Efficacy and Safety of Tacrolimus-Based Maintenance Regimens in De Novo Kidney Transplant Recipients: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Financial support: This study was sponsored by Astellas

Conflict of interest: All authors report non-financial support from Astellas during the conduct of the study. Additionally, RC and MTA are employees of Astellas, and WPY received personal fees from ICON Clinical Research Limited during the conduct of the study.

Background: Tacrolimus is an established component of immunosuppressive regimens for kidney transplant recipients (KTRs); however, data comparing long-term outcomes between formulations are lacking. We conducted a systematic literature review and network meta-analysis assessing tacrolimus (primarily Advagraf [once-daily] and Prograf [twice-daily])-based maintenance regimens.

Material/Methods: Embase, MEDLINE, and Cochrane databases and congress proceedings were searched to identify studies of adult de novo KTRs who received tacrolimus-based therapy in phase II/III randomized controlled trials. Outcomes were acute rejection, graft/patient survival, and incidence of new-onset diabetes mellitus after transplantation (NODAT) and cytomegalovirus (CMV) infection. Bayesian network meta-analysis was used to analyze treatment effects on graft/patient survival.

Results: Sixty-eight publications (61 primary) were included. Of 21 publications reporting graft rejection following Advagraf or Prograf treatment in ≥1 study arm, 12-month biopsy-proven acute rejection (BPAR) ranged from 3.3% with Prograf to 55.0% with mycophenolic acid (MPA)+corticosteroids (CS); >24 month BPAR ranged from 0% to 58.7% (the latter with bleselumab-based therapy). Fourteen publications reported graft loss following Advagraf (0-9.6%) or Prograf (0-7.5%). Patient mortality ≤24 months after transplantation (14 publications) ranged from 0% to 8.1% with Advagraf or Prograf. Advagraf+MPA+CS and reference treatment, Prograf+MPA+CS, were associated with a similar risk of graft loss (odds ratio 1.19; 95% credible-interval 0.51, 3.06) and mortality (odds ratio 1.21; 95% credible-interval 0.1557, 9.03). Incidence of NODAT and CMV varied by treatment arm.

Conclusions: Graft loss and patient mortality rates were generally comparable between Advagraf- and Prograf-based regimens. Further prospective studies are needed to evaluate longer-term outcomes.

Keywords: Immunosuppression • Kidney Transplantation • Maintenance • Meta-Analysis • Review • Tacrolimus

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/933588
Background

Chronic kidney disease results in reduced kidney function, with stage 5 chronic kidney disease occurring when the estimated glomerular filtration rate (eGFR) is below 15 mL/min/1.73 m² [1,2]. Patients with stage 5 chronic kidney disease require either dialysis or kidney transplantation, with transplantation the preferred strategy owing to improved quality of life and life expectancy and superior cost-effectiveness compared with dialysis [3]. However, improvements in immunosuppressive regimens are needed to optimize long-term post-transplant outcomes. In particular, there is a need to improve adherence to immunosuppressive regimens. Non-adherence increases the likelihood of graft rejection [4-6], whereas simplifying treatment can help improve adherence among patients taking immunosuppressive regimens [6]. In a meta-analysis of 14 publications, the median proportion of non-adherent patients between kidney transplantation and the time of the study was 22.3%, and in turn, non-adherence was associated with a median of 36.4% of graft losses, ranging from 7.1% to 80.0% [4].

For over 2 decades, tacrolimus (TAC) has been an established component of maintenance immunosuppressive regimens following kidney transplantation. A once-daily (QD), prolonged-release formulation (Advagraf®) is available, which may improve overall adherence compared with twice-daily (BID) dosing, especially in transplant recipients likely to be non-compliant with their treatment regimen [7-9]. While improved adherence to maintenance immunosuppressive regimens could reduce the risk of kidney transplant rejection, there is a need for further analysis of potential differences in long-term outcomes between the QD and BID dosing regimens. We conducted a systematic literature review and network meta-analysis to assess TAC-based maintenance regimens in kidney transplant recipients, with a focus on identifying differences in patient and graft survival between TAC QD and BID dosing regimens.

Material and Methods

Systematic Literature Review

Searches were consistent with recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, Centre for Reviews and Dissemination guidelines, and Cochrane Collaboration handbook [10-12]. Searches included free-text and comprehensive disease terms, combined with filters to identify randomized controlled trials published by the Scottish Intercollegiate Guidelines Network. The search had neither time nor language restrictions. Searches were performed using Embase (January 1, 1974, to October 3, 2019), Ovid MEDLINE (January 1, 1946, to October 1, 2019) and Evidence-Based Medicine Reviews: Cochrane Central Register of Controlled Trials (August 2019). The search strategies can be found in Supplementary Table 1. The proceedings from 2017 to 2019 for the American Transplant Congress and the Annual Congress of the European Renal Association – European Dialysis and Transplant Association were screened. Abstracts were also searched for the previous 2 International Conferences of the Transplantation Society (2016 and 2019) and the Congresses of the European Society for Organ Transplantation (2017 and 2019).

Eligibility criteria for the efficacy and safety studies followed those proposed in the Population, Intervention, Comparator, Outcomes, and Study design statement. Key eligibility criteria included adult (aged ≥18 years) de novo kidney transplant patients receiving TAC-based monotherapy or combination immunosuppressive regimens. Efficacy outcomes were acute rejection and graft and patient survival. Safety outcomes were cytomegalovirus (CMV) infection and new-onset diabetes after transplant (NODAT). Only phase II/III randomized controlled trials published in English and including regimens used as maintenance therapy were considered. Secondary publications were included if they contained data relevant to this study, beyond those cited in the primary report.

Two reviewers examined each abstract and each full-text paper. Any studies queried at either stage were referred to a third reviewer, and consensus was reached. After the initial search and screening of full text articles, additional criteria were applied. Advagraf was launched in 2007, and outcome data with this formulation was mostly published from 2008 onward. Since combination immunosuppressive therapies after kidney transplantation have generally remained the same clinically since 2008 [13], publications before 2008 were excluded. Publications reporting only efficacy and safety outcomes before 6 months after transplantation were not considered. Treatment modifications after randomization can introduce a source of bias. Therefore, studies for which 1 or more treatments were withdrawn over the course of the trial were excluded.

The following data were extracted independently by 1 reviewer directly into a template: study characteristics (including study design, inclusion/exclusion criteria, interventions, sample size, and primary endpoints), patient baseline characteristics (including recipient and donor age, sex, race, body mass index [BMI], previous transplant history, and living and/or deceased donors), efficacy outcomes (patient survival, graft survival, acute rejection, and/or biopsy-proven acute rejection [BPAR], and timing of rejection), and safety outcomes. A second reviewer validated all data extracted. Discrepancies were resolved by discussion with a third reviewer. The risk of bias was assessed based on the recommendations of the Cochrane guide for systematic reviews [11].
Network Meta-Analysis

The network meta-analysis was conducted according to the International Society for Pharmacoeconomics and Outcomes Research Taskforce guidelines [14] using methodologies based on the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document [15]. In line with the focus of the present study, the efficacy endpoints analyzed were graft loss and mortality, examined for the period 6 to 12 months after transplantation. Rejection, NODAT, and CMV infection were not assessed. The studies evaluated a variety of TAC doses, and reporting was heterogeneous. Therefore, the number of comparators was consolidated by combining treatments based on whether TAC was given QD or BID. The analysis assumed that maintenance therapies accounted for most of the treatment effects at 6 to 12 months. Data from the upper limit were used when studies reported outcomes for a time range.

Mycophenolate mofetil (MMF) is hydrolyzed to mycophenolic acid (MPA). Therefore, MMF and MPA were combined. All treatment combinations with MMF were labeled as MPA for consistency. The treatment of TAC BID plus MPA plus a corticosteroid (CS) was included in most networks and was therefore chosen as the reference treatment. Pairwise comparisons between all included treatments were used in the base case and meta-regression analyses.

