Tacrolimus-Based, Steroid-Free Regimens in Renal Transplantation: 3-Year Follow-Up of the ATLAS Trial

Bernhard K. Krämer,[1,2,24] Marian Klinger,[3] Štefan Vítko,[4] Maciej Glyda,[5] Karsten Midtvedt,[6] Sergio Stefoni,[7] Franco Citterio,[8] Frank Pietruck,[9] Jean-Paul Squifflet,[10,11] Giuseppe Segoloni,[12] Bernd Krüger,[1,2] Heide Sperschneider,[13] Bernhard Banas,[2] Lars Bäckman,[14] Markus Weber,[15] Mario Carmellini,[16] Ferenc Perner,[17] Kerstin Claesson,[18] Wojciech Marcinkowski,[19] Marek Ostrowski,[20] Grzegorz Senatorski,[21] Johan Nordström,[22] and Kaija Salmela[23]

Background. Long-term use of corticosteroids is associated with considerable morbidity, including cardiovascular and metabolic adverse effects.

Methods. This study evaluated the long-term efficacy and safety of two steroid-free regimens compared with a triple immunosuppressive therapy in renal transplant recipients. This was a 3-year follow-up to a 6-month, open-label, randomized, multicenter study.

Results. Data from 3 years were available for 421 (93.3%) of 451 patients in the original intent-to-treat population (143 tacrolimus/basiliximab [Tac/Bas], 139 tacrolimus/mycophenolate mofetil [Tac/MMF], and 139 tacrolimus/MMF/

The original 6-month ATLAS study and statistical analyses were supported by Astellas Pharma Europe, Staines, UK.

B.K.K. has received lecture fees and honoraria from Astellas, Novartis, Teva, and Wyeth; served on advisory/safety boards for Astellas, Bristol-Myers Squibb, Novartis, Teva, and Wyeth; received research grants from Astellas and Novartis; and participated in clinical trials sponsored by Astellas, Bristol-Myers Squibb, Novartis, Roche, and Wyeth. J.-P.S. has received research grants from Novartis, Astellas, Roche, Wyeth, Fresenius, and Genzyme. B.B. participated in studies sponsored by Astellas, Bristol-Myers Squibb, Genzyme, Novartis, Roche, and Wyeth. B.K. participated in clinical trials sponsored by Astellas and Novartis. S.S. participated in advisory boards and received fees from Novartis, Bristol-Myers Squibb, and Bellco. M.C. has served on advisory boards for Astellas, Bristol-Myers Squibb, and Roche and participated in clinical trials sponsored by Astellas, Novartis, Roche, and Wyeth.

M.K., M.G., L.B., G.Sen, W.M., M.W., F.C., F.P., G.S., H.S., F.Pe., S.V., K.C., K.M., K.S., and J.N. declare no conflicts of interest.

[1] V. Medizinische Klinik, Universitätsklinikum Mannheim, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany.
[2] Klinik und Poliklinik für Innere Medizin II—Nephrologie, Klinikum der Universität Regensburg, Regensburg, Germany.
[3] Department of Nephrology and Transplantation Medicine, Wroclaw Medical University, Wrocław, Poland.
[4] Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.
[5] Department of Transplantology, Province Hospital, Poznan, Poland.
[6] Department of Nephrology, Oslo University Hospital—Rikshospitalet, Oslo, Norway.
[7] U.O. Nefrologia, Dialisi e Trapianto, Ospedale Policlinico S. Orsola, Bologna, Italy.
[8] Divisione di Chirurgia Sostitutiva e dei Trapiatanti d'Organo, Policlinico Universitario Agostino Gemelli, Rome, Italy.
[9] Klinik für Nephrologie, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany.
[10] Cliniques Universitaires Saint Luc, Brussels, Belgium.
[11] Department of Transplantation, CHU Liege, Belgium.
[12] Azienda Ospedaliera San Giovanni Battista, Torino, Italy.
[13] KfH-Nierenzentrum Jena, Zur Lämmerlaide 1, Jena, Germany.
[14] Transplantation and Liver Surgery, Uppsala University Hospital, Uppsala, Sweden.
[15] Department of Chirurgie, Klinik für Visceral- und Transplantationschirurgie, Universitätsspital Zürich, Zürich, Switzerland.
[16] Department of Surgery and Bioengineering, University of Siena, Policlinico le Scotte, Siena, Italy.
[17] Director of Transplantation and Surgical Clinic, Semmelweis Medical University, Budapest, Hungary.
[18] Medical Products Agency, Uppsala, Sweden.
[19] Formerly, Department of Nephrology and Metabolic Diseases, Silesian University, Medical School Katowice, Katowice, Poland; currently, Medical Vice-Director, Fresenius NephroCare, Poznan, Poland.
[20] Klinika Chirurgii Ogólnej I Transplantcyjnej, Pomorski Uniwersytet Medyczny, Szczecin, Poland.
[21] Department of Clinical Immunology, Transplantology, and Internal Diseases, Transplantation Institute, Medical University of Warsaw, Warsaw, Poland.
[22] Department of Transplantation Surgery, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden.
[23] Department of Surgery, Helsinki University Hospital, Helsinki, Finland.
[24] Address correspondence to: Bernhard K. Krämer, Prof. Dr. med., V. Medizinische Klinik, Universitätsklinikum Mannheim, Medizinische Fakultät Mannheim der Universität Heidelberg, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, Germany.
E-mail: bernhard.kraemer@umm.de

