Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial

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Summary

Background Standard practice for immunosuppressive therapy after renal transplantation is quadruple therapy using antibody induction, low-dose tacrolimus, mycophenolate mofetil, and corticosteroids. Long-term steroid intake significantly increases cardiovascular risk factors with negative effects on the outcome, especially post-transplantation diabetes associated with morbidity and mortality. In this trial, we examined the efficacy and safety parameters of rapid steroid withdrawal after induction therapy with either rabbit antithymocyte globulin (rabbit ATG) or basiliximab in immunologically low-risk patients during the first year after kidney transplantation.

Methods In this open-label, multicentre, randomised controlled trial, we randomly assigned renal transplant recipients in a 1:1:1 ratio to receive either basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and steroid maintenance therapy (arm A), rapid corticosteroid withdrawal on day 8 (arm B), or rapid corticosteroid withdrawal on day 8 after rabbit ATG (arm C). The study was done in 21 centres across Germany. Only participants aged between 18 and 75 years with a low immunological risk who were scheduled to receive a single-organ renal transplant from either a living donor or a deceased donor were considered for enrolment. Patients receiving a second renal transplant were eligible, provided that the first allograft was not lost due to acute rejection within the first year after transplantation. Donor and recipient had to be ABO compatible. Grafts with pre-transplant existing donor-specific human leukocyte antigen (HLA) antibodies were not eligible and the recipients had to have a panel-reactive antibody concentration of 30% or less. Pregnant women and nursing mothers were excluded from the study. The primary endpoint was the incidence of biopsy-proven acute rejection (BPAR) at 12 months. All analyses were done by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00724022.

Findings Between Aug 7, 2008, and Nov 30, 2013, 615 patients were randomly assigned to arm A (206), arm B (189), and arm C (192). BPAR rates were not reduced by rabbit ATG (9·9%) compared with either treatment arm A (11·2%) or B (10·6%; A versus C: p=0·75, B versus C p=0·87). As a secondary endpoint, rapid steroid withdrawal reduced post-transplantation diabetes in arm B to 24% and in arm C to 23% compared with 39% in control arm A (A versus B and C: p=0·0004). Patient survival (94·7% in arm A, 97·4% in arm B, and 96·9% in arm C) and censored graft survival (96·1% in arm A, 96·8% in arm B, and 95·8% in arm C) after 12 months were excellent and equivalent in all arms. Safety parameters such as infections or the incidence of post-transplantation malignancies did not differ between the study arms.

Interpretation Rabbit ATG did not show superiority over basiliximab induction for the prevention of BPAR after rapid steroid withdrawal within 1 year after renal transplantation. Nevertheless, rapid steroid withdrawal after induction therapy for patients with a low immunological risk profile can be achieved without loss of efficacy and is advantageous in regard to post-transplantation diabetes incidence.

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Introduction

More than two million people worldwide suffer from end-stage kidney disease and need renal replacement therapy.[1] Although kidney transplantation is the best renal replacement therapy compared with dialysis, many transplant recipients die prematurely with a functioning graft because of complications of immunosuppressive therapy (eg, life-threatening infections, cancer, or cardiovascular events). Based on the findings of the ELITE-Symphony study,[2] the present gold standard of immunosuppressive therapy after renal transplantation consists of a chimeric monoclonal interleukin-2-receptor (CD 25 antigen) antibody induction therapy followed by low-dose tacrolimus, mycophenolate mofetil (MMF), and steroids. Nevertheless, in the Symphony study, the low-dose tacrolimus regimen compared with all other treatment arms had the highest incidence rates of post-transplantation diabetes.[2] Steroids can induce or worsen hypertension, hyperlipidaemia, and diabetes, which in turn can increase a transplant recipient's cardiovascular risk profile. Cardiovascular events are the leading cause of death in renal transplant recipients with a functioning

Research in context

Evidence before this study

The harmony trial was designed predominantly based on the 1-year results of the ELITE-Symphony trial, showing that low-dose tacrolimus, mycophenolate mofetile, and steroids together with monoclonal interleukin-2-receptor (CD 25 antigen) antibody induction therapy has a better efficacy than all other regimens tested. Although this therapy regimen became the new gold standard of immunosuppressive therapy within the next few years, the low-dose tacrolimus treatment arm also showed increased incidence of post-transplantation diabetes. Previous studies had also shown a detrimental association between NODAT and cardiovascular events and mortality, the leading cause of death in renal transplant recipients. Corticosteroid-free or rapid withdrawal regimens were encouraging regarding influence of NODAT rates, but only at the price of an increased rate of T-cell-mediated acute rejections. We searched MEDLINE and PubMed for reports published until March 2008, using the terms "renal transplantation", "kidney transplantation", "acute rejection rate", "steroid withdrawal", "cardiovascular risk profile", "patient and graft survival" with no data or language restrictions. Unfortunately, the absence of post-transplantation diabetes incidence data in the scientific literature as prospectively assessed by predefined (ADA) criteria did not allow calculatation of case numbers for the Harmony trial, whereas sufficient evidence on biopsy-proven acute rejection (BPAR) rates enabled us to choose BPAR as the primary endpoint. In general, rabbit antithymocyte globulin (ATG) therapy was considered to be better than interleukin-2-receptor antagonistic induction therapy in the prevention of BPAR, but this comparison had not been tested in rapid steroid withdrawal in an immunologically low-risk transplant population.

Added value of this study

To our knowledge, the Harmony trial is the first study to provide evidence for the most efficacious and safe protocol for rapid steroid withdrawal and optimised choice of induction therapy (basiliximab versus rabbit ATG) within the first year after kidney transplantation. Our findings imply that rabbit ATG induction combined with rapid steroid withdrawal does not further reduce the rate of biopsy-proven acute rejections in an immunologically low-risk patient population compared with basiliximab induction either with or without rapid steroid withdrawal based on the present gold standard therapy of low-dose tacrolimus and mycophenolate mofetil maintenance immunosuppression. However, the data of the Harmony trial show for the first time that rapid steroid withdrawal together with low-dose tacrolimus and mycophenolate mofetil immunosuppression can be achieved with either induction therapy in more than 80% of renal transplant recipients without any negative effect on efficacy (rejections, survival, etc), but with a marked decrease of the cardiovascular risk factor post-transplantation diabetes within the first year after transplantation.

Implications of all the available evidence

Despite the restrictions and limitations (long-term follow-up investigation, etc) discussed in this Article, we view these 1-year results as a major step towards the justification and stratification of rapid steroid withdrawal after renal transplantation. The Harmony study provides novel evidence for a new standard immunosuppressive strategy including rapid steroid withdrawal in an immunologically low-risk recipient population.

