American Journal of Transplantation 2012; 12: 2446–2456
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04127.x

Randomized Phase 2b Trial of Tofacitinib (CP-690,550) in *De Novo* Kidney Transplant Patients: Efficacy, Renal Function and Safety at 1 Year

F. Vincenti[a,*], H. Tedesco Silva[b], S. Busque[c], P. O'Connell[d], J. Friedewald[e], D. Cibrik[f], K. Budde[g], A. Yoshida[h], S. Cohney[i], W. Weimar[j], Y. S. Kim[k], N. Lawendy[l], S.-P. Lan[l], E. Kudlacz[l], S. Krishnaswami[l] and G. Chan[l]

[a] *University of California, San Francisco, CA*
[b] *Hospital do Rim e Hipertensão, São Paulo, Brazil*
[c] *Stanford University, Stanford, CA*
[d] *Westmead Hospital, Sydney, Australia*
[e] *Northwestern University, Chicago, IL*
[f] *University of Michigan, Ann Arbor, MI*
[g] *Charité Universitätsmedizin, Berlin, Germany*
[h] *Henry Ford Hospital, Detroit, MI*
[i] *Royal Melbourne Hospital, Melbourne, Australia*
[j] *Erasmus Medisch Centrum, Rotterdam, The Netherlands*
[k] *Seoul National University College of Medicine, Seoul, Korea*
[l] *Pfizer Inc., Groton, CT*
***** *Corresponding author: Flavio Vincenti, Flavio.Vincenti@ucsfmedctr.org*

In this Phase 2b study, 331 low-to-moderate risk *de novo* kidney transplant patients (approximately 60% deceased donors) were randomized to a more intensive (MI) or less intensive (LI) regimen of tofacitinib (CP-690, 550), an oral Janus kinase inhibitor or cyclosporine (CsA). All patients received basiliximab induction, mycophenolic acid and corticosteroids. Primary endpoints were: incidence of biopsy-proven acute rejection (BPAR) with a serum creatinine increase of ≥0.3 mg/dL and ≥20% (clinical BPAR) at Month 6 and measured GFR at Month 12. Similar 6-month incidences of clinical BPAR (11%, 7% and 9%) were observed for MI, LI and CsA. Measured GFRs were higher ($p < 0.01$) at Month 12 for MI and LI versus CsA (65 mL/min, 65 mL/min vs. 54 mL/min). Fewer ($p < 0.05$) patients in MI or LI developed chronic allograft nephropathy at Month 12 compared with CsA (25%, 24% vs. 48%). Serious infections developed in 45%, 37% and 25% of patients in MI, LI and CsA, respectively. Anemia, neutropenia and posttransplant lymphoproliferative disorder occurred more frequently in MI and LI compared with CsA. Tofacitinib was equivalent to CsA in preventing acute rejection, was associated with improved renal function and less chronic allograft histological injury, but had side-effects at the doses evaluated.

Key words: cyclosporine, kidney, renal function, tofacitinib

Abbreviations: AUC_{0-12}, 0–12-h area under the plasma concentration–time curve; BID, twice daily; BPAR, biopsy-proven acute rejection; CAN, chronic allograft nephropathy; cg, allograft glomerulopathy; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine; cv, vascular fibrous intimal thickening; DGF, delayed graft function; EBV, Epstein-Barr virus; IF, interstitial fibrosis; IFG, impaired fasting glycemia; JAK, Janus kinase; K-M, Kaplan-Meier; LI, less intensive tofacitinib; LOCF, last observation carried forward; M, Months; MDRD, Modification of Diet in Renal Disease; MI, more intensive tofacitinib; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NK, natural killer; NODAT, new-onset diabetes after transplantation; PRA, panel-reactive antibody; PTLD, posttransplant lymphoproliferative disorder; TA, tubular atrophy; TWC2, time-weighted average concentrations at 2 h postdose during the first 6 months.

Received 17 January 2012, revised 06 April 2012 and accepted for publication 17 April 2012

Introduction

The incidence of acute rejection in kidney transplant patients has fallen progressively without a proportionate increase in long-term allograft survival (1). Calcineurin inhibition remains the cornerstone of posttransplant immunosuppressive protocols. Long-term use of calcineurin inhibitors (CNIs) has been associated with chronic nephrotoxicity (2), prompting interest in CNI-free regimens. However, CNI-free protocols have been hampered by unacceptably high rates of acute rejection (3–5) and other side effects (6).

Tofacitinib (CP-690,550) is an oral Janus kinase (JAK) inhibitor that suppresses intracellular signal transduction of multiple cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, which are essential for homeostasis and function of T cells, B cells and natural killer (NK) cells. A small pilot study with tofacitinib showed promise in preventing acute rejection in kidney allografts (7). The current study was conducted to evaluate the efficacy and safety of tofacitinib when combined with basiliximab induction, mycophenolic

acid (MPA) and corticosteroids in *de novo* kidney transplant patients.

Methods

Patients

Patients were immunologically low-to-moderate-risk recipients of primary kidney allografts from deceased donors or HLA-mismatched living donors. Key exclusion criteria were current panel-reactive antibody (PRA) >30% or peak PRA >50%, positive B cell crossmatch, or pretransplant donor-specific anti-HLA antibodies. Allografts from extended-criteria donors and cardiac-death donors were excluded.

Study design

This was a randomized, multicenter, Phase 2b study (ClinicalTrials.gov identifier NCT00483756) conducted in 57 centers in 15 countries. The trial was approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centers participating in the study or a central IRB. It was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

Following kidney transplantation, patients were randomized 1:1:1 to one of two tofacitinib regimens or cyclosporine (CsA) microemulsion (Novartis, Basel, Switzerland). A computer generated randomization schedule was used to assign patients to treatment groups and randomization was stratified with respect to donor source. In the more intensive (MI) tofacitinib group, patients received tofacitinib 15 mg twice daily (BID) in Months 1–6, then 10 mg BID in Months 7–12. In the less intensive (LI) tofacitinib group, patients received tofacitinib 15 mg BID in Months 1–3, then 10 mg BID in Months 4–12. Patients and investigators were blinded to the assignment to MI versus LI but were aware of assignment to tofacitinib versus CsA. In the control group, CsA was started at 8–10 mg/kg/day and adjusted to achieve 12-h trough whole blood levels of 125–400 ng/mL in Months 1–3 and 100–300 ng/mL in Months 4–12.

All patients received basiliximab induction (20 mg intravenously on Days 0 and 4), MPA products at an initial dose of 2 g/day mycophenolate mofetil (MMF), or 1.44 g/day enteric-coated MPA, and corticosteroids through at least Month 12. Cytomegalovirus (CMV) prophylaxis was required for 3 months in CMV-seronegative recipients of kidneys from CMV-seropositive donors, while other donor–recipient CMV combinations received prophylaxis according to local practice. GFR was measured at Months 6 and 12 by determining iohexol serum clearance. Protocol biopsies of the allograft were required at the time of implantation and Month 12. Patients underwent periodic monitoring of Epstein–Barr virus (EBV) load in whole blood and BK virus load in plasma according to the protocol. Patients who completed 12 months of treatment were eligible for a long-term extension study.