Study ID: Cochrane Renal Group CRG020800135

B.K.K. participated in organizing and performing the research, writing, and collecting and analyzing data. B.K. and B.B. participated in writing and collecting and analyzing data; M.K.: participated in performing the research and collecting and analyzing data; K.C., M.W., J.N., M.K., S.V., M.G., K.M., S.S., F.C., F.P., J.-P.S., G.S., H.S., L.B., M.C., F.Pe., W.M., M.O., G.Sen., K.S. participated in performing the research and collecting data. All authors participated in critical reading, commenting, and making final acceptance of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Received 26 January 2012. Revision requested 21 February 2012.
Accepted 24 April 2012.

ISSN: 0041-1337/12/9405-492
DOI: 10.1097/TP.0b013e31825c1d6c

steroids [triple therapy]). In the time interval from 6 months to 3 years after transplantation, the incidence of biopsy-proven acute rejection was low and similar (Tac/Bas, 2.1%; Tac/MMF, 2.2%; triple therapy, 2.2%); Most rejection episodes occurred during the first 6 months of the study. Graft survival was high (Kaplan-Meier estimates: 92.7%, 92.5%, and 92.5%), as was patient survival (93.1%, 96.4%, and 97.0%). There were 10 graft losses (n=2, 4, and 4) and 12 patient deaths (n=5, 2, and 5). Renal function was well preserved throughout the study and similar between groups. There was a trend toward improved cardiovascular risk factors in the Tac/Bas group, including reduced total and low-density lipoprotein cholesterol and lower new-onset insulin use. There were no between-group differences in the incidence or type of adverse events.

Conclusion. Higher rates of acute rejection early in treatment were seen with the steroid-free regimens, but this did not translate into poorer long-term outcomes, such as graft and patient survival and renal function. A trend for a more favorable cardiovascular risk profile was observed for steroid-free immunosuppression with Tac/Bas.

Keywords: Tacrolimus, Renal transplant, Immunosuppression, Steroid, Long term.

(*Transplantation* 2012;94: 492–498)

Corticosteroids form part of the immunosuppressive regimen used in many transplant centers. However, the long-term use of even low doses of corticosteroids has been associated with considerable morbidity, with adverse effects including hypertension, hyperlipidemia, diabetes mellitus, osteoporosis, fractures, Cushing syndrome, serious infections, and gastrointestinal events (*1–3*). Studies in various patient groups have reported that prednisolone use (even at low doses) significantly increased the risk of developing hypertension, diabetes, fractures (e.g., hip or spine), cataracts, bruising, and muscle weakness, as well as more risk for hospitalization for pneumonia (*4–7*). Furthermore, increasing duration of low-dose corticosteroid use (≤7.5-mg prednisolone) has been shown to be associated with acne, skin bruising, weight gain, and cataracts, whereas escalating dose was associated with fractures and sleep disturbances (*8*).

As a consequence of the detrimental effects of long-term corticosteroid use, research has been undertaken to evaluate the effects of corticosteroid avoidance or early withdrawal in renal transplant recipients. Most meta-analyses and reviews of published data have shown that steroid avoidance at transplantation or early withdrawal of steroids after transplantation was associated with increased rate or risk of acute rejection but without adversely affecting patient or graft survival (*9–14*). Moreover, a large prospective study of steroid withdrawal at least 6 months after transplantation in renal transplant recipients showed significantly improved patient and graft survival, as well as significantly improved cardiovascular risk factors, and similar rates of acute rejection compared with steroid continuation in retrospectively matched control patients (*15*). However, the data are not completely consistent because an earlier review of steroid-withdrawal studies in renal transplant recipients found that the increased risk of acute rejection also was accompanied by an increase in graft failure (*16*).

Tacrolimus is well established as a mainstay of immunosuppressive treatment after renal transplantation (*17–19*), but this agent also allows corticosteroid-sparing strategies to be implemented. For example, substituting cyclosporine with tacrolimus enables lower doses of maintenance corticosteroids to be used (*20–22*), and growing evidence indicates that combining tacrolimus with mycophenolate mofetil (MMF) or antibody induction therapy may allow early steroid withdrawal or complete avoidance of steroids in the posttransplantation setting (*23, 24*). However, long-term data investigating the effects of corticosteroid-free regimens are lacking.