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graft.[3] In the population at large, diabetes doubles the risk of death from cardiovascular events.[4] A detrimental association between post-transplantation diabetes and cardiovascular events or mortality has been shown in a previous study.[5] Registry data[6] as well as a case control study[7] suggest that steroid-withdrawal protocols lead to a lower incidence of post-transplantation diabetes as well as superior long-term graft and patient survival. Nevertheless, these retrospective data are compromised by a selection bias, and so far, corticosteroid-free or corticosteroid-withdrawal regimens have been associated with increased T-cell-mediated acute rejection rates.[8,9] Although Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest rapid steroid withdrawal in the early phase of renal transplantation in patients with low immunological risk, this recommendation is only based on level 2B evidence (2: suggested, B: moderate quality of evidence).[10] In addition, the use of the interleukin-2-receptor antagonist basiliximab as induction therapy in general is based on level 1B evidence (1: recommended, B: moderate quality of evidence).[10]

Thus, we did a randomised, multicentre study (Harmony) to assess which of the two induction therapies was most efficacious at permitting rapid steroid withdrawal in tacrolimus-based and MMF-based immunosuppressive therapy within the first year after kidney transplantation. Efficacy of steroid withdrawal was assessed against the accepted gold standard immunosuppressive regimen (low tacrolimus plus MMF plus corticosteroid regimen, from the ELITE-Symphony trial). Two rapid steroid withdrawal study arms with different induction therapies were examined in an immunologically low-risk population. We tested whether induction therapy with rabbit antithymocyte globulin (ATG) was superior to induction therapy with basiliximab with respect to frequency of biopsy-proven acute rejection (BPAR) rate in the situation of rapid steroid withdrawal or corticosteroid maintenance therapy.

As secondary outcome parameters, we further tested the hypotheses that rapid steroid withdrawal does not compromise patient or graft survival or graft function while improving a recipient's cardiovascular risk profile, especially with respect to post-transplantation diabetes.

Methods

Study design and participants

The Harmony trial was an investigator-initiated, prospective, randomised, open-label, multicentre study in three parallel study arms of adult renal transplant recipients. Patients were recruited from 21 centres in Germany. The safety population and the intention-to-treat population consisted of all patients who received at least one dose of a study drug or underwent renal transplantation. The per-protocol population was strictly defined to include only patients who received treatment according to protocol throughout the study period and reached the final follow-up after 12 months. Only participants aged between 18 and 75 years with a low immunological risk who were scheduled to receive a single-organ renal transplant from either a living donor or a deceased donor were considered for enrolment. Patients receiving a second renal transplant were eligible, provided that the first allograft was not lost due to acute rejection within the first year after transplantation. Donor and recipient had to be ABO compatible. The direct crossmatch had to be negative (complement-dependent cytotoxicity crossmatch, CDC-test). Grafts with pre-transplant existing donor-specific human leukocyte antigen (HLA) antibodies were not eligible and the recipients had to have a reactive antibody concentration of 30% or less. Pregnant women and nursing mothers were excluded from the study. Women of childbearing age had to use contraceptives. Further exclusion criteria were patients with symptoms of somatic or psychiatric disease; patients incapable of comprehending the nature, meaning, or consequences of the trial and thus unable to participate; patients unable to communicate sufficiently; patients incapable of following the study guidelines or giving their informed consent; patients with signs of alcohol or other drug misuse; patients with multiorgan transplantation; patients with paediatric en-bloc kidney transplantation; recipients of kidneys from HLA-identical or non-heart beating donors; patients with incompatibility with study drug; patients with a history of cancer within the last 5 years (except for non-melanoma skin cancer); patients with signs of ongoing infections, or recipients who were seropositive for hepatitis B surface antigen, antibody against hepatitis B core antigen, hepatitis C virus, or HIV; patients with bowel disease with malabsorption; patients with primary focal sclerotic or membrano-proliferative glomerulonephritis, autoimmune disease with need for corticosteroid therapy, thrombocytopenia of 70 tsd/µL or less, leucopenia of 2·5 tsd/µl or less, or neutropenia of 1·5 tsd/µL or less; patients with liver cirrhosis Child-Pugh score B and C or other serious liver disease; and cold ischaemic time of the graft of 30 h or more.

See Online for appendix

The study was done in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed written consent and were allowed to withdraw from the study at any time.

Randomisation and masking

Participants were centrally randomly assigned in a 1:1:1 ratio. The randomisation list was computer generated with SAS (version 8.1) and stratified according to individual centres. Each participating centre received consecutively numbered, sealed envelopes. After receiving informed consent, the envelopes were opened to determine the type of immunosuppressive therapy. Neither patients nor those giving treatment or assessing outcomes and analysing data were masked to the patients' study group assignment.

Procedures

Patients were randomly assigned to one of three study arms (A, B, and C; figure 1). Arm A was the control group, in which patients received induction therapy with basiliximab (Simulect; Novartis, Basel, Switzerland) 20 mg intravenously on day 0 before allograft reperfusion and on day 4, and prolonged release tacrolimus (Advagraf; Astellas Pharma GmbH, München, Germany) once daily at 0·2 mg/kg of bodyweight per day with intended drug trough level of 7–12 ng/mL within the first month, 6–10 ng/mL during months 2 and 3, and 3–8 ng/mL during months 4–12); MMF (CellCept; Roche Pharma AG, Reinach, Switzerland) at two 1 g doses per day; and prednisolone (Solu Decortin; Merck Serono, Darmstadt, Germany) on the day of surgery (day 0) and tapering according to the institutional standard with a requirement of reaching a dose of 10 mg of prednisolone per day after 4 weeks and a maintenance dose of 2·5–5·0 mg per day after 3 months. In arm B, patients received the same treatment as those in arm A with the exception that corticosteroids were withdrawn from day 8. Hereby, 500 mg prednisolone on day 0 were followed by 100 mg on day 1, 75 mg on day 2, 50 mg on day 3, and 25 mg per day on days 4– 7. In arm C, patients received the same treatment as those in arm B, except induction was achieved with rabbit ATG (Thymoglobulin; Sanofi, Paris, France) instead of basiliximab. Treatment with rabbit ATG was started intraoperatively, before graft reperfusion with a dose of 1·5 mg per kg of bodyweight given intravenously. Rabbit ATG was given daily for up to four days, aiming for a total dose of 6·0 mg/kg bodyweight on postoperative day 3. The fourth dose of rabbit ATG on day 3 was omitted if the total count of lymphocytes was below 200/µL the day after the third dose (appendix).

