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

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Efficacy and Safety of a Tofacitinib-based Immunosuppressive Regimen After Kidney Transplantation: Results From a Long-term Extension Trial

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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.

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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 effects of CNI has prompted interest in CNI minimization and avoidance of immunosuppressive regimens. The extent to which calcineurin inhibitors (CNI) contribute to allograft IFTA over the long term has been disputed. 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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
of 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-
ation 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 expo-
sure (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. For expo-
sure analysis, the total number of patients available for evalu-
ation 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.

**FIGURE 1.** Treatment groups and dosing regimens are shown from the full analysis set, including the parent study (A3921030; NCT00483756) and the LTE study (A3921050; NCT00658359). CsA 125 to 400 ng/mL and 100 to 300 ng/mL represent the target 12-hour trough whole blood levels. All patients received concomitant mycophenolic acid product and corticosteroid taper through month 72.

![FIGURE 1](image1.png)

**FIGURE 2.** Patient disposition data, presented from the LTE study only (A3921050; NCT00658359). N, total number of patients per treatment group; n, number of patients.

![FIGURE 2](image2.png)
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 11.1% (P = 0.06) for tofacitinib LI and MI, respectively, in the parent study. From month 12 through month 72, additional treated clinical acute rejection and death-censored allograft survival (to month 36) for either of the tofacitinib groups versus CsA (Table 2).

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

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**Table 2.** Efficacy outcomes through month 72

<table>
<thead>
<tr>
<th></th>
<th>CsA (n = 64)</th>
<th>Tofacitinib LI (n = 60)</th>
<th>Tofacitinib MI (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient survival, cumulative KM% (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>98.4 (1.6)</td>
<td>100.0 (0.0)</td>
<td>91.0 (4.5)</td>
</tr>
<tr>
<td>Month 72</td>
<td>94.1 (3.4)</td>
<td>100.0 (0.0)</td>
<td>91.0 (4.5)</td>
</tr>
<tr>
<td>Graft survival, death censored, cumulative KM% (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>96.5 (2.4)</td>
<td>100.0 (0.0)</td>
<td>100.0 (0.0)</td>
</tr>
<tr>
<td>Month 72</td>
<td>96.5 (2.4)</td>
<td>100.0 (0.0)</td>
<td>100.0 (0.0)</td>
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<tr>
<td>BPAR, cumulative KM% (SE)</td>
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<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>11.2 (4.0)</td>
<td>10.0 (3.9)</td>
<td>7.4 (3.6)</td>
</tr>
<tr>
<td>Month 72</td>
<td>13.3 (4.4)</td>
<td>10.0 (3.9)</td>
<td>7.4 (3.6)</td>
</tr>
<tr>
<td>Treated clinical acute rejection, cumulative KM% (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>23.9 (5.4)</td>
<td>11.7 (4.1)</td>
<td>11.1 (4.3)</td>
</tr>
<tr>
<td>Month 72</td>
<td>29.7 (5.9)</td>
<td>11.7 (4.1)</td>
<td>11.1 (4.3)</td>
</tr>
<tr>
<td>BPAR, extension study period only, n²</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Treated clinical acute rejection, extension study period only, n²</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>eGFR by MDRD, mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>54.4 (3.0)</td>
<td>69.1 (3.1)</td>
<td>63.3 (3.3)</td>
</tr>
<tr>
<td>Month 72</td>
<td>49.6 (3.5)</td>
<td>64.3 (3.6)</td>
<td>59.2 (3.8)</td>
</tr>
</tbody>
</table>

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**Table 1.** Demographics and baseline characteristics at the time of transplantation