The antibody, tacrolimus, and steroid withdrawal (ATLAS) study evaluated the feasibility of two corticosteroid-free immunosuppressive regimens (basiliximab induction therapy followed by tacrolimus monotherapy, and tacrolimus plus MMF) compared with a standard tacrolimus-based triple regimen after renal transplantation. The 6-month and 1-year follow-up data showed the rate of acute rejection was higher with both steroid-free regimens, but patient and graft survival was similar across the groups (*25, 26*). The present analysis reports the 3-year follow-up data for the ATLAS study, including patient and graft survival, incidence of acute rejection, renal function and tolerability.

RESULTS

Study Population

Of the 451 patients included in the full 6-month analysis set, 3-year follow-up data were available for 421 (93.3%) patients: tacrolimus/basiliximab (Tac/Bas), 143 (93.5%) of 153; tacrolimus/MMF (Tac/MMF), 139 (92.1%) of 151; and tacrolimus/MMF/steroids (triple therapy), 139 (94.6%) of 147. These rates of follow-up were only slightly lower than at 1 year with 432 (95.8%) patients. Demographics and baseline characteristics for patients included in the 3-year analysis were similar across treatment groups. Most patients were male (61.5%, 64.7%, and 61.2%) and the mean ages (SD) were 46.1 (11.5), 47.2 (11.8), and 45.7 (12.9) years in the Tac/Bas, Tac/MMF, and triple therapy groups, respectively.

Immunosuppression

At the 3-year visit, the mean doses of tacrolimus were similar in the Tac/MMF (4.5 mg) and triple therapy arms (4.4 mg) but were slightly higher in the Tac/Bas group (4.9 mg) (see **Table, SDC,** http://links.lww.com/TP/A679). Mean (SD) tacrolimus trough levels were 8.3 (3.01), 7.9 (2.46), and 8.1 (2.69) ng/mL in the Tac/Bas, Tac/MMF, and triple therapy groups, respectively.

At 3 years, 48.5% in the Tac/Bas group, 57.9% in the Tac/MMF group, and 42.6% in the triple therapy group remained on their original randomized immunosuppressive regimen (from 1 year proportions of 58.2%, 63.7%, and 69.7%, respectively). High numbers of patients remained on the components of their original randomized study treatments, largely preserving the steroid-free nature of the two test

treatment arms (Fig. 1). At 3 years, 64.0% in the Tac/Bas group, 77.6% in the Tac/MMF group, and 33.7% of patients in the triple therapy group were not receiving corticosteroids. Compared with the results at 1 year, the proportions for the Tac/Bas and Tac/MMF groups were slightly lower (71.0% and 74.8%, respectively), whereas the proportion in the triple therapy group increased considerably (22.1%); the changes from baseline in the use of corticosteroids were statistically significant at 1 year ($P<0.0001$) (see **Table, SDC,** http://links.lww.com/TP/A679). The proportions of patients on tacrolimus monotherapy at 3 years were 48.5% in the Tac/Bas group, 9.3% in the Tac/MMF group, and 3.0% in the triple therapy group (see **Table, SDC,** http://links.lww.com/TP/A679); the equivalent proportions at 1 year were 58.2%, 5.6%, and 0.8%, respectively.

Acute and Chronic Rejection

Biopsy-proven acute rejection (BPAR) incidence in all three groups was similar and infrequent at 3 years. Between the 6-month and 3-year visits, there were three BPAR episodes in the Tac/Bas group (2.1%), three episodes in the Tac/MMF (2.2%), and four episodes in the triple therapy group (2.2%). Most acute rejection episodes occurred during the main 6-month study, when the incidence was higher in the corticosteroid-free groups (26.1% in the Tac/Bas group and 30.5% in the Tac/MMF group vs. 8.2% in the triple therapy group; $P<0.001$).

The Kaplan-Meier estimates for the number of patients free from acute rejection were similar at 3 years to those at 1 year and 6 months within each treatment group: 71.7% versus 71.7% and 73.1% in the Tac/Bas group, 67.6% versus 67.6% and 69.1% in the Tac/MMF group, and 89.8% versus 91.5% and 91.5% and in the triple group, respectively (P=not significant at 3 years, Fig. 2). Of the total acute rejection episodes that occurred after the main 6-month study during the 3-year follow-up, four were in the Tac/Bas treatment group (one corticosteroid-resistant and three corticosteroid-sensitive episodes), five were in the Tac/MMF treatment group (four corticosteroid-sensitive episodes and one episode classified as ''other''), and four in the triple therapy group (all corticosteroid-sensitive).