Blinding

The investigator and patient were aware of the treatment assignment if the patient was randomized to the control arm (CsA) but were blinded to assignment to MI versus LI if the patient was randomized to tofacitinib. Patients in the tofacitinib arms received the same dose during the first 3 months (15 mg BID) and after Month 6 (10 mg BID); therefore, the blinding period was limited to Months 4–6, during which time patients in the MI group received 15 mg BID and patients in the LI group received 10 mg BID. During Months 4–6, each patient randomized to tofacitinib received three bottles of identical appearance containing tofacitinib 5 mg tablets or matching placebo. The patient was instructed to take one tablet from each bottle in the morning and in the evening.

Efficacy and safety endpoints

The primary efficacy endpoint was the incidence of first clinical biopsy-proven acute rejection ("clinical BPAR") at Month 6. To meet this endpoint, the patient must have had BPAR and an increase in serum creatinine of ≥0.3 mg/dL and ≥20% from the prerejection baseline. The other primary endpoint was measured GFR at Month 12. Allograft biopsies were reviewed by a central pathologist. A separate secondary endpoint of "total BPAR" was also analyzed based on the central pathologist's finding of acute/active cellular rejection or antibody-mediated rejection according to the Banff 2003 classification (8), regardless of clinical evidence of changes in renal function. All for-cause, surveillance, and protocol biopsies were included in the assessment for total BPAR.

Secondary endpoints included total BPAR rate at Months 6 and 12, estimated GFR at Month 12 calculated from the Modification of Diet in Renal Disease (MDRD) (9) and Nankivell (10) equations, chronic allograft lesions at Month 12, and adverse events. New-onset diabetes after transplantation (NODAT) was defined as the need for treatment of hyperglycemia for ≥30 consecutive days or fasting serum glucose ≥126 mg/dL. Impaired fasting glycemia was defined as fasting serum glucose 110–125 mg/dL. Stage-1 hypertension was defined as systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg.

Drug exposure and exposure-response analyses

The 0–12-h area under the plasma concentration–time curve (AUC_{0-12}) of MPA at steady state was ascertained using population pharmacokinetics from 2476 MPA concentrations from 276 patients who received tofacitinib or CsA.

Prespecified exploratory exposure-response analyses were performed to evaluate the relationship between tofacitinib exposure and clinical events. Individual tofacitinib exposure was measured as time-weighted average concentrations at 2 h postdose (TWC2). TWC2 was calculated by dose normalizing and averaging individual 2-h concentrations over the first 6 months, and recalculating the 2-h concentration for the assigned dose (10 or 15 mg BID) through Month 6.

Statistical analyses

All efficacy and safety analyses were based on the full analysis set, defined as patients who received at least one dose of study treatment. Primary analyses were performed to evaluate both noninferiority in the 6-month incidence of clinical BPAR and superiority in 12-month measured GFR between MI or LI and the CsA control group. The Hochberg multiple comparison procedure was used to test each tofacitinib group versus CsA, and a step-down procedure was used for evaluating the two primary endpoints (clinical BPAR before measured GFR) at the overall one-sided type-I error level of 20%. To meet the noninferiority criterion for 6-month clinical BPAR incidence, the upper one-sided 80% confidence limit of the difference (tofacitinib–CsA) had to be <12%. The noninferiority margin of 12% was chosen based on a literature review of the treatment effect of the CNIs and was applied to both clinical BPAR and total BPAR evaluations. A sample size of 100 patients per group would provide 81% power to declare noninferiority in the 6-month clinical BPAR rate and superiority in the 12-month measured GFR jointly between at least one of the tofacitinib groups and CsA.

Clinical BPAR and total BPAR data were evaluated using the Kaplan–Meier survival method. Measured GFR at Month 12 and estimated GFR were analyzed using a linear mixed-effects model for repeated measures as the primary analysis, with sensitivity analyses performed using last observation carried forward (LOCF) and imputation of graft loss or death as zero, where applicable.

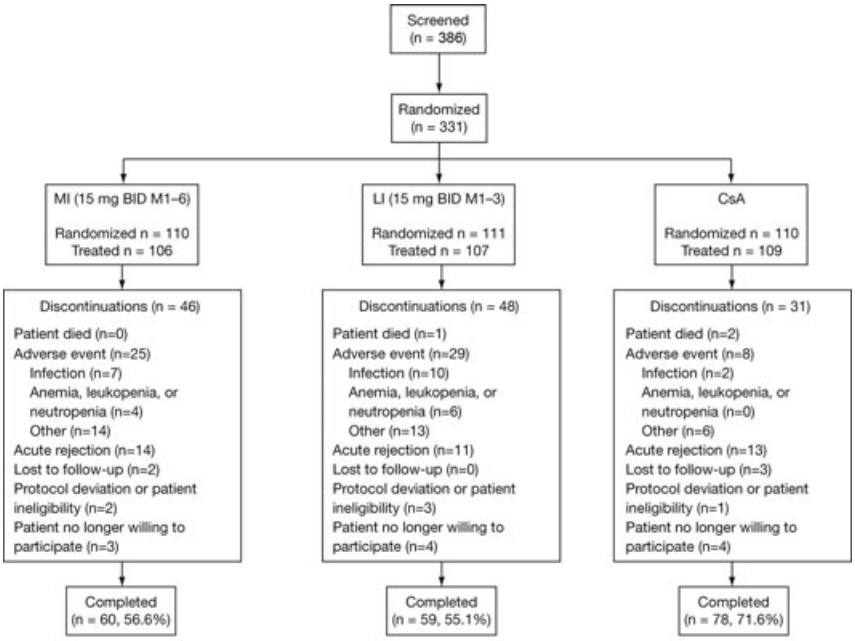

Figure 1: Patient disposition.

BID, twice daily; CsA, cyclosporine; LI, less intensive tofacitinib; M, Months; MI, more intensive tofacitinib.

Results

Patient disposition and demographics

In total, 331 patients were randomized and 322 patients received study treatment (106 in MI, 107 in LI and 109 in CsA; Figure 1). These patients were randomized from 13 February 2008 to 27 February 2009. Baseline characteristics were similar among the treatment groups (Table 1). More patients discontinued MI and LI than CsA prior to Month 12 (43.4% vs. 44.9% vs. 28.4%, respectively). A similar proportion of patients in each group discontinued due to lack of efficacy, but more patients in MI and LI discontinued because of infection or hematological abnormalities (Figure 1).