The proportion of patients who experienced graft loss and mortality was modeled over 6 to 12 months [16]. The effect of race (White vs Black and/or Asian) as a covariate was included in the linear predictor model for each endpoint analysis. Imputed values were used for missing data. Estimates of the treatment effect were iteratively sampled using Bayesian methods. For binary endpoints, the mean log odds ratio (OR) was calculated. The credible intervals (CrI) were estimated. A 95% CrI indicates that there is a 95% probability that the true value of the parameter lies within the lower 2.5 and upper 97.5 percentiles. CrIs that included 1 were deemed to signify no significant difference in the effects of 2 treatments. Forest plots were constructed for graft loss and mortality. Meta-regression analyses were conducted to evaluate the effect of the proportion of White race in the patient population on both graft loss and mortality.

Results

Systematic Literature Review

Overview of included studies

Following removal of duplicates, abstracts for 3574 unique publications were screened. Subsequently, 3288 publications were excluded, and 286 full-text articles were screened (Figure 1). Most conference abstracts were secondary to a primary full-text publication; however, 18 were included. Following full-text review, 78 publications detailing 61 primary articles (55 full text, 6 conference abstracts) and 17 secondary articles (5 full text, 12 conference abstracts) were included. Of these, 10 conference abstracts were secondary publications that did not contain any additional data to the primary publication. Therefore, this review focuses on 68 publications (61 primary and 7 secondary studies) that report efficacy and/or safety data (Table 1 and Supplementary Table 2) [17-79]. Among these publications, the most frequently evaluated regimens were combinations of TAC BID+MPA+CS (41 studies) and TAC QD+MPA+CS (22 studies). In studies in which the authors specified the name of the TAC formulation, Prograf was the most frequently used (21 studies); Advagraf (including Astagraf XL® and Graceptor®) was assessed in 8 studies.

Patient Demographics and Characteristics

Table 2 and Supplementary Table 3 provide a summary of the key baseline characteristics among the 55 primary publications (ie, after excluding secondary publications [to avoid duplication] and conference abstracts [due to limited information]). Of the 20 primary studies in which 1 or more treatment arms used Advagraf or Prograf, mean or median age was reported in all studies except 1 (De Graav et al [25]). Mean age ranged from 29.36 years in the TAC BID+MPA+CS arm of Bakr et al to 53.60 years in the TAC BID+MPA+CS arm of Ferguson et al (Table 2) [22,28]. The proportion of female patients was also reported in all studies except 1 (Asher et al [21]). The percentage of female patients ranged from 17.1% of 35 patients in the TAC BID+MPA+CS arm of Arns et al to 76.2% of 21 patients in the TAC BID+sirolimus (SRL)+CS arm of Chen et al [19,23]. The proportion of female patients was ≤35% of the population in at least 1 study arm in 14 studies.

Six of the 20 primary studies, in which 1 or more treatment arms used Advagraf or Prograf, measured BMI at baseline, with mean values that varied from 21.8 kg/m² to 29.2 kg/m² [17,19,24,31,36,80]. Based on 2 studies, the percentage of patients with diabetes in individual treatment arms was between 6.9% of 390 patients and 28.3% of 212 patients [26,37]. People of White race (11 studies) accounted for between 65.8% of 243 and 95.8% of 309 patients in individual treatment arms [17,19,24-26,28,29,32,35,37,80]. People of Black race accounted for between 0.9% of 117 and 26.7% of 243 patients in individual treatment arms [17,25,26,28,29,32,35,37,80]. Ten studies reported the proportions of patients of Asian race, which varied from 0% of 107 to 100% of 20 to 63 patients in individual treatment arms [17,18,23,25,26,32,35,37,80] (Table 2).
Acute Rejection and Biopsy-Proven Acute Rejection

Overall, 64 studies reported rates of acute rejection and BPAR (Table 3 and Supplementary Table 4). Of the 21 studies that reported on graft rejection following treatment with Advagraf or Prograf (Table 3), the rates of BPAR at 12 months varied from 3.3% (1/30 patients) and 3.8% (1/26 patients) with TAC BID+MPA+CS and SRL+CS, respectively, to 54.2% (of 296 patients) with SRL+MPA+CS and 55.0% (11/20 patients) with MPA+CS [25,26,28]. Liu et al reported BPAR at 24 months, which was 5.6% (2/36 patients) and 8.3% (3/36 patients) with cyclosporin (CsA) BID+MPA+CS and TAC BID+MPA+CS, respectively [36].

Four of the studies that included treatment with Advagraf or Prograf reported outcomes beyond 24 months [20,30,34,80]. Hamdy et al reported no rejection episodes in 132 patients beyond the second year of follow-up [30]. Harland et al reported BPAR rates of 34.1% (15/44 patients), 35.4% (17/48 patients), and 58.7% (27/46 patients) in the TAC BID+bleselumab (BLES)+CS, TAC BID+MPA+CS, and BLES+MPA+CS arms, respectively, at 36 months [80]. Between 6 and 36 months after transplantation in the ATLAS study, the BPAR rates were 2.1% (3/143 patients), 2.2% (3/139 patients), and 2.9% (4/139 patients) in the TAC BID, TAC BID+MPA, and TAC BID+MPA+CS arms, respectively [34]. Arriola et al reported acute rejection rates of 12.7% (of 55 patients) and 11.5% (of 52 patients) in the TAC BID+MPA+SRL+CS and TAC QD+MPA+everolimus (EVR)+CS arms, respectively [26].
Table 1. Overview of included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study                        | TAC formulation | Phase | Blinding | Center       | Region*       | Sample size | Efficacy outcomes | Safety outcomes | No. of arms |
|------------------------------|-----------------|-------|----------|--------------|---------------|-------------|-------------------|-----------------|-------------|
| Albano 2013                  | Advagraf, Prograf | 4     | Open-label | Multicenter  | International | 1251        | Y                 | Y               | 4           |
| Anuttrakulchai 2019          | Prograf         | –     | Open-label | Single-center | Asia          | 126         | Y                 | N               | 2           |
| Arriola 2018 (CA)            | Advagraf, Prograf | –     | –        | –            | –             | 107         | Y                 | Y               | 2           |
| Asher 2014                   | Prograf         | –     | Open-label | Single-center | Europe        | 62          | Y                 | N               | 2           |
| Bakr 2018                    | Advagraf, Prograf | –     | –        | Single-center | Africa        | 99          | Y                 | N               | 2           |
| Chen 2008                    | Prograf         | –     | Single-blind | –            | Asia          | 41          | Y                 | Y               | 2           |
| Cockfield 2019               | Advagraf        | –     | Open-label | Multicenter  | North America | 281         | Y                 | Y               | 2           |
| De Graa 2017                 | Prograf         | –     | Open-label | Single-center | Europe        | 40          | Y                 | N               | 2           |
| Demirbas 2009                | Prograf         | 4     | Open-label | Multicenter  | International | 1645        | Y                 | Y               | 4           |
| Ekberg 2010 (SP to Demirbas 2009) | Prograf      | 4     | Open-label | Multicenter  | International | 1645        | Y                 | Y               | 4           |
| Ferguson 2011                | Prograf         | 2     | Open-label | Multicenter  | International | 89          | Y                 | Y               | 3           |
| Frei 2010 (SP to Demirbas 2009) | Prograf      | 4     | Open-label | Multicenter  | International | 1645        | Y                 | N               | 4           |
| Gaston 2009                  | Prograf         | 4     | Open-label | Multicenter  | North America | 720         | Y                 | Y               | 3           |
| Hamadeh 2008                 | Prograf         | –     | –        | Single-center | Africa        | 132         | Y                 | Y               | 2           |
| Harland 2019                 | Prograf         | 2a    | Open-label | Multicenter  | North America | 149         | Y                 | Y               | 3           |
| Huh 2017                     | Advagraf        | 4     | Open-label | Multicenter  | East Asia     | 158         | Y                 | N               | 2           |
| Kramer 2010a                 | Prograf         | 3     | Open-label | Multicenter  | Europe        | 451         | Y                 | Y               | 3           |
| Kramer 2010b                 | Advagraf, Prograf | 3     | Mixed*   | Multicenter  | International | 676         | Y                 | Y               | 2           |
| Kramer 2012 (SP to Kramer 2010a) | Prograf      | 3     | Open-label | Multicenter  | Europe        | 451         | Y                 | Y               | 3           |
| Langer 2012                  | Prograf         | 3     | Open-label | Multicenter  | International | 228         | Y                 | Y               | 2           |
| Liu 2015                     | Prograf         | –     | Open-label | Single-center | Asia          | 72          | Y                 | Y               | 2           |
| Tedesco-Silva 2014           | Astagraf (Advagraf), Prograf | 3     | Open-label | Multicenter  | International | 668         | Y                 | Y               | 3           |
| Tsuchiya 2013                | Graceptor (Advagraf), Prograf | –     | Open-label | Multicenter  | Asia          | 102         | Y                 | Y               | 2           |

* Region refers to the geographical region identified based on the study locations and could be any of either Africa, Asia, East Asia, Europe, North America, South America, or International if the study was carried out in multiple regions across the world.