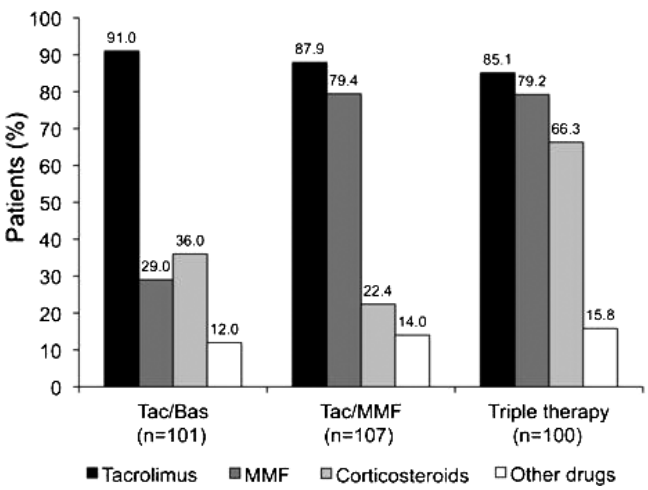

FIGURE 1. Immunosuppressive regimen of patients remaining on treatment at 3-year visit.

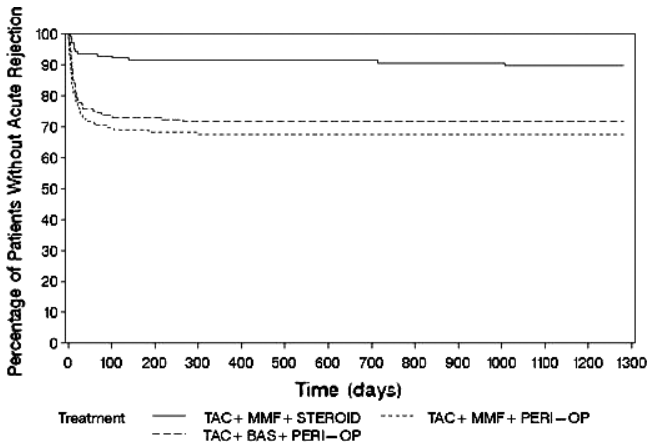

FIGURE 2. Patients free from acute rejection for 3 years (±6 months) (Kaplan-Meier estimate). Data collected during the main study (up to 6 months), at 1 year (with a 6-month window), and at 3 years (with a 6-month window). Bas, basiliximab; MMF, mycophenolate mofetil; Tac, tacrolimus.

Between 6 months and 3 years, chronic rejection was bioptically diagnosed in 3 (2.1%), 6 (4.3%), and 5 patients (3.6%) in the Tac/Bas, Tac/MMF, and triple therapy groups, respectively.

Graft and Patient Survival

Three-year graft survival (Kaplan-Meier estimate) was almost identical across the treatment groups at 92.7% in the Tac/Bas group and 92.5% in both the Tac/MMF and triple therapy groups (P=not significant, Fig. 3A). These rates were similar to those observed at 1 year (93.4%, 95.3%, and 95.9%, respectively) and 6 months (93.4%, 96.0%, and 95.9%, respectively).

In total, 10 graft losses occurred between the 6-month and 3-year visits, 2 in the Tac/Bas group (one due to recurrence of the primary disease and one with unknown cause), 4 in the Tac/MMF group (three due to chronic rejection and one due to recurrence of the primary disease), and 4 in the triple therapy group (one due to acute refractory rejection, one due to chronic rejection, one due to recurrence of the primary disease and one with unknown cause).

There were no significant differences between the three treatment groups in patient survival rates (Kaplan-Meier estimates) at 3 years (Fig. 3B): 93.1% in the Tac/Bas group, 96.4% in the Tac/MMF group, and 97.0% in the triple therapy group. Similar patient survival rates were also seen at 1 year (99.3%, 98.6%, and 98.6%) and 6 months (all 99.3%) in the Tac/Bas, Tac/MMF, and triple therapy groups, respectively.

There were 12 deaths between the 6-month and 3-year visits: 5 in the Tac/Bas group (pulmonary edema, liver cirrhosis, acute myocardial infarction, lymphoma, and B-cell lymphoma); 2 in the Tac/MMF group (cerebral vascular accident and myocardial infarction); and 5 in the triple therapy group (breast cancer, melanoma, carcinoma of the lung, and unknown in two cases).

Renal Function

Renal function was similar between the three treatment groups throughout the study. Mean serum creatinine level at 3 years was 137.6 μM in the Tac/Bas group, 141.9 μM in