Acute rejection

The primary efficacy endpoint of 6-month incidence of clinical BPAR met noninferiority criterion for both MI and LI when compared with CsA (11.4% and 7.1% vs. 9.0%; Table 2; Figure 2, panel A). Similarly, the 6- and 12-month incidences of total BPAR for MI and LI were noninferior to CsA (Table 2; Figure 2, panel C). No clinically meaningful difference was observed between either MI or LI and CsA in the 12-month incidence of total BPAR in deceased donors or living donors, or severe cellular rejections (grade IIB or III). Antibody-mediated rejection of grade II or higher was observed in the CsA group only. Locally diagnosed and treated acute rejection was not more frequent in MI or LI compared with the CsA group. More black patients developed acute rejection while receiving tofacitinib compared with CsA but the difference did not reach statistical significance.

Renal function

The co-primary endpoint of measured GFR was significantly higher ($p < 0.01$) at Month 12 in MI and LI than CsA (64.6 mL/min vs. 64.7 mL/min vs. 53.9 mL/min, respectively; Table 3; Figure 2, panel B). This was also observed at Month 6. Similarly, estimated GFR values for MI and LI calculated from the MDRD and Nankivell equations were significantly higher than CsA at Months 6 and 12. Sensitivity analyses of estimated GFR based on LOCF and imputation of graft loss or death as zero supported these results. The higher estimated GFR values in MI and LI were observed as early as 1 month posttransplant and persisted through Month 12 (Figure 2, panel D).

Chronic allograft damage

At Month 12, significantly fewer ($p < 0.05$) patients in MI or LI developed chronic allograft nephropathy (CAN) according to the Banff 2003 criteria compared with CsA (Table 3). In particular, fewer patients in MI or LI developed grade-II or grade-III CAN. When Month 12 protocol biopsies were compared with implantation biopsies, fewer patients in MI or LI showed progression (increase in CAN grade or Banff chronicity score). With regard to the individual Banff chronic lesion scores, a significantly lower proportion of patients showed an increase in ci (interstitial fibrosis [IF]) and/or ct (tubular atrophy [TA]) scores in the tofacitinib groups (Table 3).

Patient and allograft survival

No statistically significant difference in patient survival was observed between either MI or LI and CsA (96.4% [MI] and 96.6% [LI] vs. 96.9% [CsA]; Table 2). Infection was implicated as the cause of death in six of eight patients.

Table 1: Baseline characteristics, demography and concomitant immunosuppressant dosage

	MI (N = 106)	LI (N = 107)	CsA (N = 109)
Recipient			
Age, years, mean (SD)	47.8 (12.1)	45.8 (12.6)	47.1 (12.9)
Male, n (%)	82 (77.4)	80 (74.8)	70 (64.2)
Race			
White, n (%)	66 (62.3)	71 (66.4)	78 (71.6)
Black, n (%)	16 (15.1)	21 (19.6)	12 (11.0)
Other, n (%)	24 (22.6)	15 (14.0)	19 (17.4)
HLA-mismatch, mean (SD)			
Deceased donors	3.1 (1.9)	3.1 (2.0)	3.4 (1.7)
Living donors	3.9 (1.5)	3.9 (1.4)	3.6 (1.3)
CMV D+R-, n (%)	17 (16.0)	16 (15.0)	10 (9.2)
Negative recipient EBV serostatus, n (%)	7 (6.6)	6 (5.6)	9 (8.3)
Diabetic pretransplant, n (%)	21 (19.8)	25 (23.4)	25 (22.9)
On dialysis pretransplant, n (%)	100 (94.3)	99 (92.5)	99 (90.8)
Donor			
Deceased, n (%)	65 (61.3)	65 (60.7)	67 (61.5)
Black, n (%)	8 (7.5)	11 (10.3)	5 (4.6)
Age, years, mean (SD)	42 (13)	42 (15)	40 (13)
Cold ischemic time (hours for deceased donors), median (interquartile range)	16.0 (9.3–20.0)	16.0 (10.0–21.4)	16.1 (11.6–20.0)
Concomitant immunosuppressant dosage (median)			
MMF dose (g/day) at Month 6	1.5	2.0	2.0
MMF dose (g/day) at Month 12	1.5	1.5	2.0
Prednisone dose (mg/day) at Month 12	5	5	5

CMV = cytomegalovirus; CsA = cyclosporine; EBV = Epstein-Barr virus; LI = less intensive tofacitinib; MI = more intensive tofacitinib; MMF = mycophenolate mofetil; PRA = panel-reactive antibody; SD = standard deviation.

Among surviving patients, graft failure occurred in two, five and one patients in the MI, LI and CsA groups, respectively. In the LI group, technical complications (surgical complications or renal artery/vein thrombosis) accounted for three of five cases of graft failure. In another LI patient who discontinued tofacitinib after one day, graft failure occurred due to acute rejection approximately 9 months posttransplant.

Safety and tolerability

Adverse events occurring in >10% of patients in any treatment group, and adverse events of special interest, are shown in Table 4. Serious infections and CMV disease (Figure 2, panel E) occurred more frequently in MI and LI than in the CsA group. Fewer patients in MI or LI developed NODAT or impaired fasting glycemia (24.2% [MI] and 17.8% [LI] vs. 38.2% [CsA]).

Malignancy developed in six patients in MI, one patient in LI and one patient in CsA. The six patients in MI included three cases of solid malignancy likely to have been preexisting at the time of transplantation (one case each of renal cell carcinoma and prostate cancer that occurred within 3 months posttransplant, and one case of prostate cancer in a patient with elevated prostate surface antigen level at the time of transplantation). Posttransplant lymphoproliferative disorder (PTLD) developed in two patients in MI and one patient in LI. After Month 12, two additional patients in the MI group developed PTLD. Among the five patients who developed PTLD, four were EBV seropositive at the time of transplantation.

More patients had hemoglobin levels <8 or <10 g/dL in MI and LI, and more patients had absolute neutrophil counts <500 or <1000 cells/μL in MI than in the CsA group (Table 4). Mean cell counts of CD3+ T cells and CD56+ NK cells were lower in MI and LI than CsA at Months 6 and 12 (Table 4).

At Month 12, total serum and LDL cholesterol levels were slightly higher in LI than in the CsA group, without a difference in the LDL/HDL ratio. However, lipid-lowering agents were used less frequently in the LI group. In MI and LI, fewer patients had ≥stage-1 hypertension at Month 6, and fewer patients used >2 antihypertensive medications at Months 6 and 12.

