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ORIGINAL ARTICLE

Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study

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Summary

Regional transplant practices may affect clinical outcomes within multinational studies. This study evaluated whether the overall results from the Symphony study can be generalized to the participating countries. *De novo* adult renal transplant recipients ($n = 1645$) were randomized to receive standard-dose cyclosporine, or daclizumab induction plus low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus, all in addition to mycophenolate mofetil and steroids. Data for the highest patient-recruiting countries, Spain ($n = 275$), Germany ($n = 316$) and Turkey ($n = 258$), were compared. Patient transplant characteristics were different among the country subsets; only deceased donors in Spain, more expanded criteria donors in Germany, and mainly living donors in Turkey. Efficacy results for the three countries were consistent with that of the overall study – renal function and biopsy-proven acute rejection (BPAR) rates were superior with low-dose tacrolimus. Turkey had higher mean calculated glomerular filtration rate across all treatment groups (60.6–72.2 ml/min) compared with that of Spain (51.1–57.5 ml/min) and Germany (51.3–62.9 ml/min). Spain and Turkey had lower BPAR rates across the four treatment groups compared with the overall study; Germany had much higher rates (21.0–54.2%). These findings confirm the general applicability of the Symphony study results and highlight the importance of inclusion of patients from different geographic origins in randomized clinical trials.

Introduction

As the largest of a series of studies addressing calcineurin-inhibitor sparing in *de novo* renal transplantation, the Symphony study [1] assessed whether a mycophenolate mofetil plus daclizumab-based regimen improves the toxicity profile, particularly in terms of renal function associated with sirolimus or the calcineurin inhibitors cyclosporine or tacrolimus, by allowing lower doses of these immunosuppressive agents to be used while maintaining acceptable rates of acute rejection. The mycophenolate mofetil and daclizumab-based regimen plus low-dose tacrolimus and corticosteroids gave superior renal function, graft survival, and acute rejection rates compared with those of regimens of low-dose cyclosporine or low-dose sirolimus with induction, or standard-dose cyclosporine without induction [1]. Serious adverse events and premature withdrawals occurred more

frequently with the low-dose sirolimus regimen than with the other treatment regimens.

Thus, the choice of treatment regimen influences the efficacy and safety outcomes. However, other factors may also have an impact on transplant outcomes, including transplantation resources and routines, which may differ substantially from country to country [2–4]. While international databases, such as the Eurotransplant registry, are available to allow comparisons of transplant outcomes, these depend on both differences in transplant characteristics and differences in routines, including immunosuppressive regimens. Therefore, it would be very helpful to transplant physicians to understand the effect of differences in transplantation characteristics on efficacy and tolerability outcomes, by comparing outcomes of country subsets of patients treated under the same protocol. In addition, it is of interest to assess whether the results from this clinical trial are applicable across the various participating countries.

Variations in 'transplant characteristics' between countries need to be considered in the design of future clinical trials; outcomes from studies conducted in a single geographic area may have limited general applicability to other regions. The Symphony study [1] is the largest international, prospective study conducted in *de novo* renal transplant recipients, and therefore provides a unique opportunity to study the impact of different transplant conditions, such as variations in the donor pool, under the same protocol of immunosuppression and follow-up. Spain, Germany, and Turkey were three countries with striking differences in the characteristics of the donor pool, contributing between them over 50% of all patients enrolled in the Symphony study; therefore, these countries were selected for further analysis. Given that transplantation procedures (such as immunosuppressive regimens, monitoring, and follow-up) were controlled by the protocol within the study, the aim of the sub-analysis reported in this study was to assess whether the overall results may be generalized to participating countries, despite differences in patient characteristics (such as proportion of living or deceased donors, expanded criteria donors, and donor age).

Materials and methods

The Symphony study was a 12-month prospective, randomized, open-label, multi-center, four parallel arm study in adult (aged 18–75 years) *de novo* renal transplant recipients. The criteria for patient selection and treatment allocation have been described in detail elsewhere [1]. Briefly, inclusion criteria were adult patients receiving a kidney from a living or a deceased donor. Exclusion criteria, with the objective to exclude high-risk patients, included: patients receiving a graft from a nonheart-beating donor; patients with a current or prior panel reactive antibody (PRA) value of >20%, a positive cross-match, or a graft cold ischemia time of >30 h.