* Kramer 2010b used a mixed approach that comprised an initial double-blind, double-dummy phase followed by an open-label observation period post-transplant. CA – conference abstract; N – no; SP – secondary publication; TAC – tacrolimus; Y – yes.
Table 2. Key baseline characteristics among primary publications of studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study            | Treatment arm                  | N    | Mean age, years | Female, % | Mean BMI, kg/m² | Diabetes, % | White, % | Black, % | Asian, % |
|------------------|--------------------------------|------|-----------------|-----------|-----------------|-------------|----------|----------|----------|
| **Albano 2013**  | TAC BID+MPA+CS                 | 309  | 50.80           | 31.7      | 25.4            | –           | 95.8     | 2.3      | 1.9      |
|                  | TAC_QD_0.20+MPA+CS             | 302  | 50.7            | 31.8      | 25.8            | –           | 94.0     | 4.6      | 1.3      |
|                  | TAC_QD_0.30+MPA+CS             | 304  | 50.2            | 32.9      | 25.5            | –           | 95.7     | 2.3      | 2.0      |
|                  | TAC_QD_0.20+MPA+CS (+BAS)      | 283  | 49.3            | 34.6      | 25.2            | –           | 93.6     | 3.9      | 2.5      |
| **Anutarakulchai 2019** | TAC_BID_0.10+MPA+CS           | 63   | 40.68           | 31.7      | –                | –           | –        | –        | 100      |
|                  | TAC_BID_0.08-0.125+MPA+CS      | 62   | 41.77           | 40.3      | –                | –           | –        | –        | 100      |
| **Arns 2017**    | TAC BID (TacHexal)+MPA+CS      | 35   | 47.9            | 17.1      | 27.6            | –           | 94.3     | –        | –        |
|                  | TAC BID (Prograf)+MPA+CS       | 38   | 47.2            | 23.7      | 26.0            | –           | 94.7     | –        | –        |
| **Asher 2014**   | SRL_QD+MPA+CS                  | 19   | 49 (median)     | –         | –                | –           | –        | –        | –        |
|                  | TAC_BID+MPA+CS                 | 19   | 49 (median)     | –         | –                | –           | –        | –        | –        |
| **Bakr 2018**    | TAC BID+MPA+CS                 | 66   | 29.36           | 36.36     | –                | –           | –        | –        | –        |
|                  | TAC_QD+MPA+CS                  | 33   | 29.88           | 36.36     | –                | –           | –        | –        | –        |
| **Chen 2008**    | CsA BID+SRL QD+CS              | 20   | 40.2            | 65.00     | –                | –           | –        | –        | 100      |
|                  | TAC BID+SRL QD+CS              | 21   | 42.7            | 76.19     | –                | –           | –        | –        | 100      |
| **Cockfield 2019** | TAC_QD_Low+ACEi/ARB            | 71   | 50.5            | 33.8      | 27.6            | –           | 78.9     | –        | –        |
|                  | TAC_QD_Low+OAH                 | 69   | 48.0            | 30.4      | 27.3            | –           | 75.4     | –        | –        |
|                  | TAC_QD_Std+ACEi/ARB            | 71   | 50.4            | 33.8      | 28.3            | –           | 81.7     | –        | –        |
|                  | TAC_QD_Std+OAH                 | 70   | 52.4            | 30.4      | 27.0            | –           | 81.4     | –        | –        |
| **De Graav 2017**| MPA+CS                         | 20   | –               | 30         | –                | –           | 85.0     | 10.0     | 5.0      |
|                  | TAC_BID+MPA+CS                 | 20   | –               | 20.0      | –                | –           | 80.0     | 10.0     | 10.0     |
| **Demirbas 2009**| CsA_BID_Std+MPA+CS             | 390  | 45.9            | 37.7      | –                | 6.9         | 92.1     | 2.1      | 1.3      |
|                  | CsA_BID_Low+MPA+CS             | 399  | 47.2            | 33.6      | –                | 9.0         | 92.2     | 2.3      | 0.8      |
|                  | TAC_BID_Low+MPA+CS             | 401  | 45.4            | 34.2      | –                | 8.5         | 94.0     | 1.0      | 0.7      |
|                  | SRL_QD_Low+MPA+CS              | 399  | 44.9            | 33.3      | –                | 7.8         | 94.2     | 1.3      | 0.5      |
| **Ferguson 2011**| MPA+CS                         | 33   | 49.20           | 24.00     | –                | –           | 73.0     | 24.0     | –        |
|                  | SRL_QD+CS                      | 26   | 52.70           | 23.00     | –                | –           | 89.0     | 12.0     | –        |
|                  | TAC_BID+MPA+CS                 | 30   | 53.60           | 27.00     | –                | –           | 77.0     | 17.0     | –        |
| **Gaston 2009**  | CNI_Low+MPA_Controlled+CS      | 243  | 48.3            | 32.9      | –                | –           | 65.8     | 26.7     | –        |
|                  | CNI_Std+MPA_Controlled+CS      | 237  | 48.8            | 32.9      | –                | –           | 70.9     | 24.5     | –        |
|                  | CNI_Std+MPA_Fixed+CS           | 240  | 49.6            | 32.1      | –                | –           | 69.6     | 25.8     | –        |
Two studies reported T cell-mediated rejection between 12 and 24 months after transplantation [23,24]. In the study of Chen et al, a single patient in each group (CsA BID+SRL+CS and TAC BID+SRL+CS) experienced Banff IA BPAR (~5% of patients in both groups) [23]. In the study of Cockfield et al, the T cell-mediated rejection rates, including borderline changes after 24 months of follow-up, were 19.8% (14 patients) and 39.6% (27 patients) for low-dose TAC QD arms comprising angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker (ACEi/ARB) and other antihypertensive, respectively, and 24.2% (17 patients) and 16.5% (12 patients) with standard-dose TAC QD regimens comprising ACEi/ARB and other antihypertensive, respectively [24].