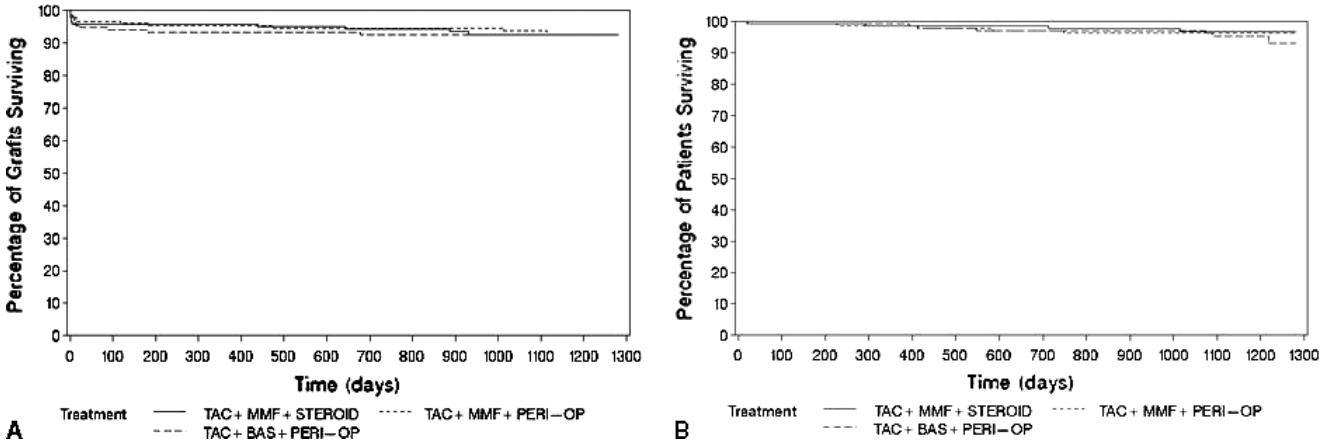

FIGURE 3. A, Graft and (B) patient survival for 3 years (±6 months) (Kaplan-Meier estimate). Data collected during the main study (up to 6 months), at 1 year (with a 6-month window), and at 3 years (with a 6-month window). Bas, basiliximab; MMF, mycophenolate mofetil; Tac, tacrolimus.

the Tac/MMF group, and 139.1 μM in the triple therapy group. The respective mean serum creatinine levels were 137.8 μM, 137.5 μM, and 129.8 μM at 1 year and 176.2 μM, 145.3 μM, and 141.8 μM at 6 months in the Tac/Bas, Tac/MMF, and triple therapy groups.

Mean estimated glomerular filtration rate was similar across the treatment groups at each assessment visit. Mean estimated glomerular filtration rate at 3 years was 54.4 mL/min per 1.73m^2 in the Tac/Bas group, 53.7 mL/min per 1.73m^2 in the Tac/MMF group, and 55.4 mL/min per 1.73m^2 in the triple therapy group; respective rates at 1 year were 53.4 mL/min per 1.73m^2, 53.5 mL/min per 1.73m^2, and 57.0 mL/min per 1.73m^2 and at 6 months were 45.9 mL/min per 1.73m^2, 50.8 mL/min per 1.73m^2, and 53.6 mL/min per 1.73m^2.

Safety

The treatment regimens were generally well tolerated. Adverse events (AEs) were similar in incidence, both overall and in the different categories, across the three treatment groups between the 1-year and 3-year follow-up visits (Table 1).

Laboratory parameters at the 3-year visit were generally similar across the three treatment groups and are summarized in Table 2. However, although total and LDL cholesterol levels decreased from baseline (transplantation) in all groups, a numerically higher decrease was seen in the Tac/Bas group compared with the other two groups (Tac/Bas vs. Tac/MMF, $P<0.05$). Similarly, antihyperlipidemic medication was administered to fewer patients in the Tac/Bas group (35 [24.5%]) compared with the Tac/MMF group (39 [28.1%]) and the triple therapy group (45 [32.4%])(P=not significant).

Blood pressure, both diastolic and systolic, was similar across the three treatment groups at the 3-year visit. At the same time point, 107 (74.8%), 111 (79.9%), and 108 (77.7%) patients were receiving antihypertensive medication in the Tac/Bas, Tac/MMF, and triple therapy groups (P=not significant).

Insulin use was reported in 8.4%, 19.4%, and 14.4% in the Tac/Bas, Tac/MMF, and triple therapy groups, respectively. New-onset insulin use between the 1-year and 3-year visits in patients who did not have diabetes at baseline (transplantation) was reported in 4 (3.0%), 9 (7.6%), and 6 (4.9%) patients, respectively, and oral antidiabetic medication use at the 3-year visit was reported in 4.9%, 3.6%, and 3.6% patients, respectively (P=not significant).

DISCUSSION

This observational, 3-year follow-up study in renal transplant recipients has shown that the two corticosteroid-free immunosuppressive regimens provided similar patient/graft survival and renal function compared with standard triple therapy, and all three strategies were generally well tolerated. Most patients in the Tac/Bas (64.0%) and Tac/MMF (77.6%) groups were corticosteroid-free at 3 years after transplantation, and 33.7% of patients in the triple therapy group remained steroid free at 3 years. The high number of patients becoming steroid-free in the original triple therapy group was unexpected and may dilute differences in efficacy or adverse effects between groups. In total, 42% to 58% of patients remained on their original randomized immunosuppression regimen. This is similar to a previous 3-year observational follow-up study in-

TABLE 1. Adverse events by category between 1-year and 3-year visits

	Tac/Bas n=143	Tac/MMF n=139	Triple Therapy n=139
Adverse event, n (%)	75 (52.4)	68 (48.9)	63 (45.3)
Infections, n (%)	22 (15.4)	30 (21.6)	26 (18.7)
Cardiovascular events, n (%)	10 (7.0)	6 (4.3)	4 (2.9)
Fractures (bone and joint disease), n (%)	5 (3.5)	6 (4.3)	4 (2.9)
Malignancies (including PTLDs), n (%)	4 (2.8)	4 (2.9)	6 (4.3)
Other, n (%)	17 (11.9)	18 (12.9)	18 (12.9)

Patients may have experienced more than one adverse event.
MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disease; Tac/Bas, tacrolimus/basiliximab.