Participants were randomized 1:1:1:1 to four treatment groups: mycophenolate mofetil, standard-dose cyclosporine and corticosteroids (standard-dose cyclosporine group), daclizumab induction, mycophenolate mofetil, and corticosteroids in combination with low-dose cyclosporine (low-dose cyclosporine group), low-dose tacrolimus (low-dose tacrolimus group), or low-dose sirolimus (low-dose sirolimus group). Randomization was stratified by investigational center and the presence of expanded criteria donors (ECDs). ECD was defined as donor age above 60 years, or above 50 years combined with 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 (133 μmol/l). Oral mycophenolate mofetil 1 g twice daily was administered in all groups (intravenous administration of mycophenolate mofetil 1.5 g twice daily was permitted as required), and daclizumab was infused over 15–20 min (2 mg/kg within 24 h before the transplant, then four doses of 1 mg/kg every 2 weeks). Cyclosporine, sirolimus, and tacrolimus were administered orally within 24 h before or after transplantation. Standard-dose cyclosporine was defined as a target trough (whole blood immunoassay) concentration of 150–300 ng/ml for the first 3 months and 100–200 ng/ml thereafter, and low-dose cyclosporine was defined as a target trough concentration of 50–100 ng/ml. Target trough concentrations for low-dose tacrolimus and low-dose sirolimus were 3–7 and 4–8 ng/ml, respectively.

The primary efficacy parameter was the glomerular filtration rate (GFR) 12 months after transplantation, determined from the serum creatinine level using the Cockcroft–Gault formula [5]. Missing values were imputed based on the last-observation-carried-forward method for serum creatinine and weight, but 10 ml/min was imputed after graft loss. Secondary parameters included the incidence of biopsy-proven acute rejection (BPAR), and graft and patient survival. Treatment failure was defined as the occurrence of any of the following: discontinuation of any study medication for >14 consecutive days or >30 cumulative days; use of additional immunosuppressive drugs; necessity for treatment with other investigational drugs or other medications prohibited by the protocol; death of the patient; or graft loss.

In this analysis, data from patients enrolled in Spain, Germany, and Turkey are presented separately, alongside summary data from the main study. Patient populations analyzed included the safety population (patients who received at least one dose of study medication) and the intent-to-treat (ITT) population (patients who received at

least one dose of study medication and were transplanted). Statistical analyses were performed on the Turkish, German, and Spanish subsets, and descriptive statistics for the variables of interest were calculated (e.g., Kaplan–Meier estimates of the incidence of selected efficacy outcomes or adverse events). Statistical comparisons between treatment groups for primary and secondary efficacy endpoints in the overall patient population have been previously described elsewhere [1]. In addition, in this study we carried out specific analyses including only patients from the three countries of interest to assess differences between treatments and between countries. In particular, an analysis of between-group differences controlling for the country factor was performed (analysis of variance for GFR and Mantel–Haenszel test stratified for country for acute rejection and similar variables). In addition, for each country and for the main efficacy variables, global comparisons of the four treatment groups (i.e., assessing a difference between any of the groups) and pairwise comparisons of the low-dose tacrolimus group against each of the other groups were carried out using nonparametric methods (log-rank test for survival analysis, Kruskal–Wallis test for continuous variables, and Fisher's exact test for categorical variables). For safety variables, the comparison against low-dose tacrolimus was not carried out. For demographic data, the three considered countries were compared in a global test based on the same methods. Medication data (mycophenolate mofetil dose and cyclosporine, tacrolimus and sirolimus trough levels) were displayed graphically by group and country and the average dose or trough level over the study period was compared among countries. All statistical tests were exploratory and no correction for multiplicity was used.

Results

Demographics and patient disposition

Overall, 1645 patients were enrolled into the main study, of which 1602 made up the safety population and 1589 the ITT population [1]. Of the overall study population, 275 patients enrolled from Spain, 316 from Germany, and 258 from Turkey, of which 271, 301, and 249 patients were included in the safety population, respectively. The respective number of patients excluded from the ITT population because they were lost to follow-up or did not receive any study medication or a transplant was 3, 40, and 13 (overall Symphony study population); 1, 3, and 2 (Spain); 2, 13, and 5 (Germany); and 0, 9, and 3 (Turkey).