Pharmacokinetics and exposure-response analysis

Through Month 6, model-predicted MPA $AUC_{0–12}$ was 37.4% higher (90% confidence interval: 25.4, 50.6%) in the tofacitinib groups compared with the CsA group. Geometric mean (90% confidence interval) model-predicted MPA $AUC_{0–12}$ for MMF 1 g BID for the CsA group was 42.8 (39.0, 46.9) mg h/L. Exposure-response analysis indicated that at tofacitinib TWC2 below the median (125 ng/mL), the 12-month incidences of total BPAR, serious infections, and CMV disease were comparable to those in the CsA group (Figure 2, panel F), whereas higher

Table 2: Efficacy, death and graft loss

	MI (N = 106)		LI (N = 107)		CsA (N = 109)	
Efficacy	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
Patients with first clinical BPAR, n (%)[1]	11 (11.4)	11 (11.4)	7 (7.1)	7 (7.1)	9 (9.0)	9 (9.0)
Difference (60% CI)	2.5 (−1.2, 6.1)	2.5 (−1.2, 6.1)	−1.8 (−5.1, 1.5)	−1.8 (−5.1, 1.5)	–	–
Difference (95% CI)	2.5 (−6.0, 11.0)	2.5 (−6.0, 11.0)	−1.8 (−9.4, 5.8)	−1.8 (−9.4, 5.8)	–	–
Patients with first total BPAR, n (%)[1]	16 (16.1)	17 (17.4)	12 (12.4)	14 (15.4)	18 (17.7)	19 (18.8)
Difference (60% CI)	−1.7 (−6.2, 2.8)	−1.4 (−6.1, 3.2)	−5.4 (−9.6, −1.1)	−3.4 (−8.0, 1.3)	–	–
Difference (95% CI)	−1.7 (−12.1, 8.7)	−1.4 (−12.2, 9.3)	−5.4 (−15.3, 4.6)	−3.4 (−14.2, 7.4)	–	–

	Month 12	Month 12	Month 12
Total BPAR in deceased donor recipients, n (%)[1]	7 (11.8)	8 (13.9)	10 (16.4)
Total BPAR in living donor recipients, n (%)[1]	10 (25.7)	6 (18.0)	9 (22.3)
Total BPAR in black patients, n (%)[1]	4 (30.2)	4 (29.5)	1 (8.3)
Total BPAR: acute/active cellular rejection, n (%)	16 (15.1)	13 (12.1)	18 (16.5)
Grade IA	2 (1.9)	0	1 (0.9)
Grade IB	3 (2.8)	0	4 (3.7)
Grade IIA	7 (6.6)	11 (10.3)	8 (7.3)
Grade IIB	3 (2.8)	2 (1.9)	5 (4.6)
Grade III	1 (0.9)	0	0
Total BPAR: antibody-mediated rejection, n (%)	2 (1.9)	1 (0.9)	5 (4.6)
Grade I	2 (1.9)	1 (0.9)	1 (0.9)
Grade II	0	0	4 (3.7)
Grade III	0	0	0
Patients with locally diagnosed and treated acute clinical rejection (adverse event), n (%)[1]	26 (26.9)	18 (18.7)	25 (24.8)
Black patients, n (%)[1]	4 (28.2)	5 (27.0)	2 (16.7)
Repeat rejection, n (%)[1]	0	1 (1.5)	4 (4.5)
Death	Month 12	Month 12	Month 12
Patient survival at Month 12,%[1]	96.4	96.6	96.9
Deaths within 12 months, n	3	2	3
Cause of death	• Pneumonia, sepsis • Rhabdomyolysis, brain edema • Bronchopulmonary aspergillosis, brain infarction, aspiration pneumonia	• Cardiac arrest (electromechanical dissociation) • Bronchopulmonary aspergillosis	• Sepsis, brain infarction • Pneumonia • Peritonitis, sepsis
Graft loss	Month 12	Month 12	Month 12
Graft survival (death-censored) at Month 12,%[1]	98.0	94.2	99.1
Graft loss (excluding death) at Month 12, n	2	5	1
Cause of graft loss			
Acute rejection	-	2	-
Primary nonfunction	1	-	-
Surgical complication	-	1	-
Thrombosis	1	2	1

BPAR = biopsy-proven acute rejection; CI = confidence interval; CsA = cyclosporine; LI = less intensive tofacitinib; MI = more intensive tofacitinib. n = number of patients with condition.
[1]Kaplan–Meier estimates.

tofacitinib exposure was associated with evidence of over-immunosuppression or was associated with more infections and CMV. All five PTLD cases were associated with above-median tofacitinib TWC2s.

Discussion

The primary objectives of this study were to demonstrate noninferiority of tofacitinib over CsA in preventing acute rejection, and superiority of tofacitinib with respect to renal function. The rates of clinical BPAR and total BPAR in the three treatment arms fulfilled the prespecified criterion for noninferiority. The upper bounds of the 95% confidence intervals of the difference between MI or LI and CsA were also <12% (Table 2). The total BPAR rate in the CsA group (17.7% [Month 6] and 18.8% [Month 12]) was consistent with the range reported in the literature (11,12). Sub-group analyses did not reveal a higher rate of severe acute cellular rejection or humoral rejection in the tofacitinib groups.

The co-primary endpoint of measured GFR at Month 12 was significantly higher in both MI and LI compared with CsA (64.6 [MI] and 64.7 [LI] vs. 53.9 [CsA] mL/min)