All patients with either a high-risk constellation (recipient negative, donor positive) for cytomegalovirus or Epstein-Barr virus disease or patients who had induction therapy with rabbit ATG received at least a 3-month prophylaxis with valganciclovir. Additionally, Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim and sulfamethoxazole or pentamidine was mandatory for all patients for at least 6 months.

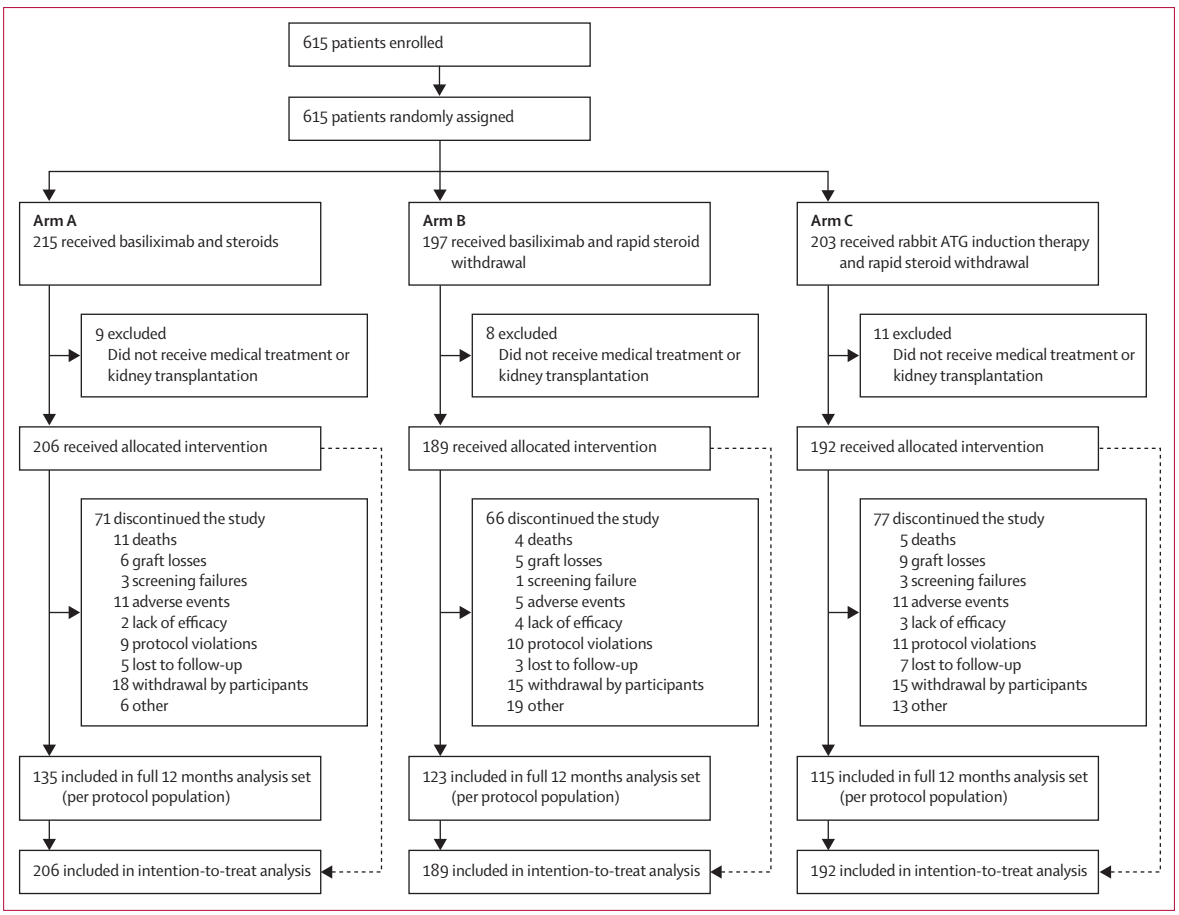

***Figure 1*: Trial profile**
The per-protocol population comprises all patients who received the allocated treatment without protocol violation during the complete follow-up period of 12 months. ATG=antithymocyte globulin.

Outcomes

The primary efficacy endpoint was the incidence of BPAR within the first year after renal transplantation. We compared the BPAR incidence rates of study arm A with arm C and study arm B with arm C. All suspected episodes of acute rejection were confirmed by biopsy, with histological characteristics described according to the Banff criteria of 2005.[11] On a centre-by-centre basis, protocol biopsies were allowed but not mandatory. Regarding the primary efficacy endpoint assessment, borderline rejections were not designated as BPAR.

Secondary endpoints were as follows: patient and graft survival; graft function with calculated glomerular filtration rate by the Cockcroft Gault formula[12] or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;[13] percentage of patients, in which steroid-free immunosuppressive treatment was maintained after 12 months; incidence of post-transplantation diabetes; systolic and diastolic blood pressure; lipids (HDL, LDL, and triglycerides); bodyweight; infections including the incidence of cytomegalovirus (PCR>1000 copies/µl), Epstein-Barr virus (PCR>1000 copies/µl), or BK virus (PCR>10 000 copies/µl) infections; incidence of malignancy; wound healing disorders; cataract formation; and osteoporosis. For post-transplantation diabetes assessment (according to the American Diabetes Association [ADA] recommendations), fasting glucose concentration was determined at each visit (0, 2, and 4 weeks, and 2, 3, 6, 9, and 12 months); HbA_{1c} concentration was measured at each visit except after 2 weeks; and an oral glucose tolerance test was done at 3 and 12 months in all patients without a present diagnosis of post-transplantation or pre-transplantation diabetes (if the diabetes or post-transplantation diabetes diagnosis was already clear using the other ADA criteria or the patient was under diabetic treatment, no additional diagnosis via OGTT was necessary or reasonable). Treatment failure was defined as the occurrence of any of the following: the use of additional immunosuppressive drugs, especially starting chronic steroid drugs in the rapid steroid withdrawal study arms B and C; the discontinuation of any study drug for more than 21 consecutive days; allograft loss; or death.