**Graft Loss**

Graft loss was reported in 14 studies of transplant recipients during follow-up of between 6 and 36 months for TAC QD or TAC BID (Advagraf or Prograf) (Table 4) and in a further 28 studies.
Table 3. Rejection outcomes: acute rejection and biopsy-proven acute rejection among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study          | Definition of rejection                                                                 | Population | Time point       | Treatment arms                                      | N   | Rejection type | Metric | Rejection, n | Rejection, % |
|----------------|----------------------------------------------------------------------------------------|------------|------------------|-----------------------------------------------------|-----|----------------|--------|--------------|--------------|
| Albano 2013    | A kidney biopsy was performed before initiation of antirejection therapy if clinical and/or laboratory signs indicated rejection and was evaluated by a local histopathologist following Banff 1997 criteria | FAS 6 months | TAC BID+MPA+CS   | 309                                                   | BPAR | Frequency      | 42     | 13.6         |
|                |                                                                                       | FAS 6 months | TAC QD_0.20+MPA+CS | 302                                                   | BPAR | Frequency      | 31     | 10.3         |
|                |                                                                                       | FAS 6 months | TAC QD_0.30+MPA+CS | 304                                                   | BPAR | Frequency      | 49     | 16.1         |
| Arns 2017      |                                                                                       | –           | ITT 6 months     | TAC BID (TacHexal)+MPA+CS                             | 35  | BPAR           | Frequency | 2            | 5.7          |
|                |                                                                                       | –           | ITT 6 months     | TAC BID (Prograf)+MPA+CS                              | 38  | BPAR           | Frequency | 3            | 7.9          |
| Arriola 2018 (CA) |                                                                                      | –           | ITT 12 months   | TAC BID+MPA+SRL+CS                                   | 55  | AR             | Frequency | 12.7         |
|                |                                                                                       | –           | ITT 12 months   | TAC QD+MPA+EVR+CS                                    | 52  | AR             | Frequency | 11.5         |
|                |                                                                                       | –           | ITT 72 months   | TAC BID+MPA+SRL+CS                                   | 55  | AR             | Frequency | 16.6         |
|                |                                                                                       | –           | ITT 72 months   | TAC QD+MPA+EVR+CS                                    | 52  | AR             | Frequency | 15.3         |
| Asher 2014     | All episodes of rejection were verified by biopsy and graded using the Banff 2013 working classification | ITT 12 months | TAC QD+MPA+CS   | 33                                                     | BPAR | Frequency      | 5      | 15.2         |
| Bakr 2018      |                                                                                       | –           | ITT 12 months   | TAC QD+MPA+CS                                        | 66  | BPAR           | Frequency | 16.7         |
|                |                                                                                       | –           | ITT 12 months   | TAC QD+MPA+CS                                        | 66  | BPAR           | Frequency | 16.7         |
|                |                                                                                       | –           | ITT 12 months   | TAC BID+SRL QD+CS                                    | 20  | BPAR Banff IA  | Frequency | 1            | 5.0          |
|                |                                                                                       | –           | ITT 12 months   | TAC BID+SRL QD+CS                                    | 21  | BPAR Banff IA  | Frequency | 1            | 4.8          |
| Chen 2008      | AR was suspected when >30% increase in serum Cr was noted. Graft biopsy was performed in every patient with suspected AR | ITT 12 months | CsA BID+SRL QD+CS | 20                                                     | BPAR | Banff IA       | Frequency | 1            | 5.0          |
| Cockfield 2019 | TCMR including borderline changes using Banff 2007 criteria                            | ITT 24 months | TAC QD_Low+ACE/ARB | 71                                                     | TCMR | Frequency      | 14     | 19.8         |
|                |                                                                                       | ITT 24 months | TAC QD_Low+OAH   | 69                                                     | TCMR | Frequency      | 27     | 39.6         |
|                |                                                                                       | ITT 24 months | TAC QD_Low+ACE/ ARB | 71                                                     | TCMR | Frequency      | 17     | 24.2         |
|                |                                                                                       | ITT 24 months | TAC QD_Low+OAH   | 70                                                     | TCMR | Frequency      | 12     | 16.5         |
|                |                                                                                       | ITT 6 months  | TAC QD_Low+ACE/ARB | 71                                                     | TCMR | Frequency      | 23     | 32.1         |
|                |                                                                                       | ITT 6 months  | TAC QD_Low+OAH   | 69                                                     | TCMR | Frequency      | 39     | 56.2         |
|                |                                                                                       | ITT 6 months  | TAC QD_Low+ACE/ARB | 71                                                     | TCMR | Frequency      | 21     | 29.6         |
| De Graaf 2017  | Total BPAR, scored as part of routine clinical care by a renal pathologist per the Banff 2015 classification. Incidence of the first rejection episode | ITT 12 months | TAC BID+MPA+CS   | 20                                                     | BPAR | Frequency      | 11     | 55.0         |

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Table 3 continued. Rejection outcomes: acute rejection and biopsy-proven acute rejection among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study       | Definition of rejection                                                                 | Population | Time point | Treatment arms | N   | Rejection type | Metric | Rejection, n | Rejection, % |
|-------------|----------------------------------------------------------------------------------------|------------|------------|----------------|-----|----------------|--------|--------------|--------------|
| Demirbas    | Excluding patients with borderline BPAR values                                          | Germany (ITT) | 12 months  | SRL QD+MPA+CS  | 296 | BPAR          | Frequency | –            | 54.2         |
|             |                                                                                       | Germany (ITT) | 12 months  | TAC BID+MPA+CS | 296 | BPAR          | Frequency | –            | 26.6         |
|             |                                                                                       | Germany (ITT) | 12 months  | CsA BID Std+MPA+CS | 296 | BPAR          | Frequency | –            | 27.2         |
|             |                                                                                       | Germany (ITT) | 12 months  | CsA BID Low+MPA+CS | 296 | BPAR          | Frequency | –            | 27.2         |
|             |                                                                                       | Overall (ITT) | 12 months  | TAC BID+MPA+CS  | 1589| BPAR          | Frequency | –            | 12.3         |
|             |                                                                                       | Overall (ITT) | 12 months  | CsA BID Std+MPA+CS | 1589| BPAR          | Frequency | –            | 25.8         |
| Spain       |                                                                                       | Spain (ITT) | 12 months  | SRL QD+MPA+CS  | 269 | BPAR          | Frequency | –            | 23.7         |
|             |                                                                                       | Spain (ITT) | 12 months  | TAC BID+MPA+CS | 269 | BPAR          | Frequency | –            | 8.4          |
|             |                                                                                       | Spain (ITT) | 12 months  | CsA BID Std+MPA+CS | 269 | BPAR          | Frequency | –            | 20.1         |
|             |                                                                                       | Spain (ITT) | 12 months  | CsA BID Low+MPA+CS | 269 | BPAR          | Frequency | –            | 16.5         |
| Turkey      |                                                                                       | Turkey (ITT) | 12 months  | SRL QD+MPA+CS  | 269 | BPAR          | Frequency | –            | 19.4         |
|             |                                                                                       | Turkey (ITT) | 12 months  | TAC BID+MPA+CS | 269 | BPAR          | Frequency | –            | 6.7          |