TABLE 2. Mean laboratory values at 3-year visit and change from baseline (transplantation)

	Tac/Bas n=143	Tac/MMF n=139	Triple Therapy n=139
Total cholesterol, mM	4.97 (1.07)	4.94 (1.10)	5.07 (1.02)
Change from baseline, mM	−0.64 (1.35)[a]	−0.07 (1.61)	−0.27 (1.30)
LDL cholesterol, mM	2.84 (1.01)	2.87 (0.91)	2.75 (0.84)
Change from baseline, mM	−0.43 (1.131)[a]	−0.05 (1.29)	−0.30 (1.10)
Fasting plasma glucose, mM	5.20 (2.28)	5.38 (2.18)	5.26 (2.27)
Change from baseline, mM	−0.62 (1.94)	−0.42 (2.30)	−0.78 (2.89)
Blood pressure systolic/diastolic, mm Hg	132.72 (13.14)/82.30 (9.88)	135.79 (17.11)/82.90 (10.08)	133.98, (15.98)/81.79 (8.15)
Change from baseline systolic/diastolic, mm Hg	1.35 (19.33)/1.03 (12.58)	2.57 (22.31)/1.06 (12.68)	2.76 (17.86)/−0.06 (10.88)
Serum creatinine level, μM	137.61 (72.67)	141.85 (79.56)	139.09 (69.64)
Change from baseline, μM	−575.60 (238.52)	−574.50 (240.06)	−583.64 (237.32)
Hemoglobin, g/L	133.82 (24.19)	136.14 (22.06)	130.01 (25.92)
Change from baseline, g/L	9.37 (29.58)	11.46 (23.93)	8.23 (28.71)
Platelet count, $\times 10^9$/L	218.74 (57.78)	209.87 (69.74)	210.24 (57.40)
Change from baseline, $\times 10^9$/L	−12.42 (63.27)	−1.39 (69.25)	−8.86 (55.47)
White blood count, $\times 10^9$/L	7.58 (4.65)	7.12 (1.94)	7.30 (2.41)
Change from baseline, $\times 10^9$/L	0.20 (4.69)	−0.23 (2.37)	−0.28 (2.22)

[a] $P<0.05$ vs. Tac/MMF.
Data are presented as mean (SD).
Bas, basiliximab; LDL, low-density lipoprotein; MMF, mycophenolate mofetil; Tac, tacrolimus.

vestigating the withdrawal of steroids or MMF from tacrolimus-based triple therapy, in which 46% to 63% of patients remained on their original regimen (*23*). The trend for a notable proportion of patients initiated on triple therapy control arm to become steroid-free may be seen as a positive development for potentially reducing steroid-related morbidity.

Overall, the results of this 3-year study provide support for previous findings that steroid-free regimens are a feasible alternative to triple therapy in the long-term management of renal transplant recipients (*23, 27*). An observational, 3-year study of steroid withdrawal 3 months after transplantation (*23*) and a double-blind, randomized, 5-year trial of steroid withdrawal at 7 days after transplantation (*27*) demonstrated that similar rates of patient and graft survival were achieved, and renal function was well preserved compared with tacrolimus-based triple therapy (with or without antibody induction). Similar to the ATLAS study, both of these studies also showed that acute rejection occurred more frequently with the steroid-free immunosuppression regimens compared with triple therapy, with most episodes reported in the first 6 months after transplantation. Hence, the present study confirms prior observations that, although early higher rates of acute rejection may be seen with steroid-free regimens, this does not translate into poorer long-term outcomes, such as graft and patient survival and renal function.

In the present analysis, the Tac/Bas regimen offered a favorable cardiovascular risk factor profile, showing statistically nonsignificant trends for greater reduction in serum cholesterol and lower use of antihyperlipidemic and insulin medications compared with the Tac/MMF and triple therapy treatment arms. These findings are consistent with those observed at 6 months and 1 year (*25, 26*). A reduction in risk factors for posttransplantation cardiovascular disease, which is a leading cause of mortality in renal transplant recipients, is a key benefit of steroid-free immunosuppression regimens (*28*). This advantage of steroid avoidance has been demonstrated in several other studies of renal transplant patients, including the aforementioned 3- and 5-year studies, which have shown reductions compared with corticosteroid therapy in posttransplantation incidence of new-onset diabetes mellitus, new-onset metabolic syndrome, reduced serum cholesterol, and improved blood pressure (*23, 24, 27, 29*). Furthermore, several recent reviews of steroid withdrawal or avoidance that focused more on a contemporary immunosuppression (often including the use of mycophenolic acid and interleukin 2 receptor antibodies) confirmed the main findings of our study, that is, unaffected graft and patient survival rates, despite a higher rate of acute rejection, and decreased cardiovascular risk factors (*10–14*).