	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	Total (n=587)
Age (years)	54·5 (1·0)	54·0 (12·8)	53·6 (11·9)	54·1 (1·2)
Men	141 (68%)	122 (65%)	124 (65%)	387 (66%)
Caucasian	205 (100%)	186 (98%)	188 (98%)	579 (99%)
Cause of end-stage renal disease				
Hypertension or large vessel disease	77 (37%)	71 (38%)	69 (36%)	217 (37%)
Glomerulonephritis	57 (28%)	56 (30%)	48 (25%)	161 (27%)
Polycystic kidney disease (adult type, dominant)	43 (21%)	34 (18%)	36 (19%)	113 (19%)
Diabetes	27 (13%)	16 (8%)	19 (10%)	62 (11%)
Interstitial nephritis or pyelonephritis	16 (8%)	15 (8%)	13 (7%)	44 (7%)
Secondary glomerulonephritis or vasculitis	3 (1%)	7 (4%)	1 (1%)	11 (2%)
Other hereditary or congenital diseases	14 (7%)	4 (2%)	6 (3%)	24 (4%)
Neoplasms or tumours	3 (1%)	1 (1%)	3 (2%)	7 (1%)
Other	61 (30%)	59 (31%)	69 (36%)	189 (32%)
Undefined cause	10 (5%)	25 (13%)	18 (9%)	53 (9%)
Type of donor				
Deceased	174 (84%)	169 (89%)	168 (88%)	511 (87%)
Living	32 (16%)	20 (11%)	24 (13%)	76 (13%)
Donors with expanded criteria†	90 (44%)	86 (46%)	84 (44%)	260 (44%)
Donor age (years)	54·0 (14·6)	55·0 (14·4)	53·1 (15·1)	54·0 (14·7)
Antigen mismatches: A, B, and DR‡	0·8, 1·0, 0·9	0·8, 1·0, 0·8	0·8, 1·0, 0·9	0·8, 1·0, 0·9
No panel-reactive antibodies before transplantation	177 (86%)	168 (89%)	172 (90%)	517 (88%)
Previous transplants	11 (5%)	6 (3%)	6 (3%)	23 (4%)
Cold-ischaemia time: deceased donors only (min)	699 (269)	702 (295)	732 (303)	710 (289)
Cytomegalovirus serologic status: donor positive, recipient negative	51 (25%)	47 (25%)	50 (26%)	148 (25%)
Epstein-Barr virus serological status: donor positive, recipient negative	10 (5%)	11 (6%)	8 (4%)	29 (5%)

Data are n (%) or mean (SD), unless otherwise stated. ATG=antithymocyte globulin. *Between-group differences for demographic and clinical characteristics were not statistically significant. Calculated for A *vs* B *vs* C by Fisher's exact test. †Expanded criteria for donors included an age of more than 60 years, or an age of more than 50 years and at least two of the following factors: cerebrovascular accident as the cause of death, hypertension, or a serum creatinine level of more than 1·5 mg/dL. ‡A score of 2 means complete matching and 0 means no matching at all.

Table 1*: Baseline characteristics

Safety was assessed clinically, including vital signs and laboratory analyses designed to determine the incidence of all adverse and serious adverse events, infections, malignancies, and death throughout the study. Demographic and baseline data of the recipients and donors were assessed before transplantation including serostatus for cytomegalovirus and Epstein-Barr virus. Documentation of clinical signs and laboratory data were obtained at baseline, days 7 and 14, and months 1, 3, 6, 9, and 12.

Statistical analysis

The projected incidence of our primary endpoint BPAR (P_A) was estimated at 17% for our reference control study arm A with basiliximab induction therapy and chronic steroid drug treatment.[2,14] According to our working hypothesis, that early steroid withdrawal is not accompanied by an increased BPAR rate in this immunologically low-risk population, we assumed the same 17% rejection rate (P_B) for the study arm B with basiliximab induction therapy followed by rapid steroid withdrawal.[15,16] For our third study arm C (rabbit ATG induction therapy followed by rapid steroid withdrawal) we assumed a BPAR (P_C) of 6·4% based on previous studies.[17]

The aim of our study was to show superiority of arm C versus arm A with respect to the BPAR rate (ie, a test of the null hypothesis: $P_C - P_A = 0$) and to show superiority of arm C versus arm B with respect to the BPAR rate (ie, a test of the null hypothesis: $P_C - P_B = 0$).

The sample size was designed for both null hypotheses $P_C - P_A = 0$ and $P_C - P_B = 0$ to detect a difference in the BPAR rate between study arm A or B and study arm C with a statistical power of 80% and a split alpha value of 0·025. We calculated that 576 patients should be allocated to three study groups (192 patients each) to compensate for a dropout rate of 5%. Initially we had planned to enrol 610 transplant recipients. Both hypotheses were tested with the exact Fisher test ($\alpha = 0{\cdot}025$). All analyses were done on the basis of an intention-to-treat principle. Categorical variables were summarised as counts and percentages, and continuous variables as means with SDs. Categorical data were compared with Fisher's exact test, and continuous variables with the Wilcoxon-Mann-Whitney test or *t* test. The time for reaching BPAR, graft loss, or death was calculated with the Kaplan-Meier method. Treatment comparisons were done with the log-rank test. The incidences of adverse events and serious adverse events were tested by the Kruskal-Wallis Rank Sum Test. Analyses were done with SAS (version 9.4). A follow-up for data collection was done whenever possible with patients who were prematurely eliminated from the study. The study design did not include an interim assessment. This trial is registered with ClinicalTrials.gov, number NCT00724022.

Role of the funding source

The trial was designed and run by OT and CH who received financial support from Astellas Pharma GmbH, Roche Pharma AG, and Sanofi. The funders had no role in data collection, data analysis, data interpretation, or writing of the manuscript. Independent contract research organisations (ClinTrio Ltd, Hannover, Germany; Clinical Trials Unit University of Freiburg, Freiburg im Breisgau, Germany; and Koehler eClinical GmbH, Freiburg im Breisgau, Germany) were respectively responsible for data collection, monitoring, and statistical analyses. OT and CH had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

21 German centres enrolled 615 randomly assigned patients between Aug 7, 2008, and Nov 30, 2013. Of these 615 patients, 206 patients received basiliximab and steroidsin control arm A, 189 patients received basiliximab induction therapy and rapid steroid withdrawal in arm B, and 192 patients received rabbit ATG induction therapy and rapid steroid withdrawal in arm C (figure 1).

Baseline characteristics of the three study arms were well balanced (table 1). Recipient ethnicity was overall 99% (579 of 587 participants) white, with a current panel reactive antibody of 0% in 88% (517 of 587) of the transplant recipients indicating an immunologically low-risk population. Reasons for end-stage renal disease, which was mainly caused by hypertension (217 [37%] of 587 patients), glomerulonephritis (161 [28%] of 587), and adult-type polycystic kidney disease (113 [19·3%] 587), did not differ between the three groups. The donor pool consisted of 87% (511 of 587) deceased donors and 13% (76 of 587) living donors; 44% (260 of 587) of the donor allografts were transplanted with expanded criteria,[18] with a mean donor age of 54·0 years (14·6). The mean cold ischaemia time of the deceased donor grafts was 710 min (289).