|             |                                                                                       | Turkey (ITT) | 12 months  | CsA BID Std+MPA+CS | 269 | BPAR          | Frequency | –            | 15.1         |
|             |                                                                                       | Turkey (ITT) | 12 months  | CsA BID Low+MPA+CS | 269 | BPAR          | Frequency | –            | 19.8         |
| Ferguson    | Biopsy-proven and either clinically suspected for protocol-defined reasons or clinically suspected for other reasons and treated | ITT | 12 months  | MPA+CS       | 33  | BPAR          | Frequency | 5            | 15.2         |
|             |                                                                                       | ITT | 12 months  | SRL QD+CS    | 26  | BPAR          | Frequency | 1            | 3.8          |
|             |                                                                                       | ITT | 12 months  | TAC BID+MPA+CS | 30  | BPAR          | Frequency | 1            | 3.3          |
|             |                                                                                       | ITT | 6 months   | MPA+CS       | 33  | BPAR          | Frequency | 4            | 12.1         |
|             |                                                                                       | ITT | 6 months   | SRL QD+CS    | 26  | BPAR          | Frequency | 1            | 3.8          |
|             |                                                                                       | ITT | 6 months   | TAC BID+MPA+CS | 30  | BPAR          | Frequency | 1            | 3.3          |
| Frei 2010   | BPAR excluding borderline episodes. Biopsies were assessed by local pathologists using the modified Banff criteria. Protocol recommended a biopsy in cases of clinically suspected acute allograft rejection, in the absence of medical contraindication, but there was no further specific guidance. KM estimates | ITT   | 12 months  | CsA BID Std+MPA+CS | –   | BPAR          | Frequency | –            | 26           |
|             |                                                                                       | ITT   | 12 months  | TAC BID Low+MPA+CS | –   | BPAR          | Frequency | –            | 24           |
|             |                                                                                       | ITT   | 12 months  | SRL QD Low+MPA+CS | –   | BPAR          | Frequency | –            | 12           |
|             |                                                                                       | ITT   | 6 months   | CsA BID Low+MPA+CS | –   | BPAR          | Frequency | –            | 37           |
|             |                                                                                       | ITT   | 6 months   | TAC BID Low+MPA+CS | –   | BPAR          | Frequency | –            | 22           |
|             |                                                                                       | ITT   | 6 months   | CNI Std+MPA+CS | –   | BPAR          | Frequency | –            | 11           |
| Gaston 2009 | Diagnosis of BPAR was confirmed histologically using the Banff 1997 classification | ITT   | 12 months  | CNI Low+MPA, Controlled+CS | 243 | BPAR          | Frequency | 15            | 6.2          |
|             |                                                                                       | ITT   | 12 months  | CNI Std+MPA, Controlled+CS | 237 | BPAR          | Frequency | 23            | 9.7          |
|             |                                                                                       | ITT   | 12 months  | CNI Std+MPA, Fixed+CS | 240 | BPAR          | Frequency | 23            | 9.6          |
### Table 3 continued. Rejection outcomes: acute rejection and biopsy-proven acute rejection among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study          | Definition of rejection                                                                 | Population | Time point | Treatment arms          | N    | Rejection type | Metric | Rejection, n | Rejection, % |
|----------------|----------------------------------------------------------------------------------------|------------|------------|-------------------------|------|----------------|--------|--------------|-------------|
| Hamdy 2008     | Event biopsy carried out in case of nephrotic range proteinuria or episodes of renal dysfunction (25% increase in Cr from baseline) for which histopathologic examination was performed according to Banff 1997 | ITT        | >24 months | SRL QD+MPA+CS           | 67   | BPAR           | Frequency | 0            | 0           |
|                |                                                                                       | ITT        | >24 months | TAC BID+SRL QD+CS       | 65   | BPAR           | Frequency | 0            | 0           |
| Harland 2019   | Including transplant recipients lost to follow-up; BPAR defined as biopsy-proven acute (T or B cell) rejection, Banff grade ≥1 by local review | FAS        | 36 months  | TAC BID+MPA+CS          | 48   | BPAR           | Frequency | 17           | 35.4        |
|                |                                                                                       | FAS        | 36 months  | BLES+MPA+CS             | 46   | BPAR           | Frequency | 27           | 58.7        |
|                |                                                                                       | FAS        | 6 months   | TAC BID+MPA+CS          | 48   | BPAR           | Frequency | 7            | 14.6        |
|                |                                                                                       | FAS        | 6 months   | BLES+MPA+CS             | 46   | BPAR           | Frequency | 19           | 41.3        |
| Huh 2017       | Excluding borderlines values; Pathologist gathered pathology reports from participating centers and reassessed the results using the Banff 1997 classification to confirm the diagnosis of BPAR | ITT        | 12 months  | TAC QD+SRL QD+CS        | 76   | BPAR           | Frequency | 10           | 13.3        |
| Kramer 2010a   | Histologically confirmed episode for which a Banff score of I (mild), II (moderate), or III (severe) was recorded. Banff criteria published in 1993 and 1995 | FAS        | 12 months  | TAC BID                 | 153  | BPAR           | Frequency | 42           | 27.5        |
|                |                                                                                       | FAS        | 12 months  | TAC BID+MPA             | 151  | BPAR           | Frequency | 41           | 25.8        |
|                |                                                                                       | FAS        | 12 months  | TAC BID+MPA+CS          | 147  | BPAR           | Frequency | 12           | 8.2         |
|                |                                                                                       | FAS        | 0-6 months  | TAC BID+MPA             | 153  | BPAR           | Frequency | 40           | 26.1        |
|                |                                                                                       | FAS        | 0-6 months  | TAC BID+MPA+CS          | 151  | BPAR           | Frequency | 46           | 30.5        |
| Kramer 2010b   | ARs confirmed by local biopsy classified as BPAR                                       | ITT        | 12 months  | TAC BID+MPA+CS          | 336  | BPAR local     | Frequency | 50           | 14.9        |
|                |                                                                                       | ITT        | 12 months  | TAC QD+MPA+CS           | 331  | BPAR local     | Frequency | 59           | 17.8        |
| Kramer 2012 (SP) | Histologically confirmed episode for which a Banff score of I (mild), II (moderate), or III (severe) was recorded. Banff criteria published in 1993 and 1995 | ITT        | 6-36 months | TAC BID                 | 143  | BPAR           | Frequency | 3            | 2.1         |
|                |                                                                                       | ITT        | 6-36 months | TAC BID+MPA             | 139  | BPAR           | Frequency | 3            | 2.2         |
|                |                                                                                       | ITT        | 6-36 months | TAC BID+MPA+CS          | 139  | BPAR           | Frequency | 4            | 2.9         |
Table 3 continued. Rejection outcomes: acute rejection and biopsy-proven acute rejection among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study          | Definition of rejection | Population | Time point | Treatment arms | N   | Rejection type | Metric | Rejection, n | Rejection, % |
|----------------|-------------------------|------------|------------|----------------|-----|----------------|--------|--------------|--------------|
| Langer 2012    | –                       | ITT        | 12 months  | TAC BID_1.5-3 ng/mL + EVR BID + CS | 107 | BPAR           | Frequency | 20           | 18.7         |
|                |                         | ITT        | 12 months  | TAC BID_4-7 ng/mL + EVR BID + CS | 117 | BPAR           | Frequency | 9            | 7.7          |
| Liu 2015       | BPAR was classified according to the 1997-2007 update classification criteria by the local pathologist | ITT        | 24 months  | TAC BID + MPA + CS | 36  | BPAR           | Frequency | 3            | 8.3          |
| Tsuchiya 2013  | BPAR excluding borderline cases, rejection or other pathologic findings were diagnosed according to the Banff 2007 criteria | ITT        | 12 months  | TAC BID + MPA + CS | 52  | BPAR           | Frequency | 9            | 17.3         |