The main limitation of the study is that changes to the patients' immunosuppression regimens could be made at the discretion of the investigator after the main 6-month study. Although it is very encouraging to see such high numbers of patients remaining on tacrolimus-based treatment at 3 years after transplantation, the degree of switching between regimens makes it difficult to draw firm conclusions or make comparisons between groups. Specifically, patients originally randomized to the steroid-free treatment groups may not have remained steroid-free throughout the follow-up period, and this undoubtedly complicates the interpretation of the long-term effects of each treatment regimen. Another limitation of the present analysis is the duration of follow-up. Three years is probably insufficient to clearly determine the long-term effects of steroid-free immunosuppression on renal allograft function and other efficacy and safety parameters. Further research in large, randomized, double-blind clinical trials of more than 5 years may be warranted to fully investigate this treatment strategy.

In conclusion, this analysis provides evidence that corticosteroid-free regimens are feasible and effective while preserving renal function in renal transplant recipients during the long term. In addition, the effects of acute rejection episodes on the health of the patient and the graft must be considered alongside the safety implications of long-term steroid use, that is, increased risk of cardiovascular and metabolic events. It may therefore be prudent to use low-dose immunosuppression coupled with steroid withdrawal or avoidance where possible, reserving steroid-based regimens for those patients at more risk of acute rejection, although treatment benefits of steroid-free protocols did not reach statistical significance.

MATERIALS AND METHODS

Study Population

The methodology has been described in detail previously (*25*). Briefly, this study was conducted in 21 transplant centers in 10 European countries (Study ID: Cochrane Renal Group CRG020800135) in accordance with the Declaration of Helsinki and in compliance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) regulation and guidelines.

Adult patients (aged 18–65 years) with end-stage renal disease were eligible for inclusion if they were suitable candidates for primary renal transplantation from a deceased or living donor aged 5–65 years with a compatible ABO blood type. Patients were excluded from the study if they showed a panel reactive antibody grade 50% or higher in the previous 6 months or underwent retransplantation. Renal transplant recipients in the present trial showed a low immunologic risk as exemplified by being of white race, having a mean human leukocyte antigen mismatch of 2.7 to 2.9, having mean panel reactive antibody levels of 2%, and all receiving a primary renal transplant (cadaveric donor in 88%–89%). Full inclusion and exclusion criteria have been listed previously (*25*).

Study Design

This was a 3-year follow-up study to an open-label, parallel-group, randomized, multicenter study designed to assess the efficacy and safety of corticosteroid avoidance with tacrolimus (Prograf; Astellas Pharma Europe Ltd., Staines, UK) monotherapy after Tac/Bas induction and from a dual Tac/MMF regimen without antibody induction, compared with triple therapy. In the 6-month study, patients were randomized 1:1:1, stratified by center (*25*).

After the 6-month period of the original study, all patients were managed according to the center preferences, and only routine data were collected. Data were collected throughout the main study, that is, up to 6 months and then at visits at 1 year (with an additional time window of up to 6 months) and at 3 years (±6 months).

Study Treatments

In the original study, all patients received tacrolimus at an initial dosage of 0.2 mg/kg per day given in two divided doses of 0.1 mg/kg. The first dose was administered within 12 hr before reperfusion. Subsequent doses of tacrolimus were adjusted to maintain whole-blood trough levels of 10 to 20 ng/mL on days 0 to 28 and 5 to 15 ng/mL from months 1 to 6. For all treatments, dosing after the 6-month treatment period was at the discretion of the investigator.

The Tac/MMF and triple therapy groups received MMF at an initial oral dosage of 2 g/day with 1 g given within 12 hr before reperfusion. This was maintained up to day 14, after which 1 g/day was administered until the end of the main study. Patients in the Tac/Bas group received two 20 mg doses of basiliximab, one on day 0 within 2 hr of surgery, and one on day 4 after transplantation.

All patients received an intravenous perioperative dose of 500-mg methylprednisolone or more. For the corticosteroid-free groups, no further corticosteroid administration was planned after the day of surgery. Patients in the triple therapy group received an intravenous bolus of methylprednisolone 125 mg on day 1 and oral prednisolone (or equivalent) as follows: 20 mg/day on days 2 to 14, 15 mg/day on days 15 to 28, 10 mg/day on days 29 to 42, and 5 mg/day until the end of the main study.