The first dose of 20 mg basiliximab was given pre-operatively or intraoperatively; the second dose of 20 mg basiliximab was given on postoperative day 4. 363 [92%] of 395 randomly assigned patients received the intended full dose of 40 mg. Rabbit ATG was always initiated intraoperatively before reperfusion in treatment arm C. The average number of doses given were 3·7 with a mean total dose of 4·61 mg/kg bodyweight (SD 1·28) for each patient. Target trough concentrations for tacrolimus were generally met in all three study arms during the study period (appendix). The accompanying immunosuppressive drug MMF was given with a mean dose of 1638·5 mg (SD 421·9) in arm A, 1616·0 mg (SD 382·2) in arm B, and 1541·4 mg (SD 462·7) in arm C (p=0·06). Steroid-free maintenance therapy after 1 year was achieved in 158 (84%) of 189 patients in arm B and 159 (83 %) of 192 patients in arm C.

At 12 months, the incidence of the primary endpoint BPAR (excluding borderline) was similar between the three study arms (A 23 [11·2%] of 206 patients, B 20 [10·6%] of 189, and C 19 [9·9%] of 192; A *vs* C p=0·75, B *vs* C p= 0·97; figure 2A). Therefore, rabbit ATG did not show superiority over basiliximab induction for the prevention of BPAR after rapid steroid withdrawal within 1 year after renal transplantation. There was also no difference with respect to the severity of BPAR according to the Banff classification (table 2). Steroid-resistant rejections were rare, occurring in 4 (2%) of 206 patients in arm A, 5 (3%) of 189 in arm B, and 4 (2%) of 192 in arm C. The frequency of clinically indicated or protocol biopsies was within the same range among the study arms (265 in arm A *vs* 280 in arm B *vs* 267 in arm C).

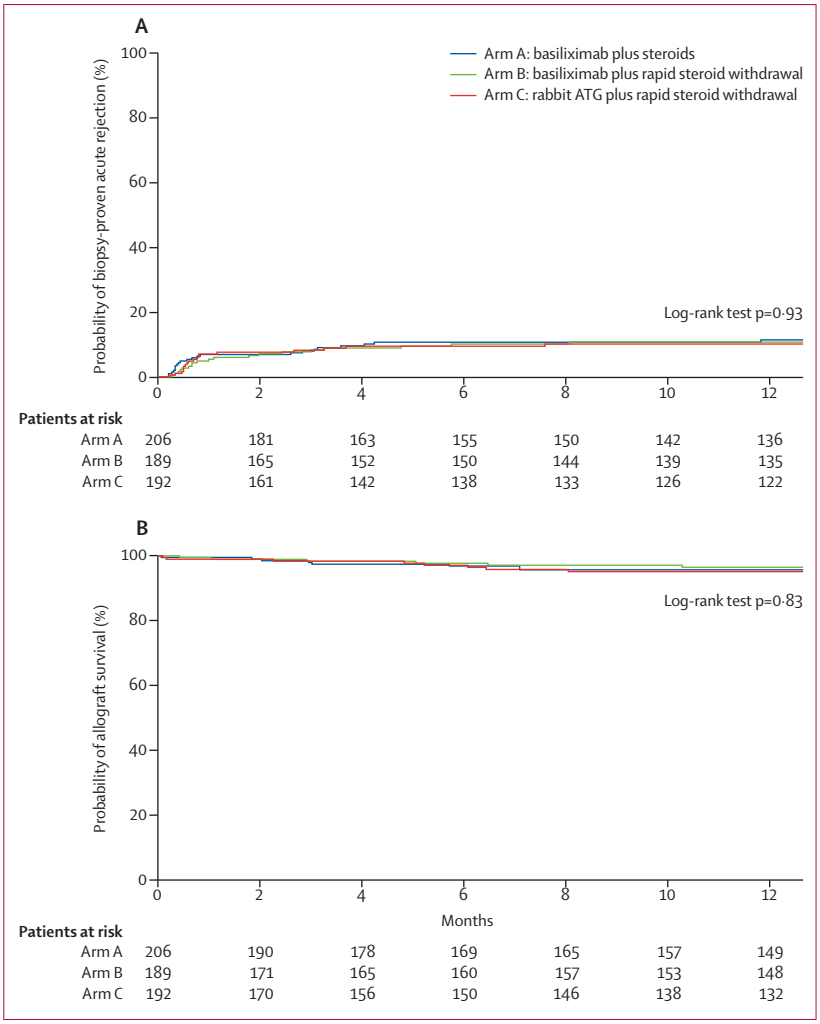

***Figure 2*: Cumulative probability of biopsy-proven rejection (panel A) and allograft survival (panel B) according to study arm**

The number at risk includes all patients in the intention-to-treat population. For the Kaplan-Meier estimates of event rates presented here, data of patients who completed the study before the first year after transplantation were censored at the time of their last visit. Patients who died with functioning grafts were removed from the Kaplan-Meier estimates of graft survival. Borderline acute rejections were excluded from the analysis of biopsy-proven acute rejection.

Patient survival in arm A (195 [94·7%] of 206), arm B (184 [97·4%] of 189), and arm C (186 [96·9%] of 192) and death-censored graft survival in arm A (198 [96·1%] of 206), arm B (183 [96·8%] of 189), and arm C (184 [95·8%] 192) were excellent after 12 months (figure 2B).

Graft function determined by the mean calculated glomerular filtration rate was 46·3, 47·4, and 50·2 mL/min (p=0·25) by the CKD-EPI formula, and 57·3, 58·0, and 62·9 mL/min (p=0·10) by the Cockcroft-Gault formula for arms A, B, and C, respectively (table 2).