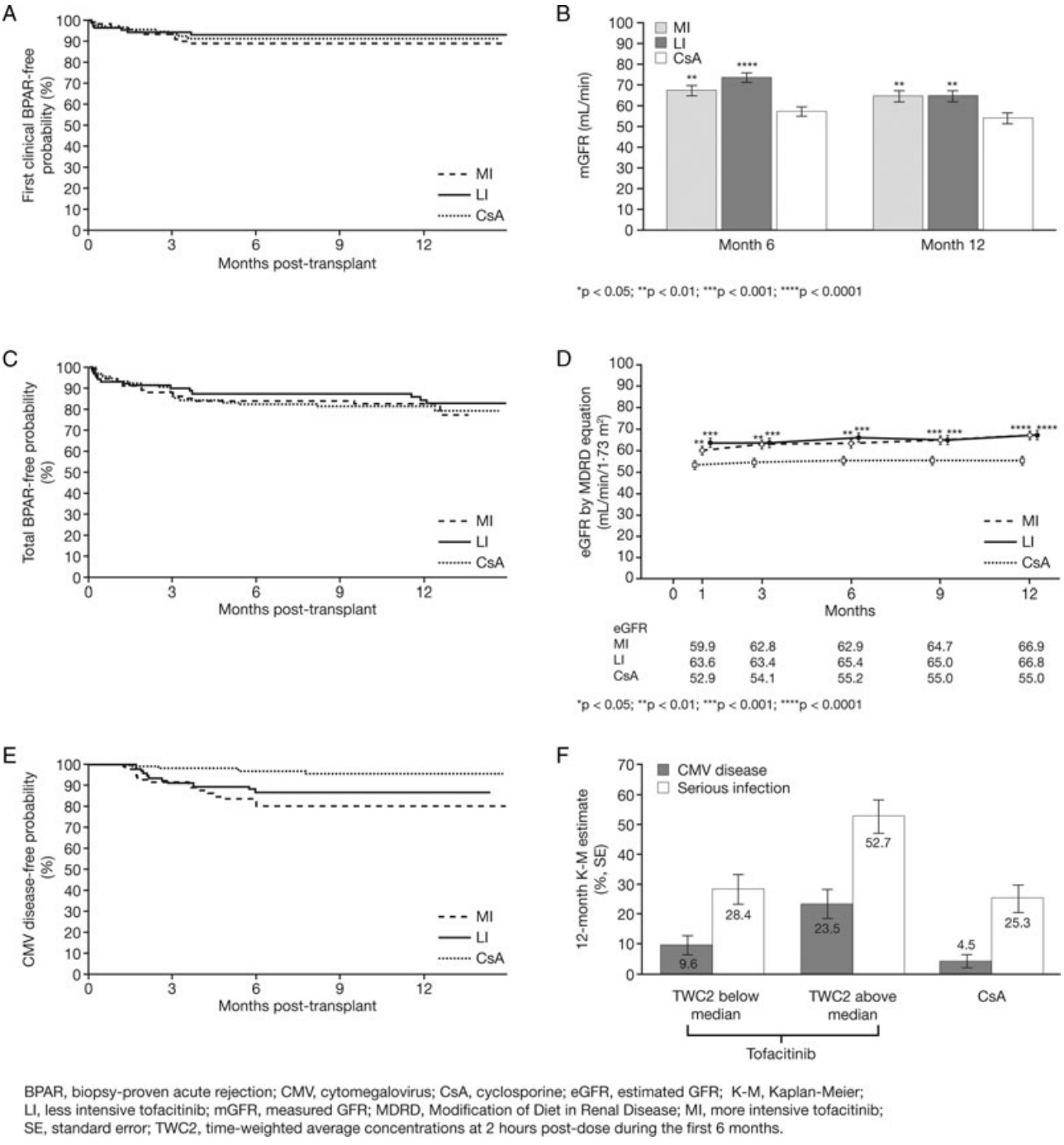

Figure 2: (Panel A) K-M survival curves for clinical BPAR. (Panel B) Least squares means of measured GFR at Months 6 and 12. (Panel C) K-M survival curves for total BPAR. (Panel D) Least squares means of estimated GFR calculated by the MDRD equation versus time. (Panel E) K-M survival curves for CMV disease through Month 12. (Panel F) Exposure-response analyses indicated that at tofacitinib exposure below the median, the 12-month incidences of CMV disease and serious infection were comparable to those in the CsA group.

(Table 3). As GFR in CNI-treated kidney transplant patients typically declines by 1–2 mL/min/year (13), the observed difference of approximately 10 mL/min between the tofacitinib groups and CsA is of clinical relevance. One-year renal function has been correlated with graft survival (14), and improved renal function in the tofacitinib groups at Month 12 may prove advantageous for long-term graft outcome.

Table 3: Renal function and allograft histology

	MI (N = 106)		LI (N = 107)		CsA (N = 109)	
Renal function	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
Measured GFR, mL/min, LSM (SE)	67.4 (2.6)	64.6 (2.7)	73.6 (2.5)	64.7 (2.6)	57.2 (2.3)	53.9 (2.4)
Difference (mL/min)	10.2**	10.6**	16.4****	10.8**	–	–
Estimated GFR (MDRD), mL/min/1.73 m^2, LSM (SE)	62.9 (2.0)	66.9 (2.1)	65.4 (2.1)	66.8 (2.1)	55.2 (1.9)	55.0 (1.9)
Difference, mL/min/1.73 m^2	7.7**	12.0****	10.2***	11.8****	–	–
Estimated GFR (MDRD, LOCF), mL/min/1.73 m^2, LSM (SE)	61.8 (2.0)**	64.3 (2.0)***	64.0 (2.0)***	64.6 (2.0)***	54.2 (1.9)	53.9 (1.9)
Estimated GFR (Nankivell, LOCF), mL/min, LSM (SE)	73.2 (1.9)*	75.6 (1.9)**	74.5 (1.9)**	75.4 (1.9)**	66.8 (1.8)	66.9 (1.8)
Estimated GFR (Nankivell, LOCF + imputed), mL/min, LSM (SE)	70.3 (2.4)	72.6 (2.4)*	71.1 (2.4)	71.5 (2.4)*	64.7(2.3)	64.8 (2.3)
Estimated GFR in deceased donor recipients (Nankivell, LOCF), mL/min, LSM (SE)	74.1 (1.9)*	78.1 (2.0)***	75.7 (2.0)**	77.6 (2.0)***	67.7 (1.8)	67.8 (1.9)
Serum creatinine, mg/dL, mean (SD)	1.32 (0.37)	1.20 (0.29)	1.26 (0.39)	1.21 (0.31)	1.42 (0.43)	1.44 (0.44)
Patients with DGF, n (%)	13 (12.3)		10 (9.4)		9 (8.3)	
DGF in deceased donor recipients, n (%)	11 (14.5)		6 (8.6)		8 (11.1)	
Patients with proteinuria						
>500 mg/day, n (%)	6 (9.2)	5 (8.6)	4 (6.0)	4 (7.0)	5 (6.3)	3(4.1)
>1500 mg/day, n (%)	0	1 (1.7)	0	0	1 (1.3)	0

Allograft histology	Month 12	Month 12	Month 12
Patients with CAN[1] n/N' (%)	13/52 (25.0)**	11/46 (23.9)*	28/58 (48.3)
Grade I	10 (19.2)	6 (13.0)	15 (25.9)
Grade II	2 (3.9)	4 (8.7)	7 (12.1)
Grade III	1 (1.9)	1 (2.2)	6 (10.3)
p-value of difference in overall distribution	0.0059	0.0111	–
Patients with increase in CAN[1] grades, n/N (%)	13/49 (26.5)	10/44 (22.7)*	23/51 (45.1)
Patients with increase in Banff chronicity score, n/N (%)	18/46 (39.1)*	19/43 (44.2)	29/48 (60.4)
Patients with increase in Banff chronic lesions scores, n/N (%)			
Increase in cg	0/46 (0)	0/43 (0)	0/48 (0)
Increase in ci	12/46 (26.1)*	10/43 (23.3)*	22/48 (45.8)
Increase in ct	13/46 (28.3)	10/43 (23.3)*	22/48 (45.8)
Increase in cv	11/46 (23.9)	11/41 (26.8)	16/47 (34.0)

Notes: LSM (SE) is based on random effects linear model for repeated measures. n, number of patients with condition. N, number of patients with both implantation and Month 12 biopsies. N', number of patients with Month 12 biopsy.
[1]According to Banff 2003 criteria.
p-value versus CsA: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$; nominal p-values ≥ 0.05 are considered not statistically significant.
CAN = chronic allograft nephropathy; cg = allograft glomerulopathy; ci = interstitial fibrosis; CsA = cyclosporine; ct = tubular atrophy; cv = vascular fibrous intimal thickening; DGF = delayed graft function; GFR = glomerular filtration rate; LI = less intensive tofacitinib; LOCF = last observation carried forward; LSM = least squares mean; MDRD = Modification of Diet in Renal Disease; MI = more intensive tofacitinib; SE = standard error; SD = standard deviation.