<table>
<thead>
<tr>
<th></th>
<th>CsA (n = 64)</th>
<th>Tofacitinib LI (n = 60)</th>
<th>Tofacitinib MI (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (SD), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (68.8)</td>
<td>41 (68.3)</td>
<td>40 (74.1)</td>
</tr>
<tr>
<td>White</td>
<td>46.4 (12.7)</td>
<td>45.7 (12.6)</td>
<td>48.5 (10.9)</td>
</tr>
<tr>
<td>Black</td>
<td>46 (71.9)</td>
<td>45 (75.0)</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (12.5)</td>
<td>7 (11.7)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7.8)</td>
<td>6 (10.0)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64 (100.0)</td>
<td>60 (100.0)</td>
<td>54 (100.0)</td>
</tr>
<tr>
<td>Black</td>
<td>22 (34.4)</td>
<td>23 (38.3)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>42 (65.6)</td>
<td>37 (61.7)</td>
<td>37 (68.5)</td>
</tr>
<tr>
<td>PRA level ≤30%, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Living, n (%)</td>
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<td></td>
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<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (68.8)</td>
<td>41 (68.3)</td>
<td>40 (74.1)</td>
</tr>
<tr>
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<td>34 (63.0)</td>
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<tr>
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<td>7 (13.0)</td>
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<tr>
<td>Other</td>
<td>5 (7.8)</td>
<td>6 (10.0)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>PRA level ≤30%, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Living, n (%)</td>
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<td></td>
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</tr>
</tbody>
</table>
Tofacitinib LI (n = 20) Vs CsA (n = 30) Vs Tofacitinib MI (n = 11) vs Tofacitinib MI (n = 11)

**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.

**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.

33.3% for CsA (Table 3). For patients with BME at month 36, based on protocol-required biopsies, the proportions of grade 2/3 IFTA were 19.4% versus 33.3% for CsA.

**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 < 0.001 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 36, LSMs of measured GFR were 78.6 mL/min (P = 0.02) versus 67.7 mL/min for CsA. Similarly, MDRD-estimated eGFR (LOCF plus imputation) was significantly higher in the BME vs CsA from 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 AEs 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.

<table>
<thead>
<tr>
<th>IFTA grade at month 36 (protocol-required biopsies)</th>
<th>CsA (n = 30)</th>
<th>Tofacitinib LI (n = 20)</th>
<th>Tofacitinib MI (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any IFTA grade, n (%)</td>
<td>23 (76.7)</td>
<td>13 (65.0)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>7 (23.3)</td>
<td>7 (35.0)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>13 (43.3)</td>
<td>9 (45.0)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (26.7)</td>
<td>4 (20.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

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### TABLE 4. Safety outcomes through month 72

<table>
<thead>
<tr>
<th>AEs</th>
<th>CsA (n = 64)</th>
<th>Tofacitinib LI (n = 60)</th>
<th>Tofacitinib MI (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AEs, n (%)</td>
<td>62 (96.9)</td>
<td>58 (96.7)</td>
<td>53 (96.1)</td>
</tr>
<tr>
<td>Most common AEs by SOC, n (%)</td>
<td>18 (28.1)</td>
<td>21 (35.0)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Patients with SAEs, n (%)</td>
<td>40 (62.5)</td>
<td>32 (53.3)</td>
<td>31 (57.4)</td>
</tr>
<tr>
<td>Most common TE infections by class, n (%)</td>
<td>19 (61.3)</td>
<td>4 (23.5)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>NODM, KM% (SE)</td>
<td>1.6 (1.6)</td>
<td>1.7 (1.7)</td>
<td>1.9 (1.8)</td>
</tr>
<tr>
<td>Month 12</td>
<td>1.6 (1.6)</td>
<td>7.1 (3.4)</td>
<td>1.9 (1.8)</td>
</tr>
<tr>
<td>Month 36</td>
<td>1.6 (1.6)</td>
<td>7.1 (3.4)</td>
<td>1.9 (1.8)</td>
</tr>
<tr>
<td>NODM, KM% (SE)</td>
<td>27.5 (6.3)</td>
<td>6.0 (3.4)</td>
<td>11.9 (5.0)</td>
</tr>
<tr>
<td>Month 12</td>
<td>27.7 (6.8)</td>
<td>14.2 (5.9)</td>
<td>28.1 (8.1)</td>
</tr>
<tr>
<td>Month 36</td>
<td>27.7 (6.8)</td>
<td>17.6 (5.8)</td>
<td>28.1 (8.1)</td>
</tr>
<tr>
<td>HZV infection (any), KM% (SE)</td>
<td>5 (7.8)</td>
<td>14 (23.3)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Month 12</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