The terms BPAR and biopsy-confirmed acute rejection were used interchangeably. ACEi/ARB – angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker; AR – acute rejection; BID – twice daily; BLES – bleselumab; BPAR – biopsy-proven acute rejection; CA – conference abstract; CNI – calcineurin inhibitor; Cr – creatinine; CS – corticosteroid; CsA – cyclosporin A; EVR – everolimus; FAS – full analysis set; ITT – intention-to-treat; MPA – mycophenolic acid; OAH – other antihypertensive; PP – per-protocol; QD – once daily; SP – secondary publication; SRL – sirolimus; Std – standard dose; TAC – tacrolimus; TCMR – T cell-mediated rejection.

Table 4. Graft loss among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study          | Population | Time point | Treatment arms       | N   | Graft loss, n | Graft loss, % |
|----------------|------------|------------|----------------------|-----|---------------|---------------|
| Albano 2013    | FAS        | 6 months   | TAC BID + MPA + CS   | 309 | 18            | 5.8           |
|                | FAS        | 6 months   | TAC QD_0.20 + MPA + CS | 302 | 29            | 9.6           |
|                | FAS        | 6 months   | TAC QD_0.20 + MPA + CS (+BAS) | 204 | 23            | 11.3          |
|                | PP         | 6 months   | TAC BID + MPA + CS   | 237 | 7             | 3.0           |
|                | PP         | 6 months   | TAC QD_0.20 + MPA + CS | 263 | 11            | 4.2           |
|                | PP         | 6 months   | TAC QD_0.20 + MPA + CS (+BAS) | 230 | 10            | 4.3           |
|                | PP         | 6 months   | TAC QD_0.30 + MPA + CS | 246 | 9             | 3.7           |
| Arns 2017      | ITT        | 6 months   | TAC BID (Prograf) + MPA + CS | 38  | 1             | 2.6           |
|                | ITT        | 6 months   | TAC BID (TacHexal) + MPA + CS | 35  | 0             | 0             |
| Bakr 2018      | ITT        | 12 months  | TAC BID + MPA + CS   | 66  | 0             | 0             |
|                | ITT        | 12 months  | TAC QD + MPA + CS    | 33  | 0             | 0             |
| Chen 2008      | ITT        | 12 months  | CsA BID + SRL QD + CS | 20  | 2             | 10.0          |
|                | ITT        | 12 months  | TAC BID + SRL QD + CS | 21  | 0             | 0             |
| Cockfield 2019 | ITT        | 24 months  | TAC QD_Low + ACEI/ARB | 71  | 2             | 2.8           |
|                | ITT        | 24 months  | TAC QD_Low + OAH     | 69  | 4             | 5.8           |
|                | ITT        | 24 months  | TAC QD_S + ACEI/ARB  | 71  | 3             | 4.2           |
|                | ITT        | 24 months  | TAC QD_S + OAH       | 70  | 2             | 2.9           |
Table 4 continued. Graft loss among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study            | Population | Time point | Treatment arms | N   | Graft loss, n | Graft loss,% |
|------------------|------------|------------|----------------|-----|---------------|--------------|
| De Graav 2017    | ITT        | 12 months  | MPA+CS         | 20  | 3             | 15.0         |
|                  | ITT        | 12 months  | TAC BID+MPA+CS | 20  | 0             | 0            |
| Ferguson 2011    | ITT        | 12 months  | MPA+CS         | 33  | 2             | 6.1          |
|                  | ITT        | 12 months  | SRL QD+CS      | 26  | 2             | 7.7          |
|                  | ITT        | 12 months  | TAC BID+MPA+CS | 30  | 0             | 0            |
| Gaston 2009      | ITT        | 12 months  | CNI_Low+MPA_Controlled+CS | 243 | 5             | 2.1          |
|                  | ITT        | 12 months  | CNI_Sld+MPA_Controlled+CS | 237 | 4             | 1.7          |
|                  | ITT        | 12 months  | CNI_Sld+MPA_Fixed+CS | 240 | 4             | 1.7          |
| Huh 2017         | ITT        | 12 months  | TAC QD+MPA+CS  | 75  | 0             | 0            |
|                  | ITT        | 12 months  | TAC QD+SRL QD+CS | 76  | 0             | 0            |
| Kramer 2010a     | FAS        | 12 months  | TAC BID        | 153 | 11            | 7.2          |
|                  | FAS        | 12 months  | TAC BID+MPA    | 151 | 7             | 4.6          |
|                  | FAS        | 12 months  | TAC BID+MPA+CS | 147 | 6             | 4.1          |
|                  | FAS        | 1-6 months | TAC BID        | 153 | 8             | 5.2          |
|                  | FAS        | 1-6 months | TAC BID+MPA    | 151 | 5             | 3.3          |
|                  | FAS        | 1-6 months | TAC BID+MPA+CS | 147 | 6             | 4.1          |
|                  | FAS        | 7-12 months| TAC BID        | 153 | 3             | 2.0          |
|                  | FAS        | 7-12 months| TAC BID+MPA    | 151 | 2             | 1.3          |
|                  | FAS        | 7-12 months| TAC BID+MPA+CS | 147 | 0             | 0            |
| Kramer 2010b     | ITT        | 12 months  | TAC BID+MPA+CS | 336 | 24            | 7.1          |
|                  | ITT        | 12 months  | TAC QD+MPA+CS  | 331 | 28            | 8.5          |
|                  | PP         | 12 months  | TAC BID+MPA+CS | 291 | 7             | 2.4          |
|                  | PP         | 12 months  | TAC QD+MPA+CS  | 280 | 9             | 3.2          |
| Kramer 2012 (SP)| ITT        | 36 months  | TAC BID        | 143 | 2             | 1.4          |
|                  | ITT        | 36 months  | TAC BID+MPA    | 139 | 4             | 2.9          |
|                  | ITT        | 36 months  | TAC BID+MPA+CS | 139 | 4             | 2.9          |
| Langer 2012      | ITT        | 12 months  | TAC_1.5–3 ng/mL+EVR BID+CS | 107 | 8             | 7.5          |
|                  | ITT        | 12 months  | TAC_4–7 ng/mL+EVR BID+CS | 117 | 2             | 1.7          |
|                  | ITT        | 4-12 months| TAC_1.5–3 ng/mL+EVR BID+CS | 107 | 1             | 0.9          |
|                  | ITT        | 4-12 months| TAC_4–7 ng/mL+EVR BID+CS | 117 | 1             | 0.9          |
| Tsuchiya 2013    | ITT        | 1 month    | TAC BID+MPA+CS | 52  | 0             | 0            |
|                  | ITT        | 12 months  | TAC QD+MPA+CS  | 50  | 0             | 0            |

ACEi/ARB – angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker; BAS – basiliximab; BID – twice daily; CNI – calcineurin inhibitor; CS – corticosteroid; CsA – cyclosporin A; EVR – everolimus; FAS – full analysis set; ITT – intention-to-treat; MPA – mycophenolic acid; OAH – other antihypertensive; PP – per-protocol; QD – once daily; SP – secondary publication; SRL – sirolimus; Std – standard dose; TAC – tacrolimus.
Table 5. Patient death among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study            | Population | Time point | Treatment arms                      | N  | Patient death, n | Patient death, % |
|------------------|------------|------------|-------------------------------------|----|------------------|------------------|
| Anutrakulchai    | ITT        | 6 months   | TAC BID 0.08-0.125+MPA+CS           | 62 | 5                | 8.1              |
|                  | ITT        | 6 months   | TAC BID 0.10+MPA+CS                 | 63 | 1                | 1.6              |
| Arns 2017        | ITT        | 6 months   | TAC (Prograf)+MPA+CS                | 38 | 1                | 2.6              |
| Arriola 2018 (CA)| ITT        | 6 months   | TAC (TacHexal)+MPA+CS               | 35 | 0                | 0                |
| Arriola 2018 (CA)| ITT        | 72 months  | TAC+MPA+EV+CS                       |     |                  | 14.5             |
|                  |            | 72 months  | TAC+MPA+EV+CS                       |     |                  | 13.4             |
| Chen 2008        | ITT        | 12 months  | CsA BID+SRL QD+CS                   | 20 | 0                | 0                |
|                  | ITT        | 12 months  | TAC BID+SRL QD+CS                   | 21 | 1                | 5.0              |
| Cockfield 2019   | ITT        | 24 months  | TAC QD_Low+ACEi/ARB                 | 71 | 0                | 0                |
|                  | ITT        | 24 months  | TAC QD_Low+OAH                       | 69 | 2                | 2.9              |
|                  | ITT        | 24 months  | TAC QD Std+OAH                       | 71  |                  |                  |
|                  | ITT        | 24 months  | TAC QD Std+OAH                       | 70 | 1                | 1.4              |
| De Graav 2017    | ITT        | 12 months  | MPA+CS                              | 20 | 0                | 0                |
|                  | ITT        | 12 months  | TAC BID+MPA+CS                      | 20 | 1                | 5.0              |
| Ekberg 2010 (SP) | ITT        | 12 months  | CsA BID_Low+MPA+CS                  | 399| 5                | 1.3              |
|                  | ITT        | 12 months  | CsA BID Std+MPA+CS                  | 390| 8                | 2.1              |
|                  | ITT        | 12 months  | SRL QD Low+MPA+CS                   | 399| 6                | 1.5              |
|                  | ITT        | 12 months  | TAC QD Std+ACEi/ARB                 | 401| 19               | 2.2              |
| Ferguson 2011    | ITT        | 12 months  | MPA+CS                              | 33 | 1                | 3.0              |
|                  | ITT        | 12 months  | SRL QD+CS                           | 26 | 0                | 0                |
|                  | ITT        | 12 months  | TAC BID+MPA+CS                      | 30 | 0                | 0                |
| Gaston 2009      | ITT        | 12 months  | CNI_Low+MPA_Controlled+CS           | 243| 4                | 1.6              |
|                  | ITT        | 12 months  | CNI Std+MPA_Controlled+CS           | 237| 2                | 0.8              |
|                  | ITT        | 12 months  | CNI Std+MPA_Fixed+CS                | 240| 6                | 2.5              |
| Hamdy 2008       | ITT        | 36 months  | SRL QD+MPA+CS                       | 67 | 1                | 1.5              |
|                  | ITT        | 36 months  | TAC BID+SRL QD+CS                   | 65 | 4                | 6.2              |
| Harland 2019     | FAS        | Through 36 months | BLES+MPA+CS               | 46 | 2                | 4.3              |
|                  | FAS        | Through 36 months | TAC BID+BLES+CS              | 44 | 2                | 4.5              |
| Huh 2017         | ITT        | 12 months  | TAC QD+MPA+CS                       | 75 | 0                | 0                |
|                  | ITT        | 12 months  | TAC QD+SRL QD+CS                    | 76 | 1                | 1.3              |
| Kramer 2010a     | FAS        | 12 months  | TAC BID                             | 153| 1                | 0.7              |
|                  | FAS        | 12 months  | TAC BID+MPA                         | 151| 2                | 1.3              |
|                  | FAS        | 12 months  | TAC BID+MPA+CS                      | 147| 0                | 0                |
| Kramer 2010b     | ITT        | 12 months  | TAC BID+MPA+CS                      | 316| 8                | 2.6              |
|                  | ITT        | 12 months  | TAC QD+MPA+CS                       | 331| 10               | 3.0              |
|                  | PP         | 12 months  | TAC BID+MPA+CS                      | 291| 3                | 1.0              |
|                  | PP         | 12 months  | TAC QD+MPA+CS                       | 206| 2                | 1.1              |
| Kramer 2012      | ITT        | 36 months  | TAC BID                             | 143| 5                | 3.5              |
| (SP)             | ITT        | 36 months  | TAC BID+MPA                         | 139| 2                | 1.4              |
|                  | ITT        | 36 months  | TAC BID+MPA+CS                      | 139| 5                | 3.6              |
Table 5 continued. Patient death among all included studies in which 1 or more of the treatment arms used Advagraf or Prograf.