Occurrence of post-transplantation diabetes was defined according to the ADA criteria and assessments took into consideration the present consensus conference recommendations on post-transplantation diabetes.[19] Although confounded by an incidence of chronic steroid treatment

of 16% (31 of 189 patients) in arm B and 17% (33 of 192) in arm C, as well as late steroid withdrawal in about 10% (20 of 206) of patients in arm A, the benefit of rapid steroid weaning on the incidence of post-transplantation diabetes was statistically significant in the intention-to-treat population independent of the starting timepoint of post-transplantation diabetes assessment according to the ADA criteria (baseline, 2 weeks, 4 weeks, 2 months, or 3 months) within the 12-month follow-up (odds ratio [OR] 0·49, 95% CI 0·30–0·82, p=0·0070). Figure 3 shows incidence rates according to the different ADA diagnostic criteria as well as centre diagnosis in the three study arms. Therefore, to avoid inclusion of transient post-transplant hyperglycaemia in the early post-transplant period,[19] post-transplantation diabetes results were considered in the 2–12 months post-transplant. The incidence of post-transplantation diabetes in the control arm (group A) was 39·2% (81 of 206 patients), whereas rapid steroid withdrawal reduced post-transplantation diabetes frequency in arm B to 24% (45 of 189) and to 23% (44 of 192) in arm C (p=0·0004 for A *vs* B and C). This effect was more pronounced in the per-protocol population: 45% (50 of 135 patients) in arm A, 18% (22 of 123) arm B, and 24% (27 of 115) in arm C (p<0·0001 for A *vs* B and C, data not shown). Most of the other metabolic profile parameters did not differ substantially between the three study arms. Only the incidence of osteoporosis (centre assessment; OR 0·48, 95% CI 0·26–0·89, p=0·0220 for A *vs* B and C) after 12 months was clinically and significantly different (table 2).

The three study arms had a similar incidence of adverse events and serious adverse events (table 2, figure 3). The total number of adverse events for arms A, B, and C was 1838, 1834, 1699, respectively (p=0·49); the total number of serious adverse events was 252, 250, 200, respectively (p=0·09). The overall incidence of infections was 51·5% (106 of 206 patients) in arm A, 57·1% (108 of 189) in arm B, and 54·2% (104 of 192) in arm C (p=0·34). The presence of a cytomegalovirus high-risk constellation at the time of transplantation was around 25% (148 of 587), which did not differ between the study arms, and was followed by subsequent 3-month prophylaxis with valganciclovir; the overall incidence of cytomegalovirus infection was 20·9% for arm A, 20·6% for arm B, and 19·8% for arm C (table 2). The detected incidence of a BK virus infection and Epstein-Barr virus viremia was similar in the study arms.

The frequency of anaemia was significantly higher after steroid withdrawal in arm B at 38·6% (73 of 189 patients) and arm C at 34·9% (67 of 192) compared with arm A at 26·7% (55 of 206; OR 1·58, 95% CI 1·09–2·30, p=0·0164). This relation was also reflected in the use of erythropoiesis-stimulating agent (erythropoetin) in approximately 10% fewer patients in arm A (OR 1·53; 95% CI 1·08–2·17, p=0·0185).

11 patients developed cancer during the study period: five patients in arm A, two in arm B, and four in arm C (table 2). Among these patients, one with a recipient Epstein-Barr virus IgG-negative and donor Epstein-Barr virus IgG-positive high-risk constellation in arm C receiving rabbit ATG developed an Epstein-Barr virus-positive post-transplantation lymphoproliferative disease, despite valganciclovir prophylaxis for 3 months. This patient was treated successfully and had a complete

	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	p value
Primary endpoint				
Acute rejection at 12 months				
Biopsy proven (excluding borderline rejection)	23 (11%)	20 (11%)	19 (10%)	..
Arm A versus arm C	..	..	..	0·75
Arm B versus arm C	..	..	..	0·87
Steroid-resistant rejection*	4 (2%)	5 (3%)	4 (2%)	0·88
Banff classification 2005				
Acute T-cell-mediated 1A	8 (4%)	9 (5%)	5 (3%)	
Acute T-cell-mediated 1B	1 (<1%)	1 (1%)	1 (1%)	..
Acute T-cell-mediated 2A	7 (3%)	7 (4%)	2 (1%)	..
Acute T-cell-mediated 2B	..	1 (1%)	1 (1%)	..
Acute antibody-mediated 1	2 (1%)	1 (1%)	2 (1%)	..
Acute antibody-mediated 2	1 (<1%)	1 (1%)	1 (1%)	..
Acute antibody-mediated 3	..	..	..	..
Secondary endpoints				
Patient survival at year 1*	195 (95%)	184 (97%)	186 (97%)	0·32
Death censored allograft survival at year 1*	198 (96%)	183 (97%)	184 (96%)	0·87
Graft loss or death at year 1*	18 (9%)	11 (6%)	13 (7%)	0·52
Malignancies*	5 (2%)	2 (1%)	5 (3%)	0·58
Post-transplant lymphoproliferative disease*	..	..	1 (1%)	0·65
Steroids at 1 year†	185 (90%)	31 (16%)	33 (17%)	0·87
Mean glomerular filtration rate (mL/min)				
Cockcroft-Gault‡	57·3 (22·5)	58·0 (22·6)	62·9 (23·5)	0·10
CKD-EPI equation‡	46·3 (19·5)	47·4 (19·8)	50·2 (20·4)	0·25
Cardiovascular risk factors				
Cholesterol (mmol/L)§	5·2	4·9	5·0	0·13
HDL cholesterol (mmol/L)§	1·3	1·2	1·2	0·0155
LDL cholesterol(mmol/L)§	3·1	2·9	3·0	0·06
Triglycerides (mmol/L) §	2·1	1·9	2·2	0·49
Body-mass index change from baseline (kg/m^2)§	+0·1	−0·2	−0·2	0·25
Bodyweight change from baseline (kg)§	+0·3	−0·6	−0·4	0·27
Mean systolic blood pressure (mmHg)§	134·6	134·7	135·8	0·80
Mean diastolic blood pressure (mmHg)§	77·8	76·9	78·9	0·95
Anaemia*	55 (27%)	73 (39%)	67 (35%)	0·0164
ESA drug (erypoetin) *	76 (37%)	88 (47%)	92 (48%)	0·0185
Anaemia and ESA drug*	22 (11%)	44 (23%)	41 (21%)	0·0005
Cataract*	2 (1%)	3 (2%)	..	1·00
Osteoporosis*	24 (12%)	10 (5%)	12 (6%)	0·0220
Fractures*	2 (1%)	..	..	0·12
Avascular necrosis*	..	..	1 (1%)	1·00
Wound-healing disorder*	14 (7%)	6 (3%)	9 (5%)	0·16

(Table 2 continues on next page)

remission of post-transplantation lymphproliferative disease; allograft function remained good with a glomerular filtration rate of 70·0 mL/min at 66 months after transplantation.

Discussion

This study was done in an immunological low-risk patient population to compare the efficacy of two induction regimens, rabbit ATG versus basiliximab in combination with tacrolimus-based and MMF-based immunosuppressive regimen with or without rapid steroid withdrawal. Although rabbit ATG did not show superiority over basiliximab induction for the prevention of BPAR after rapid steroid withdrawal within 1 year after renal transplantation, this is the first multicentre, randomised study to show that rapid steroid withdrawal can be safely done without compromising efficacy with a tacrolimus and MMF-based regimen, thus potentially improving the safety profile and reducing the incidence of post-transplantation diabetes, an important cardiovascular risk factor.

