562–2575.
13. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10:535–546.
14. Vincenti F, Larsen CP, Alberu J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant. 2012;12:210–217.
15. Lee J, Lee JJ, Kim BS, et al. A 12-month single arm pilot study to evaluate the efficacy and safety of sirolimus in combination with tacrolimus in kidney
transplant recipients at high immunologic risk. J Korean Med Sci. 2015;30:682–687.

16. Flechner SM, Gurkan A, Hartmann A, et al. A randomized, open-label study of sirolimus versus cyclosporine in primary de novo renal allograft recipients. Transplantation. 2013;95:1233–1241.

17. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant. 2011;11:1633–1644.

18. Busque S, Leventhal J, Brennan DC, et al. 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.

19. Vincenti F, Silva HT, Busque S, et al. Evaluation of the effect of tofacitinib exposure on outcomes in kidney transplant patients. Am J Transplant. 2015;15:1644–1653.

20. Vincenti F, Tedesco Silva H, Busque S, et al. 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.

21. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999;55:713–723.

22. Clark JD, Rangan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem. 2014;57:5023–5038.

23. Budde K, Lehner F, Sommerer C, et al. Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus: the randomized ZEUS study. Am J Transplant. 2015;15:119–128.