| Study               | Population | Time point | Treatment arms                          | N     | Patient death, n | Patient death, % |
|---------------------|------------|------------|----------------------------------------|-------|------------------|------------------|
| Langer 2012         | ITT        | 12 months  | TAC BID_1.5-3 ng/mL+EVR BID+CS          | 107   | 3                | 2.8              |
|                     | ITT        | 12 months  | TAC BID_4-7 ng/mL+EVR BID+CS           | 117   | 3                | 2.6              |
|                     | ITT        | 4-12 months| TAC BID_1.5-3 ng/mL+EVR BID+CS         | 107   | 2                | 2.7              |
|                     | ITT        | 4-12 months| TAC BID_4-7 ng/mL+EVR BID+CS           | 117   | 1                | 1.1              |
| Liu 2015            | ITT        | 15 months  | CsA BID+MPA+CS                         | 36    | 0                | 0                |
|                     | ITT        | 15 months  | TAC BID+MPA+CS                         | 36    | 1                | 2.8              |
| Tedesco-Silva 2014  | FAS        | 48 months  | CsA BID+MPA+CS                         | 212   | 15               | 7.1              |
|                     | FAS        | 48 months  | TAC BID+MPA+CS                         | 212   | 16               | 7.5              |
|                     | FAS        | 48 months  | TAC QD+MPA+CS                          | 214   | 13               | 6.1              |
| Tsuchiya 2013       | ITT        | 12 months  | TAC BID+MPA+CS                         | 52    | 0                | 0                |
|                     | ITT        | 12 months  | TAC QD+MPA+CS                          | 50    | 0                | 0                |

ACEi/ARB – angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker; BLES – blesemab; BID – twice daily; CA – conference abstract; CNI – calcineurin inhibitor; CS – corticosteroid; CsA – cyclosporin A; EVR – everolimus; FAS – full analysis set; ITT – intention-to-treat; MPA – mycophenolic acid; OAH – other antihypertensive; PP – per-protocol; QD – once daily; SP – secondary publication; SRL – sirolimus; Std – standard dose; TAC – tacrolimus.

with follow-up of up to 8 years in which the TAC formulation was not reported (Supplementary Table 5).

Of the 14 studies that reported graft rejection at 6 to 12 months following treatment with Advagraf or Prograf, there was variation in the incidence of graft loss, depending on the study population (intention-to-treat, per-protocol, or full analysis set) and the time since transplantation. In studies in which the TAC formulation was known, the QD regimen was associated with graft loss of between 0% [22,31,38] and 9.6% (29/302 patients) [17], while graft loss for the BID regimen ranged from 0% [22,23,25,28,33,38] to 7.5% (8/107 patients) [35]. Across the studies investigating Advagraf or Prograf, the highest rate of graft loss (15.0%; 3/20 patients) was with MPA+CS [25].

**Mortality**

Patient mortality was reported in 19 studies in which the formulation of TAC QD or TAC BID was known (Advagraf or Prograf) (Table 5) and in a further 32 publications in which the TAC formulation was not reported (Supplementary Table 6). Of the Advagraf or Prograf studies, between 6 and 24 months, mortality ranged from 0% (9 studies, various regimens) to 8.1% (5/62 patients) reported with TAC BID_0.08-0.125+MPA+CS (in which the TAC dose was adjusted between 0.08 and 0.125 mg/kg according to CYP3A4 genotype) in the study by Anutrakulchai et al [18]. The highest mortality rates were reported at 6 years in the study of Arriola et al (13.4% and 14.5% with TAC QD+MPA+EVR+CS and TAC BID+MPA+SRL+CS, respectively, although the numbers of deaths and patients treated were not reported) [20].

**CMV Infection**

CMV infection was reported in 14 studies in which the formulation of TAC QD or TAC BID was known (Advagraf or Prograf) (Supplementary Table 7) and in 30 studies in which the TAC formulation was not reported (Supplementary Table 8). Of the Advagraf or Prograf studies, incidence ranged from 1.3% (1/76 patients) with TAC QD+SRL QD+CS [31] to 15.4% (59/384 patients) with CsA BID+MPA+CS [26,27]. In the 13 primary studies in which the formulation of TAC QD or TAC BID was known (Advagraf or Prograf), the assessment period ranged from 6 months to 4 years.

**NODAT**

The incidence of NODAT was reported in 12 publications in which the formulation of TAC QD or TAC BID was known (Advagraf or Prograf) (Supplementary Table 9) and in 20 studies in which the TAC formulation was not reported (Supplementary Table 10). Of the Advagraf or Prograf studies, the incidence of NODAT ranged from 0% with CsA BIDStd+MPA+CS, SRL QD+MPA+CS, CsA BIDLow+MPA+CS, MPA+CS, and TAC BID+MPA+CS, all reported at 12 months [26,28,38], to 57.6% (19 patients) at 6 months with TAC BID+MPA+CS [80]. The longest assessment period for reporting NODAT was 6 years, with an incidence of 12.7% with TAC BID+MPA+SRL+CS and 11.5% with TAC QD+MPA+EVR+CS (number of patients not reported) [20].
Figure 2. **Risk of bias among the 61 primary studies as a percentage of the total included studies.** Risk of bias was assessed based on the recommendations of the Cochrane guide for systematic reviews. Figure created using R 3.6.0, The R Foundation.

Figure 3. **Network plot for graft loss at 6 to 12 months.** The plot is based on 23 studies (8 studies in which 1 or more of the treatment arms used Advagraf or Prograf, and 15 studies in which the tacrolimus formulation was unknown). Figure created using R 3.6.0, The R Foundation. BID – twice daily; CS – corticosteroids; CsA – cyclosporin; EVR – everolimus; FK778 – manitimus; MPA – mycophenolic acid; QD – once daily; SRL – sirolimus; STN – sotrastaurin; TAC – tacrolimus.
Risk of Bias

Across the studies, most domains were at low risk of bias. Risk of bias among the 61 primary studies is shown in Figure 2. Thirty studies were assessed as being at high risk of bias in 1 or more domains. Of these, most studies had a high risk of bias in 1 domain, 4 studies had a high risk of bias in 2 domains, and 1 study had a high risk of bias in 3 domains.

Network Meta-Analysis

Data for mortality and graft loss are presented for the random-effects model, which was a better fit based on deviance information criterion (posterior mean deviance plus the number of parameters) and total residual deviance than fixed-effects models. Among the 61 included primary publications, the network analysis was based on 27 studies that evaluated graft loss or mortality. Of these, the formulation of TAC was named as Advagraf or Prograf in 9 studies [17,22,23,25,27,28,32,33,38], and the TAC formulation was not cited in the remaining 18 studies [39,42,44,45,48-50,52-62]. Figures 3 and 4 show the network diagrams for graft loss and mortality rates, respectively. The networks are connected, with no studies disconnected from the larger network of evidence.

Graft Loss

The ORs of graft loss (6-12 months) compared with the reference treatment Prograf+MPA+CS, adjusted for White race, are presented in Supplementary Table 11. Advagraf+MPA+CS and Prograf+MPA+CS were associated with a statistically similar risk of graft loss (median OR 1.19; 95% CrI 0.51, 3.06) since

Figure 4. Network plot for mortality rate at 6 to 12 months. The plot is based on 25 studies (7 studies in which 1 or more of the treatment arms used Advagraf or Prograf, and 18 studies in which the tacrolimus formulation was unknown). Figure created using R 3.6.0, The R Foundation. AZA – azathioprine; BEL – belimumab; BID – twice daily; CS – corticosteroids; CsA – cyclosporin; EVR – everolimus; FK778 – manitimus; MPA – mycophenolic acid; QD – once daily; SRL – sirolimus; STN – sotrastaurin; TAC – tacrolimus.
Compared with Prograf+MPA+CS, the risk of graft loss was higher with TAC BID+EVR BID+CS (median OR 3.0; 95% CrI 1.03, 11.36), MPA+CS (median OR 9.49; 95% CrI 2.12, 58.56), and SRL QD+CS (median OR 13.60; 95% CrI 1.02, 221.41).