Furthermore, our finding suggests that, in this low immunological risk population, both induction drugs ATG and basiliximab are equipotent.

Compared with the chimeric monoclonal interleukin-2 antibody basiliximab, rabbit ATG is considered to have a greater immunosuppressive effect by direct depletion of immunocompetent cell populations and is preferred in immunologically high-risk populations.[20] The fact that rabbit ATG versus basiliximab was not superior in our study might be due to the low immunological risk profile of the recipients and a relative low total dose of rabbit ATG; however, the concept of a low total dose of rabbit ATG, as used in the Harmony trial, has been effective in several studies before.[21] Although we cannot exclude the possibility that a higher total rabbit ATG dose might have resulted in lower incidence of BPAR, the cumulative ATG dose is in line with studies showing similar efficacy and good safety compared with higher cumulative doses.[20,22] In the early steroid withdrawal studies more than 15 years ago using cyclosporin-based regimens, the success of corticosteroid withdrawal was limited because of the perceived threat of renal allograft loss.[23,24] In later studies using tacrolimus and MMF regimens, corticosteroid withdrawal was still linked to an increased risk of T-cell-mediated acute rejection.[5,8,25,26] The fact that our study is the first to show that rapid steroid withdrawal can be achieved without any negative effect on efficacy might be related to the low immunological risk profile of our mostly white study population. As in the ELITE-Symphony Study, patients were maintained on daily doses of 2 g MMF daily or more and at the upper end of the target range of tacrolimus concentrations (despite a wide range), which might reflect the conservative approach of investigators in transplant studies in general. Tacrolimus concentrations were balanced in all groups at all timepoints except for one point shortly after corticosteroid withdrawal. Therefore, patients without rapid steroid withdrawal (study arm A) had slightly lower tacrolimus trough concentrations, because tacrolimus is a P450 3A4 and P-glycoprotein substrate and corticosteroids are known to induce these enzymes.[27] In addition, there was a tendency towards decreased daily MMF doses in the rabbit ATG group compared with both basiliximab groups, for which we cannot exclude some negative effect with regards to the endpoint BPAR.

This result in our study is consistent with the work of Matas and colleagues,[28] who showed that rapid steroid withdrawal with calcineurin inhibitor and MMF maintenance after induction therapy with rabbit ATG does not lead to an increased BPAR rate if compared with their historical controls. By contrast, other trials without induction therapy and late steroid withdrawal[5,24] or steroid avoidance protocols[8] always showed increased BPAR rates. Whether the general timing of steroid withdrawal or the influence of induction therapy is responsible for the difference in rejection rates is still under debate.

Although efficacy was equivalent in all study arms, the second major finding of our study is that rapid corticosteroid withdrawal decreased the incidence of post-transplantation diabetes. Although the tacrolimus, MMF, and corticosteroids arm in the ELITE-Symphony Study showed superior efficacy over the three non-tacrolimus-based regimens, the incidence of post-transplantation diabetes was higher in this arm than in the cyclosporine treatment arms.[2] Furthermore, the definition of post-transplantation diabetes in that study was based on notifications of an adverse event. In our study, we used the internationally accepted criteria to define post-transplantation diabetes (ie, ADA criteria of fasting glucose, OGTT, and HbA_{1c}). The Harmony study data show that, along with equivalent efficacy, rapid steroid

	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	p value
(Continued from previous page)				
Infections				
Infections*	106 (51%)	108 (57%)	104 (54%)	0·53
Opportunistic infection*	71 (34%)	59 (31%)	59 (31%)	0·69
Non-opportunistic infection*	61 (30%)	71 (38%)	69 (36%)	0·20
Cytomegalovirus infection*	43 (21%)	39 (21%)	38 (20%)	0·96
BK virus infection*	26 (13%)	14 (7%)	21 (11%)	0·21
Epstein-Barr virus infection*	6 (3%)	2 (1%)	7 (4%)	0·25

Data are n (%) or mean (SD), unless otherwise stated. The intention-to-treat population consists of all patients who received at least one dose of a study drug. The calculated GFR was determined from the serum creatinine level with the use of the Cockcroft-Gault formula or the CKD-EPI equation to calculate the creatinine clearance. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. ESA=erythropoiesis-stimulating agent. *Fisher´s exact test: p value calculated for study arm A *vs* B *vs* C. †Fisher´s exact test: p value calculated for study arm B *vs* C. ‡Student's *t* test: p value calculated for study arm A *vs* B *vs* C. §Student's *t* test: p values calculated for study arm A *vs* B and C.