The lower prevalence of CAN in both tofacitinib groups was consistent with the observed improvement in GFR. An increase in the prevalence of CAN from implantation to Month 12 was seen in all treatment groups but less in the tofacitinib groups. The between-group difference in progression of allograft lesions from implantation to Month 12 was driven primarily by an increase in the severity of IF and TA, and to a lesser extent by an increase in arterial intimal thickening in the CsA group. This may indicate a long-term benefit from use of tofacitinib, as early tubulointerstitial

Table 4: Safety

	MI (N = 106)	LI (N = 107)	CsA (N = 109)
Adverse events (all causality) occurring >10% in any treatment group, n (%)			
Anemia	49 (46.2)	43 (40.2)	28 (25.7)
Leukopenia	31 (29.2)	19 (17.8)	12 (11.0)
Neutropenia	14 (13.2)	6 (5.6)	2 (1.8)
Abdominal distension	6 (5.7)	8 (7.5)	11 (10.1)
Abdominal pain	18 (17.0)	5 (4.7)	16 (14.7)
Constipation	36 (34.0)	38 (35.5)	30 (27.5)
Diarrhea	28 (26.4)	29 (27.1)	22 (20.2)
Nausea	29 (27.4)	27 (25.2)	24 (22.0)
Vomiting	17 (16.0)	13 (12.1)	19 (17.4)
Fatigue	9 (8.5)	15 (14.0)	11 (10.1)
Edema	15 (14.2)	11 (10.3)	12 (11.0)
Edema peripheral	25 (23.6)	19 (17.8)	30 (27.5)
Pyrexia	21 (19.8)	17 (15.9)	14 (12.8)
Transplant rejection	22 (20.8)	13 (12.1)	23 (21.1)
BK virus infection	15 (14.2)	19 (17.8)	6 (5.5)
CMV infection	14 (13.2)	9 (8.4)	3 (2.8)
CMV viremia	29 (27.4)	19 (17.8)	12 (11.0)
Urinary tract infection	25 (23.6)	27 (25.2)	27 (24.8)
Upper respiratory tract infection	17 (16.0)	9 (8.4)	17 (15.6)
Graft complication	12 (11.3)	17 (15.9)	10 (9.2)
Incision-site pain	9 (8.5)	11 (10.3)	3 (2.8)
Procedural pain	21 (19.8)	15 (14.0)	14 (12.8)
Blood creatinine increased	17 (16.0)	20 (18.7)	20 (18.3)
Weight increased	15 (14.2)	12 (11.2)	14 (12.8)
Fluid overload	11 (10.4)	5 (4.7)	6 (5.5)
Hyperglycemia	10 (9.4)	7 (6.5)	13 (11.9)
Hyperkalemia	18 (17.0)	20 (18.7)	14 (12.8)
Hyperlipidemia	10 (9.4)	10 (9.3)	13 (11.9)
Hypocalcemia	12 (11.3)	4 (3.7)	4 (3.7)
Hypokalemia	13 (12.3)	11 (10.3)	3 (2.8)
Hypophosphatemia	14 (13.2)	10 (9.3)	13 (11.9)
Back pain	7 (6.6)	12 (11.2)	4 (3.7)
Headache	13 (12.3)	21 (19.6)	14 (12.8)
Tremor	8 (7.5)	8 (7.5)	19 (17.4)
Insomnia	6 (5.7)	10 (9.3)	13 (11.9)
Dysuria	13 (12.3)	8 (7.5)	8 (7.3)
Hematuria	16 (15.1)	11 (10.3)	11 (10.1)
Cough	16 (15.1)	7 (6.5)	7 (6.4)
Dyspnea	11 (10.4)	9 (8.4)	7 (6.4)
Acne	14 (13.2)	18 (16.8)	4 (3.7)
Rash	12 (11.3)	6 (5.6)	7 (6.4)
Hypertension	24 (22.6)	23 (21.5)	30 (27.5)
Hypotension	18 (17.0)	13 (12.1)	7 (6.4)
AEs of special interest at Month 12, n (%)			
Serious infections[1]	37 (44.5)**	33 (37.0)	24 (25.3)
Clinically significant infection[1]	38 (45.2)	38 (42.8)	32 (32.8)
CMV disease (including CMV syndrome)[1]	16 (19.5)**	11 (13.3)*	4 (4.5)
BK virus nephropathy[1]	2 (2.6)	3 (3.9)	1 (1.1)
Malignancy	6 (5.7)	1 (0.9)	1 (0.9)
PTLD[1]	2 (3.1)	1 (1.6)	0
NODAT[1]	7 (9.9)	6 (9.3)	14 (20.8)
IFG[1]	10 (17.9)	6 (10.4)*	19 (28.6)
NODAT/IFG[1]	15 (24.2)	11 (17.8)*	26 (38.2)

damage has been shown to predict long-term graft survival (15). Early-onset IF–TA may result from unchecked alloimmunity, chronic antibody-mediated rejection or direct CNI toxicity, though the relative contribution of these factors continues to be debated and will vary between individuals (16–18). Similarly, the mechanism(s) through which tofacitinib is associated with less IF–TA is unknown, though the absence of CNI is likely to be a contributing factor.

Table 4: Continued.

Laboratory and vital signs	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
Hemoglobin, g/dL, mean (SD)	12.0 (1.8)	12.9 (1.7)	12.2 (1.5)	12.9 (1.4)	12.6 (1.7)	13.0 (1.5)
Patients with hemoglobin <8 g/dL, n (%)	16 (15.2)		11 (10.6)		8 (7.4)	
Patients with hemoglobin <10 g/dL, n (%)	68 (64.8)		68 (65.4)		55 (50.9)	
Absolute neutrophil count, K/mm^3, mean (SD)	4.0 (2.3)	4.0 (1.9)	3.6 (2.4)	3.8 (1.7)	4.2 (1.9)	4.3 (2.2)
Patients with neutrophil counts <500/mm^3, n (%)	4 (3.8)		2 (1.9)		2 (1.9)	
Patients with neutrophil counts <1000/mm^3, n (%)	19 (18.1)***		4 (3.8)		4 (3.7)	
Total WBC count, K/mm^3, mean (SD)	5.7 (2.7)	5.7 (2.2)	5.3 (2.4)	5.7 (2.1)	6.4 (2.3)	6.7 (2.4)
Absolute lymphocyte count, K/mm^3, mean (SD)	1.1 (0.6)	1.1 (0.5)	1.2 (0.5)	1.2 (0.6)	1.6 (0.7)	1.7 (0.6)
Absolute platelet count, K/mm^3, mean (SD)	265 (107)	246 (93)	253 (91)	242 (70)	245 (61)	239 (64)
Absolute CD3+ T cell count, cells/μL mean (SD)	812 (379)	797 (369)	970 (410)	956 (522)	1268 (693)	1353 (648)
Absolute CD56+ NK cell count, cells/μL, mean (SD)	68 (64)	96 (101)	65 (49)	77 (58)	170 (123)	169 (123)
Total serum cholesterol, mg/dL, LSM	201	195	204	209	200	194
Serum LDL cholesterol, mg/dL, LSM	111	111	110	115	114	108
Serum LDL/HDL ratio, LSM	2.3	2.2	2.4	2.3	2.4	2.2
Patients who used lipid-lowering drugs, n (%)	38 (56.7)	28 (59.6)	26 (37.7)	17 (37.8)	44 (52.4)	38 (55.9)
Patients with ≥stage-1 hypertension, n (%)	17 (25.8)****	21 (35.6)	26 (37.7)	20 (33.9)	39 (48.8)	32 (41.6)
Patients who used >2 anti-hypertensive medications, n (%)	32 (47.8)**	24 (51.1)*	38 (55.1)*	25 (55.6)	59 (70.2)	49 (72.1)