Figure 5 shows the Forest plots for the random-effects model of graft loss. The following treatments were associated with significantly higher odds of graft loss at 6 to 12 months compared with the reference treatment, Prograf+MPA+CS: TAC BID+EVR BID+CS (OR 3.00; 95% CrI 1.03, 11.33), MPA+CS (OR 9.46; 95% CrI 2.11, 58.30), and SRL QD+CS (OR 13.64; 95% CrI 1.02, 221.77). No treatments were associated with significantly lower odds of graft loss than Prograf+MPA+CS.

In the meta-regression model adjusted for White race, the effect estimate of 0.04 (95% CrI -0.07, 0.17) indicated that race did not significantly affect graft loss.

Mortality

The adjusted ORs of mortality (6-12 months) compared with the reference treatment, Prograf+MPA+CS, are presented in Supplementary Table 11. Advagraf+MPA+CS and Prograf+MPA+CS were associated with a significantly similar risk of mortality (median OR 1.21; 95% CrI 0.1557, 9.03). The risk of mortality associated with each evaluated treatment regimen, including those incorporating TAC QD, TAC BID, and agents other than TAC, was similar to that associated with the Prograf+MPA+CS reference regimen, since the CrI for each comparison includes 1.

Figure 6 shows the Forest plots for the random-effects model for mortality. All treatments were associated with a significantly similar risk of mortality at 6 to 12 months compared with Prograf+MPA+CS. For the adjusted model, the covariate for White (%) was -0.031 (95% CrI -0.089, 0.027) and did not indicate that race significantly affected mortality.

Discussion

This systematic literature review and network meta-analysis included randomized controlled trials evaluating TAC...
immunosuppression in kidney transplant recipients. To the best of our knowledge, this is the most up-to-date systematic review and network meta-analysis of the literature, summarizing the most recent trials relating to TAC. No notable differences were evident from the network meta-analysis between known formulations of TAC QD and TAC BID in relation to graft loss or patient mortality.

Once-daily dosing with TAC is expected to improve overall adherence and potentially improve exposure to immunosuppressive therapy and transplant outcomes, compared with twice-daily dosing [8,9]. However, findings to date have been partially contradictory. A previous systematic literature review compared 12-month post-kidney transplant outcomes between TAC QD and TAC BID in randomized controlled trials and observational studies, with the authors finding no significant differences between the regimens in relation to BPAR, graft survival, or patient survival [81]. By contrast, a more recent systematic literature and meta-analysis of observational studies revealed a 30% lower risk of BPAR at 12 months with TAC QD compared with TAC BID, with no difference in graft or patient survival or kidney function [82]. Herein, none of the treatments analyzed was associated with increased (or decreased) mortality risk compared with the reference regimen, Prograf+MPA+CS. Three regimens, TAC BID+EVR BID+CS, MPA+CS, and SRL+CS, were associated with increased odds of graft loss compared with the reference regimen. The remaining regimens, including those with TAC QD, appeared to offer similar protection against graft loss. The wide CrIs for many of the pairwise comparisons could be accounted for by the small sample sizes for some of the treatment comparisons.

While we did not find evidence for improved transplant outcomes with TAC QD compared with TAC BID, the studies included in the review (and indeed in the previous reviews cited above) were limited regarding the long-term data available for assessment. Data were mainly confined to 6 to 12 months after transplantation, and there were limited published reports

Figure 6. Forest plot for the random-effects model for mortality (6-12 months) relative to reference treatment with Prograf plus mycophenolic acid plus a corticosteroid. The plot is based on 25 studies (7 studies in which 1 or more of the treatment arms used Advagraf or Prograf, and 18 studies in which the tacrolimus formulation was unknown). Figure created using R 3.6.0, The R Foundation. AZA – azathioprine; BEL – belimumab; BID – twice daily; CrI – credible interval; CS – corticosteroids; CsA – cyclosporin; EVR – everolimus; FK778 – manitimus; MPA – mycophenolic acid; QD – once daily; SRL – sirolimus; STN – sotrastaurin; TAC – tacrolimus.

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© Ann Transplant, 2021; 26: e933588
META-ANALYSIS
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of longer-term outcomes, preventing comprehensive analyses beyond this time period. As such, there is need for more prospective, long-term studies to evaluate efficacy outcomes, and it may be useful to stratify patient outcomes by adherence with immunosuppressive regimens and other factors, such as patient characteristics, which could impact post-transplant outcomes.

In the model adjusted for White race, the small, non-significant effect size of the covariate suggested there was limited evidence of a relationship between race (White vs Black and Asian) and graft loss or mortality. However, adequately powered prospective studies are needed to determine any potential effect associated with race or pharmacogenomic variations, as it is known that race can impact TAC dose requirements, for instance [83].

This systematic review and network meta-analysis had limitations. Pooling of results was limited by heterogeneity in the reporting of rejection outcomes, as the terms acute rejection and BPAR were used interchangeably. Furthermore, methods of determining acute rejection were heterogeneous, ranging from clinical judgment and laboratory values to biopsy, and therefore, comparing data across studies was problematic. Several studies did not provide detail regarding TAC formulation, dosing characteristics and trough concentrations. In addition, some studies allowed dose adjustments based on target TAC trough levels at various time points, while other studies did not state whether dose adjustments were allowed. Due to this lack of consistency, it was not always possible to determine whether TAC was administered at a bioequivalent dose across the studies, which in turn could undermine the interpretation of treatment effects.

As some studies were designed to assess the efficacy of induction therapy, they were not necessarily powered to examine the effectiveness of TAC-based maintenance immunosuppression. In addition, for the network meta-analysis, treatments were grouped according to QD or BID dosing of TAC, rather than the dosages of other medications, and so some studies effectively became single-arm trials and were excluded from the analysis because they lacked a comparator. Furthermore, numerous factors influence short- and long-term graft survival, including donor and recipient matching and recipient characteristics, such as age, sex, and history of prior transplantation [84]. These factors were often reported inconsistently across the studies we analyzed. For example, only 2 studies reported the percentage of patients with diabetes [26,37], despite diabetes being a known risk factor for renal transplant outcomes, including lower graft and patient survival [85,86]. However, despite these limitations, to the best of our knowledge, this is the current systematic review of TAC-based maintenance regimens in kidney transplant recipients.

**Conclusions**

In this comprehensive review, the treatment effect on graft loss and patient mortality at 6 to 12 months after transplantation was comparable between regimens of QD TAC (Advagraf) and BID TAC (Prograf) when combined with MPA and CS. Race did not significantly impact graft loss and mortality based on the regimen used, although this finding may be limited by the heterogeneity among studies. Conclusions regarding graft rejection were unclear due to lack of consistency in definitions between the studies. Further prospective research may be necessary to evaluate the long-term outcomes of and factors optimizing maintenance immunosuppression in kidney transplant recipients.

**Acknowledgements**

This systematic review and network meta-analysis was initiated and supported by Astellas Pharma Inc. Medical writing support was provided by Mark Greener, BSc, MRSB, for Cello Health MedErgy, funded by Astellas Pharma Inc.

**Data statement**

Researchers can request access to anonymized participant level data, trial level data, and protocols from Astellas sponsored clinical trials at [www.clinicalstudydatarequest.com](https://www.clinicalstudydatarequest.com). For the Astellas criteria on data sharing see: [https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx](https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx).

**Declaration of figures’ authenticity**

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
Supplementary Table 5. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was not reported.

Supplementary Table 6. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was reported.

Supplementary Table 7. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was reported.

Supplementary Table 8. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was reported.

Supplementary Table 9. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was reported.

Supplementary Table 10. Incidence of new-onset diabetes after transplant in studies in which the formulation of tacrolimus was reported.

Supplementary Table 11. Meta-regression analyses of graft loss and mortality adjusting for baseline proportion of White patients.

Supplementary Tables 1-11 available from the corresponding author on request.

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