Efficacy and Safety Assessments

The main efficacy endpoints in this 3-year follow-up were incidences of BPARs, patient and graft survival, renal function (measured by serum creatinine levels and glomerular filtration rates [calculated using the Modified Diet in Renal Disease equation]) (*30*). Criteria for efficacy endpoints have been described previously (*25*). Safety was assessed by monitoring AEs for specific body systems and parameters, recording comedications, changes in laboratory parameters (including serum lipids), and vital signs.

Statistical Analysis

Statistical analysis of the data is considered as exploratory and based on observational data. Efficacy was analyzed using the intent-to-treat population, which included all randomized patients who were transplanted and received at least one dose of study medication (basiliximab and tacrolimus for the Tac/Bas group, tacrolimus and MMF for the Tac/MMF, and triple therapy groups). Safety was based on the intent-to-treat patients who provided data for the 3-year follow-up period.

Incidences of and times to first BPAR and first acute rejections, as well as patient and graft survival for the original 6-month study and up to 3 years after transplantation were analyzed using Kaplan-Meier survival procedures, with the standard error computed according to the Greenwood formula. Differences between treatment groups were analyzed using the Wilcoxon-Gehan test. No adjustment was carried out for multiple comparisons. The frequency of acute rejections, the proportion of corticosteroid-free patients, and the proportion of patients on specific medications at year 3 were analyzed using a chi-square statistic. Continuous parameters like renal function were compared globally among treatment groups using the Mann-Whitney *U* test. Fisher exact test was used to compare the incidence of AEs.

ACKNOWLEDGMENTS

The authors would like to thank Caroline Anthony, a professional medical writer with Acumed, for her assistance in drafting and revising the article.

REFERENCES

1. Ansell BM. Overview of the side effects of corticosteroid therapy. *Clin Exp Rheumatol* 1991; 9(suppl 6): 19.
2. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994; 96: 115.
3. Fellstrom B. Risk factors for and management of post-transplantation cardiovascular disease. *BioDrugs* 2001; 15: 261.
4. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; 56: 279.
5. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with systemic and topical corticosteroids. *J Intern Med* 2005; 257: 374.
6. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; 54: 628.
7. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. *Arthritis Rheum* 2008; 58: 2612.
8. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; 55: 420.
9. Hricik DE, O'Toole MA, Schulak JA, et al. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. *J Am Soc Nephrol* 1993; 4: 1300.
10. Pascual J, Quereda C, Zamora J, et al. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. *Transplantation* 2004; 78: 1548.

11. Pascual J, Zamora J, Galeano C, et al. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009: 1: CD005632.
12. Pascual J, Galeano C, Royuella A, et al. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation* 2010; 90: 343.
13. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation* 2010; 89: 1.
14. Knight SR, Morris PJ. Steroid avoidance or withdrawal in renal transplantation. *Transplantation* 2011; 91: e25.
15. Opelz G, Döhler B, Laux G, et al. Long-term prospective study of steroid withdrawal in kidney and heart transplant recipients. *Am J Transplant* 2005; 5(4 pt 1): 720.
16. Kasiske BL, Chakkera HA, Louis TA, et al. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol* 2000; 11: 1910.
17. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; 359: 741.
18. Mayer AD. Chronic rejection and graft half-life: five-year follow-up of the European tacrolimus multicenter renal study. *Transplant Proc* 2002; 34: 1491.
19. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; 357: 2562.
20. Mayer AD, Dmitrewski J, Squifflet J-P, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection. *Transplantation* 1997; 64: 436.
21. Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation* 2002; 73: 775.
22. Montagnino G, Krämer BK, Arias M. Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in kidney transplantation: twelve-month follow-up. *Transplant Proc* 2002; 34: 1635.
23. Pascual J, van Hooff JP, Salmela K, et al. Three-year observational follow-up of a multicenter, randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplant. *Transplantation* 2006; 82: 55.
24. Rostaing L, Cantarovich D, Mourad G, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation* 2005; 79: 807.
25. Vitko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens—tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil—in comparison with a standard triple regimen in renal transplantation: results of the ATLAS study. *Transplantation* 2005; 80: 1734.
26. Krämer BK, Klinger M, Wlodarczyk Z, et al. Tacrolimus combined with two different corticosteroid-free regimens compared with a standard triple regimen in renal transplantation: one-year observational results. *Clin Transplant* 2010; 24: E1.
27. Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg* 2008; 248: 564.
28. Briggs JD. Cardiovascular complications in renal transplantation. *Nephrol Dial Transplant* 2001; 16(suppl 6): 156.
29. Rike AH, Mogilishetty G, Alloway RR, et al. Cardiovascular risk, cardiovascular events, and metabolic syndrome in renal transplantation: comparison of early steroid withdrawal and chronic steroids. *Clin Transplant* 2008; 22: 229.
30. Levey AS, Bosch JP, Lewis JB, et al. 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.