***Table 2*: Primary endpoint and selected secondary endpoints at 1 year**

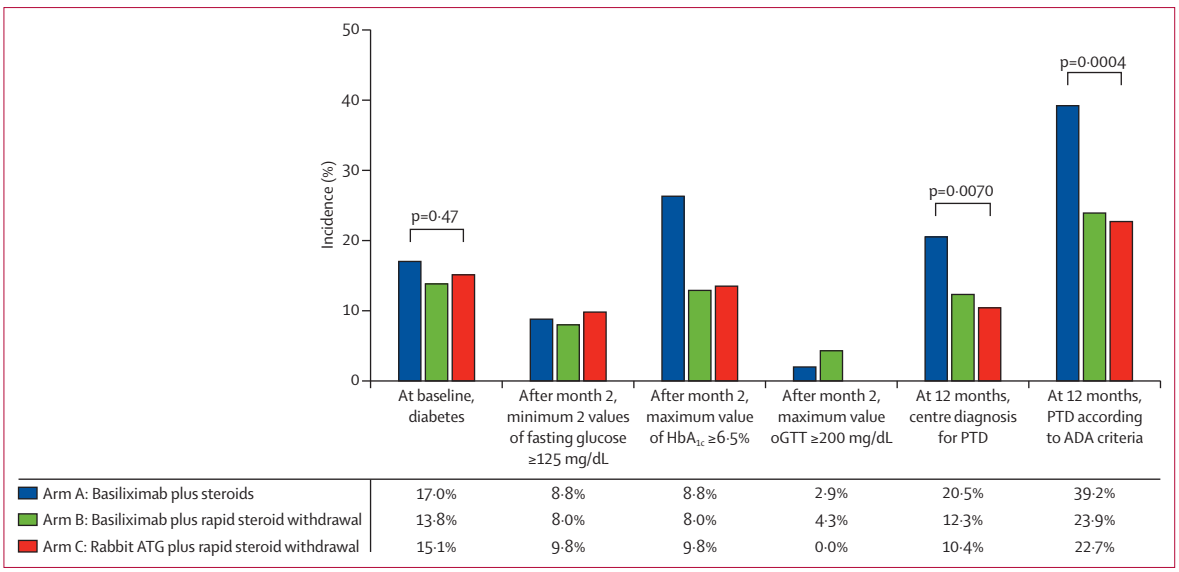

***Figure 3*: Cumulative probability of post-transplantation diabetes mellitus from two to twelve months according to all diagnostic criteria and study group**
Excluding renal transplant recipients with the diagnosis of diabetes at baseline (left column), the cumulative incidence of the diagnosis of post-transplantation diabetes according to all criteria (fasting glucose, oGTT, HbA_{1c} value) starting 2 months after transplantation and ending at 12 months is reported. Interestingly, diagnosis by centre judgement alone in the electronic case report form shows underreporting of post-transplantation diabetes compared with using all criteria. Diagnosis of post-transplantation diabetes in the same patient via different criteria is accounted for in the post-transplantation diabetes total incidence (right column). p values for comparisons between the study groups were calculated with the use of Fisher's exact test, two-sided. Calculation of p value is for group A *vs* group B and C.oGTT=oral glucose tolerance test. ADA=American Diabetes Association.

withdrawal significantly decreases the incidence of post-transplantation diabetes by more than 40% (intention-to-treat assessment), an effect that is enhanced in the per-protocol population. Considering that patients with end-stage kidney disease have substantial pre-existing cardiovascular disease regardless of their age,[29] any minimisation of risk factors for atherosclerosis progression is desirable. This is highly relevant because the updated Framingham General Cardiovascular Risk Score of 2008 deemed diabetes and chronic kidney disease as coronary heart disease risk equivalents, with the same 10-year risk as individuals with previous coronary heart disease.[30] In addition, the effect of this improvement in cardiovascular risk profile after steroid withdrawal has been shown in a large 7-year patient cohort study[6] and in large registry studies.[7] Although the reduced incidence of post-transplantation diabetes after rapid (within a few days) corticosteroid withdrawal in the Harmony study is consistent with these studies in all assessments considering different time periods and diagnostic diabetes criteria (centre judgement or ADA criteria), it is the first study to show such a clear-cut effect with a tacrolimus-based immunosuppressive regimen.[26,31,32] The relatively low tacrolimus target concentrations in the Harmony trial might be relevant to this success compared with former studies targeting higher trough concentrations.[32,33,34] Because a recent meta-analysis of corticosteroid withdrawal between 3 and 6 months after renal transplantation did not show a substantial effect on post-transplantation diabetes incidence, our early timepoint of steroid withdrawal might be crucial to this success.[35] The fact that the frequency of post-transplantation diabetes diagnosis by ADA criteria was about twice as high as that of the centre judgement in the Harmony study, and compared with most other trials (not incorporating all ADA criteria), suggests that post-transplantation diabetes is frequently overlooked, with all the potential negative consequences for the transplant patient.

The incidence of adverse and serious adverse events was similar in all three study arms. Safety with respect to infections did not differ significantly. In particular, the incidence of cytomegalovirus or Epstein-Barr virus infection was not statistically different; valganciclovir prophylaxis was given to all patients with rabbit ATG induction, but only to high-risk patients (cytomegalovirus or Epstein-Barr virus recipient negative, donor positive) in the basiliximab induction group. These data are in accordance with the observations of other studies.[24,33,34,35,36] The incidence of BK virus infection was not significantly different in all treatment arms, but a numerical decrease by more than 40% was noted in the corticosteroid withdrawal basiliximab treatment arm (arm B). No difference regarding development of cancers was noted in the treatment study arms during the follow-up period of 12 months.

In our study, both rapid corticosteroid withdrawal groups were associated with a significantly higher incidence of anaemia and erythropoiesis-stimulating agent use. It seems probable that this effect is attributable to corticosteroids, because other studies comparing basiliximab with rabbit ATG did not detect different hemoglobulin levels at any timepoint.[20,33]

Our study has some limitations. It is underpowered because of premature study discontinuation of nearly a third of the patients and the unexpectedly low incidence of BPAR. The robust decrease of the incidence of post-transplantation diabetes after rapid steroid withdrawal is very likely to be clinically relevant but was assessed only as a predefined secondary endpoint. Although rabbit ATG did not show superiority to basiliximab, this observation is clinically relevant because it provides physicians with viable alternatives for induction therapy. Furthermore, we cannot completely exclude the possibility that the lack of blinding influenced the study outcome because the decision about indication for biopsy involves subjective interpretation. Nevertheless, the biopsy frequency was equivalent in all groups. Another weakness of the study is that the follow-up period of 1 year is too short to examine if steroid-free maintenance therapy has an effect on the development of donor-specific antibodies with impact on the long-term transplant outcome. 1-year follow-up is also too short to show a lasting effect on the incidence of cardiovascular events or mortality. It remains to be proven that the improvement in post-transplantation diabetes incidence might result in better patient and graft survival during the Harmony follow-up period of 5 years, which is currently being investigated. Clearly, these study results are limited to an immunologically low-risk population of white ethnicity and cannot be extrapolated to a different study population with other ethnicities or an immunologically high-risk constellation.

In conclusion, our large investigator-initiated trial compared, for the first time, head-to-head a typical European induction protocol using basiliximab with the most frequently used one in the USA, namely rabbit ATG, to achieve the benefits of rapid corticosteroid withdrawal. Although rabbit ATG did not reduce the incidence of BPAR compared with basiliximab with or without corticosteroids, both induction drugs proved to be equally successful in maintaining steroid-free immunosuppression in more than 80% of renal transplant recipients, with substantial benefits in regard to post-tranplantation diabetes and without any loss of efficacy or safety signals besides anaemia within the first year after transplantation. We view these results as a major step towards the justification and stratification (rapid and in an immunologically low-risk population) of corticosteroid withdrawal. Therefore, according to our study results, rapid steroid withdrawal in a low-dose tacrolimus and MMF-based therapy regimen has the potential to become the new standard immunosuppressive strategy for an immunologically low-risk population of renal transplant recipients.

Contributors

OT and CH contributed to the study design, data collection, data interpretation, and drafting of the manuscript. All authors were involved in the provision of study materials and patient care and contributed content and revisions to the manuscript. All authors have approved the final version of the manuscript for submission.

Declaration of interests

OT and CH received grant support, consulting fees, and lecture fees from Astellas, Sanofi, Genzyme, Roche Pharma, Novartis, and Wyeth/Pfizer. All other authors declare no competing interests.

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