### Laboratory data

### Hematology

| Mild anemia, nadir Hgb, <8.0, g/dL, n (%) | 8 (12.5) | 1 (1.7) | 2 (3.7) |
| Moderate to severe anemia, nadir Hgb, <3.0 g/dL, n (%) | 1 (1.6) | 1 (1.7) | 0 (0.0) |
| Hgb, mean, g/dL, (SD)c | 13.1 (1.8) | 14.2 (1.6) | 13.2 (2.0) |
| Absolute platelet count, mean, K/mm³ (SD)c | 220.0 (69.8) | 226.8 (76.6) | 206.3 (55.6) |
| WBC count, mean, K/mm³ (SD)c | 6.7 (2.2) | 5.1 (1.2) | 6.4 (1.8) |
| Creatinine, >2.0 × ULN, n (%) | 5 (7.8) | 11 (18.3) | 13 (24.1) |
| Mild neutropenia, ANC <1000 mm³, n (%) | 3 (4.7) | 7 (11.7) | 0 (0.0) |
| Moderate to severe neutropenia, ANC <1000 mm³, n (%) | 1 (1.6) | 1 (1.7) | 1 (1.9) |
| ANC, mean, K/mm³ (SD)c | 4.3 (1.9) | 3.4 (1.1) | 4.7 (1.5) |
| ALC, mean, K/mm³ (SD)c | 1.7 (0.7) | 1.1 (0.3) | 1.1 (0.5) |

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

| Filgrastim or pegfilgrastim use, n (%) | 0 (0.0) | 1 (1.7) | 1 (1.9) |

### Liver function tests

| ALT, IU/L, >3.0 × ULN, n (%) | 1 (1.6) | 2 (3.3) | 4 (7.4) |
| AST, IU/L, >3.0 × ULN, n (%) | 1 (1.6) | 1 (1.7) | 1 (1.9) |

### Serum lipids

| LDL cholesterol, mean, mg/dL, (SD)c | 114.2 (26.9) | 112.0 (46.4) | 94.3 (21.1) |
| HDL cholesterol, mean, mg/dL, (SD)c | 50.7 (13.1) | 58.6 (24.6) | 55.6 (15.6) |
| Triglycerides, mean, mg/dL, (SD)c | 142.4 (74.4) | 172.2 (100.5) | 150.9 (86.7) |

### Viral tests

| EBV copies/500 ng DNA by PCR, n (%)c,d | 0 (0.0) | 4 (23.5) | 5 (45.5) |

### Use of erythropoiesis-stimulating agents, n (%) | 0 (0.0) | 0 (0.0) | 3 (5.6) |

### FIGURE 5. KM estimates of serious infection events in the study period.

*P < 0.05 for comparison of CsA and tofacitinib MI; Wald test. P = 0.53.

At month 36, the cumulative serious infection rate was 45.8% (P = 0.33) for the BME group versus 37.1% for CsA.

### Continued next column
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.

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.

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 CsA (1.7 K/mm³) than in each of the tofacitinib groups (both 1.1 K/mm³).

Mean serum high-density lipoprotein-cholesterol values were modestly higher at month 72 in the tofacitinib groups compared with CsA, and mean triglyceride values were modestly higher in the tofacitinib LI group than in the CsA group. In contrast, mean serum low-density lipoprotein-cholesterol values in the tofacitinib groups were generally comparable to those in the CsA group. The use of lipid-lowering agents was common with 42.4% or greater of patients in each of the treatment groups receiving these medications; there was no statistically significant difference between the tofacitinib groups and the CsA group at any time point.

The proportion of patients with no BKV or low-grade viremia was similar among the tofacitinib and CsA groups. A higher proportion of patients in the tofacitinib groups had low-grade EBV. At month 72, more patients in the tofacitinib groups versus CsA had EBV counts of 1 to 30 copies/500 ng DNA (DNA) or 51 to 100 copies/500 ng DNA.

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 showing 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 also 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...
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, 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 CsA20 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.

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REFERENCES