[1]Kaplan–Meier estimates.

p-value versus CsA: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

CMV = cytomegalovirus; CsA = cyclosporine; IFG = impaired fasting glycemia; LI = less intensive tofacitinib; LSM = least squares mean; MI = more intensive tofacitinib; NODAT = new-onset diabetes after transplantation; PTLD = posttransplant lymphoproliferative disorder; WBC = white blood cell.

The main concerns identified with the tofacitinib regimens in this study were the increased rates of infection and PTLD. Beyond Month 12, two additional patients in the MI group developed PTLD. These findings suggest an excessive level of immunosuppression with the regimens used in the study and correlated with elevated tofacitinib exposure. In this study, tofacitinib dose reduction was not permitted until Month 3 (LI) or Month 6 (MI). Among tofacitinib-treated patients, the incidence of CMV disease was reduced by approximately one-third by the use of ganciclovir/valganciclovir prophylaxis (data not shown). Exposure-response analysis indicated that below-median tofacitinib exposure was associated with a lower incidence of infection while providing comparable protection from total BPAR as compared to higher tofacitinib exposure.

The higher incidence of anemia and neutropenia in the tofacitinib groups in the early posttransplant period may be partly due to inhibition of JAK2, a tyrosine kinase that mediates hematopoiesis. It should be noted that, due to a lack of pharmacokinetic interaction between MPA and tofacitinib, MPA exposure was higher among tofacitinib-treated patients in the first 6 months posttransplant. A decrease of the mean MMF dose in tofacitinib-treated patients later posttransplant (1.5 g/day in MI and LI vs. 2.0 g/day in the CsA group at Month 12; Table 1) would have resulted in more comparable MPA exposure among the treatment groups. Indeed the elevated MPA exposure in tofacitinib-treated patients may have partly accounted for the efficacy of the MI and LI groups, as well as some adverse events, such as over-immunosuppression and hematological abnormalities. Compared with CsA, fewer patients in the tofacitinib groups experienced NODAT or impaired fasting glycemia, though this difference did not reach statistical significance. If confirmed, the lower diabetogenicity of a tofacitinib-based regimen will be important given the adverse impact of NODAT on patient and graft outcome (19).

A potential limitation of this study is the use of a CsA-based control group. Tacrolimus is now the most frequently used CNI in kidney transplantation, largely attributable to the lower rates of acute rejection reported with tacrolimus. However, very low rejection rates can now be achieved with CsA (20), and recent studies with the microemulsion formulation of CsA have reported similar rejection rates compared with tacrolimus (21–24). Therefore, this study remains relevant to clinical practice. In addition, discontinuation rates were high in all three treatment groups, ranging from 28% in the CsA group to 44–45% in the tofacitinib groups. The discontinuation rate due to lack of efficacy was similar in each group, suggesting that the improved renal function in MI and LI cannot be attributed to a bias in selecting nonrejecting patients.

The overall findings of this Phase 2b study suggest that tofacitinib, when combined with MPA at conventional doses, is effective in preventing allograft rejection and has a beneficial effect on renal allograft function and parenchymal preservation. However, this result was achieved at the expense of hematological toxicity and over-immunosuppression as demonstrated by increased incidences of serious infection, opportunistic viral infection and PTLD. Exposure-response analyses have identified tofacitinib levels that are tentatively associated with lower infection risk without loss of efficacy. This suggests that adjustments to the tofacitinib regimens used in this study may permit the benefits of improved GFR and less CAN without over-immunosuppression, indicating the need for additional concentration-controlled studies to optimize tofacitinib-based immunosuppression in kidney transplant patients. Overall, this study suggests that tofacitinib has the potential to be used in a CNI-free regimen for the prevention of renal allograft rejection.

Acknowledgments

This research was sponsored by Pfizer Inc. Editorial support was provided by Gary Dever, PhD, and Karen Irving, PhD, at Complete Medical Communications and was funded by Pfizer Inc. The authors would like to thank the staff, patients and investigators involved in this study, as well as Wenjin Wang, PhD, and Manisha Lamba, PhD, of Pfizer Inc.

We gratefully acknowledge the contribution of the principal investigators from the A3921030 Study Group: Matthew Cooper, University of Maryland Medical Center; Venkat Ram Peddi, California Pacific Medical Center; Flavio Vincenti, University of California San Francisco Medical Center; Steven Marc Steinberg, California Institute of Renal Research; Jonathan Bromberg, Mount Sinai School of Medicine; Daniel Conlon Brennan, Washington University School of Medicine; Diane Marie Cibrik, University of Michigan Health System; Alexander Clark Wiseman, University of Colorado Health Sciences; Khalid M. H. Butt, Westchester Medical Center; Junaid Ahmed, LifeLink HealthCare Institute; Randal Detwiler, University of North Carolina; Youmin Wu, University of Arkansas for Medical Sciences; Shamkant Mulgaonkar, St Barnabas Medical Center; Atsushi Yoshida, Henry Ford Hospital; Alan H. Wilkinson, UCLA Kidney Transplant Research Center; Goran B. Klintmalm, Baylor University Medical Center; Herwig Ulf, Meier-Kriesche University of Florida; Stephan Busque, Stanford School of Medicine; Didier Mandelbrot, Beth Israel Deaconess Medical Center; Anil Kumar, Hahnemann University Hospital; Mark Dale Stegall, Mayo Clinic; Michael Jack Germain, Western New England Renal and Transplant Associates; John J. Friedewald, Northwestern University-Feinberg School of Medicine; J. Michael Millis, University of Chicago; Douglas James Norman, Oregon Health & Sciences University; Stanley C. Jordan, Cedars-Sinai Medical Center; Angello Lin, Medical University of South Carolina; Sanjay Kulkarni, Yale University School of Medicine; Allan Gilbert Murray, University of Alberta Hospital; Valter Duro Garcia, Irmandade da Santa Casa de Misericordia de Porto Alegre Hospital Dom Vicente Scherer; Helio Tedesco Silva, Hospital do Rim e Hipertensao; Federico Oppenheimer Salinas, Hospital Clinic Provincial de Barcelona; Jose Maria Grinyo, Boira Hospital Universitari De Bellvitge; Marco Castagneto, Universita' Cattolica del Sacro Cuore; Sergio Stefoni, Universitaria di Bologna; Anders Hartmann, Rikshospitalet-Radiumhospitalet HF; Magdalena Durlik, SPZOZ Szpital Kliniczny Dzieciatka Jezus Centrum Leczenia Obrazen; Marian Klinger, SPZOZ Akademicki Szpital Kliniczny im; Christophe Legendre, Hopital Necker; Magali Giral, CHU Nantes; Fernando Nolasco, Hospital Curry Cabral; Alfredo Mota, Hospitais da Universidade de Coimbra; Willem Weimar, Erasmus Medisch Centrum; Stefan Vitko, Institut Klinicke a Experimentalni Mediciny Transplantcentrum; Yves Vanrenterghem, Universitaire Ziekenhuizen Leuven; Daniel Abramowicz, Hopital Erasme/Nephrologie; Bjoern Nashan, Universitaetsklinikum Hamburg; Klemens Budde, Centrum 13 Medizinische Klinik; Lionel Rostaing, CHU Rangueil-Service de Néphrologie; Michele Kessler, CHRU de Nancy-Brabois; Josette Eris, Royal Prince Alfred Hospital; Philip O'Connell, Westmead Hospital; Graeme R. Russ, The Queen Elizabeth Hospital; Solomon Cohney, Royal Melbourne Hospital; John Kanellis, Monash Medical Centre; Duck Jong Han, Asan Medical Center; Yon Su Kim, Seoul National University Hospital; Yu Seun Kim, Yonsei University College of Medicine Severance Hospital.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*:

Dr. Vincenti has received grants from Pfizer Inc., Astellas, Novartis, Bristol-Myers Squibb, and Amgen.

Dr. Tedesco Silva has received grants from Pfizer Inc.; and has acted as a consultant for, and has received payment for lectures from Pfizer Inc., Novartis, and Bristol-Myers Squibb.

Dr. Busque has received grants from Novartis.

Dr. O'Connell has acted as a consultant for, and has received travel support from, Pfizer Inc.; is a member of the board for Novartis, Roche, Janssen-Cilag, and Bristol-Myers Squibb; and has received payment for lectures and travel support from Astellas.

Dr. Friedewald has no conflicts of interest.

Dr. Cibrik has acted as a consultant for Pfizer Inc., Novartis, and Tolera Therapeutics.

Dr. Budde has received a grant from Pfizer Inc; has acted as a consultant for Pfizer Inc., Novartis, Life Cycle Pharma, Bristol-Myers Squibb, Pfizer Inc., TCL Pharma, and Hexal; has provided expert testimony for Fitzpatrick, Cella, Harper and Scinto (on behalf of Novartis); and has received payment for lectures from Astellas, Novartis, Life-Cycle Pharma, Wyeth, Pfizer Inc., Roche AG, Bristol-Myers Squibb, and Siemens.

Dr .Yoshida has no conflicts of interest.

Dr. Cohney has acted as a consultant and member of the board for Novartis and Wyeth; has received grants from Roche, Amgen, and Janssen-Cilag; and has received payment for lectures from Bristol-Myers Squibb and Roche.

Dr. Weimar has received grants from Pfizer Inc., Genzyme, Roche, and Novartis; has acted as a consultant for Novartis, Astellas, and Wyeth; and has received payment for lectures from Astellas.

Dr. Kim has no conflicts of interest.

Dr. Lawendy is an employee of Pfizer Inc. and holds stock/stock options in Pfizer Inc.

Dr. Lan is an employee of Pfizer Inc.

Dr. Kudlacz is an employee of Pfizer Inc. and holds stock/stock options in Pfizer Inc.

Dr. Krishnaswami is an employee of Pfizer Inc. and holds stock/stock options in Pfizer Inc.

Dr. Chan is an employee of Pfizer Inc., holds stock/stock options in Pfizer Inc., and has received travel support from Pfizer Inc.

This research was sponsored by Pfizer Inc.

References

1. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4: 378–383.
2. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003; 349: 2326–2333.
3. Flechner SM. Sirolimus in kidney transplantation indications and practical guidelines: De novo sirolimus-based therapy without calcineurin inhibitors. Transplantation 2009; 87: S1–S6.
4. Srinivas TR, Schold JD, Guerra G, Eagan A, Bucci CM, Meier-Kriesche HU. Mycophenolate mofetil/sirolimus compared to other common immunosuppressive regimens in kidney transplantation. Am J Transplant 2007; 7: 586–594.
5. Vincenti F, Ramos E, Brattstrom C, et al. Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. Transplantation 2001; 71: 1282–1287.
6. Weir MR, Diekmann F, Flechner SM, et al. mTOR inhibition: The learning curve in kidney transplantation. Transpl Int 2010; 23: 447–460.
7. 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.
8. Racusen LC, Colvin RB, Solez K, et al. Antibody-mediated rejection criteria—An addition to the Banff 97 classification of renal allograft rejection. Am J Transplant 2003; 3: 708–714.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461–470.
10. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. Predicting glomerular filtration rate after kidney transplantation. Transplantation 1995; 59: 1683–1689.
11. 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.
12. Silva HT, Jr., Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant 2007; 7: 595–608.
13. Gill JS, Tonelli M, Mix CH, Pereira BJ. The change in allograft function among long-term kidney transplant recipients. J Am Soc Nephrol 2003; 14: 1636–1642.
14. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62: 311–318.
15. Nankivell BJ, Fenton-Lee CA, Kuypers DR, et al. Effect of histological damage on long-term kidney transplant outcome. Transplantation 2001; 71: 515–523.
16. Gaston RS. Chronic calcineurin inhibitor nephrotoxicity: Reflections on an evolving paradigm. Clin J Am Soc Nephrol 2009; 4: 2029–2034.
17. Gaston RS, Cecka JM, Kasiske BL, et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation 2010; 90: 68–74.
18. Yates PJ, Nicholson ML. The aetiology and pathogenesis of chronic allograft nephropathy. Transpl Immunol 2006; 16: 148–157.
19. Hjelmesaeth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 2006; 69: 588–595.
20. 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.
21. Goldfarb-Rumyantzev AS, Smith L, Shihab FS, et al. Role of maintenance immunosuppressive regimen in kidney transplant outcome. Clin J Am Soc Nephrol 2006; 1: 563–574.
22. Kaplan B, Schold JD, Meier-Kriesche HU. Long-term graft survival with neoral and tacrolimus: a paired kidney analysis. J Am Soc Nephrol 2003; 14: 2980–2984.
23. Opelz G, Dohler B. Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. Transplantation 2009; 87: 795–802.
24. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007; 7: 1506–1514.