Baseline demographics of ITT patients in the overall study and the three country subsets are shown in Table 1. Compared with the overall study population, Spanish patients were at higher risk of inferior renal function in terms of donor type (twofold greater proportion of ECDs, and no living donors); German patients were also at higher risk in terms of donor type (including more ECDs and only 11.2% of organs were from a living donor) and had a twofold higher incidence of cytomegalovirus (CMV) donor-positive/recipient-negative status. Turkish patients were at lower risk in terms of donor type (almost all living) and CMV status (>fivefold lower incidence of donor-positive/recipient-negative CMV status), but at somewhat higher risk in terms of PRA levels. In summary, the Turkish patient population was different in almost all respects from the Spanish and German populations. The latter two populations had significantly ($P < 0.05$) different proportions of living or deceased donor types and of ECD, proportions of HLA-DR mismatches, and of CMV serostatus.

Premature withdrawal

In the overall study ITT population, 1088 patients (68.5%) completed the 12-month treatment period. It has to be noted, however, that 80% of withdrawn patients were followed up until the end of the study and provided safety and efficacy data (in particular renal function). More patients from the low-dose tacrolimus group (321/401; 80.0%) and markedly fewer from the low-dose sirolimus group (204/399; 51.1%) completed the study, with a similar trend observed in each country analysis. Also, in the three countries of interest, the lowest proportion of premature withdrawal (that included discontinuation of the assigned treatment) was reported in the low-dose tacrolimus group (18.8%, 35.1%, and 20.0% of patients in Spain, Germany, and Turkey, respectively) and the highest proportion in the low-dose sirolimus group (44.8%, 70.7%, and 31.1%). The standard-dose cyclosporine (25.4%, 36.1%, and 21.7%) and the low-dose cyclosporine group (22.5%, 45.8%, and 24.2%) had intermediate and comparable withdrawal rates. In Germany, there was a higher overall withdrawal rate (139/296; 47.0%) compared with that of the entire study, and in Turkey, there was a lower withdrawal rate (57/246; 23.2%). These differences among countries were statistically significant ($P < 0.001$, Cochran–Mantel–Haenszel test).

Treatment failure was the main reason for premature withdrawal from the study and was reported in 64.0% (48/75), 68.3% (95/139), and 59.6% (34/57) of prematurely withdrawn patients in Spain, Germany, and Turkey, respectively, versus 65.5% of 501 patients in the overall study.

The proportion of patients who discontinued from the safety population because of an adverse event was 3.7% (overall study), 3.3% (Spain), 3.3% (Germany), and 1.2% (Turkey).

Table 1. Baseline patient demographics of the intent-to-treat populations for the Symphony study overall and for the participating country subsets of Turkey, Spain, and Germany (all treatment groups combined).

	Overall (*N* = 1589)	Spain (*N* = 269)	Germany (*N* = 296)	Turkey (*N* = 246)	*P*
Recipient age, years					
Mean ± SD	45.8 ± 14.1	50.0 ± 12.7	51.2 ± 12.7	33.3 ± 10.1	<0.001
Median (min–max)	47.0 (18.1–75.8)	51.1 (20.7–74.1)	52.4 (18.6–72.5)	31.5 (18.1–59.4)	
Donor age, years					
Mean ± SD	45.5 ± 15.3	47.4 ± 16.9	48.0 ± 16.2	47.4 ± 11.8	0.55
Median (min–max)	47.0 (1.0–82.0)	52.0 (9.0–79.0)	49.0 (1.0–82.0)	48.0 (11.0–72.0)	
Recipient race, *n* (%)					
Caucasian	1480 (93.1)	262 (97.4)	291 (98.3)	246 (100)	0.027
Other	109 (6.9)	7 (2.6)	5 (1.7)	0	
Type of donor, *n* (%)					
Deceased	1020 (64.2)	268 (99.6)	262 (88.5)	16 (6.5)	<0.001
Living related	465 (29.3)	0	21 (7.1)	198 (80.5)	
Living unrelated	102 (6.4)	0	12 (4.1)	32 (13.0)	
Missing	2 (0.1)	1 (0.4)	1 (0.3)	0	
ECD (deceased donors only), *n* (%)	286 (18.0)	97 (36.1)	82 (27.7)	2 (0.8)	<0.001
≥1 HLA-DR mismatch, *n* (%)	1086 (68.3)	213 (79.2)	183 (61.8)	196 (79.7)	<0.001
CMV D+/R–, *n* (%)	220 (13.8)	29 (10.8)	79 (26.7)	6 (2.4)	<0.001
Panel reactive antibodies >5%, *n* (%)	124 (7.8)	6 (2.2)	11 (3.7)	44 (17.9)	<0.001

P indicates the *P*-value of tests comparing the three countries (Fisher's exact test for categorical variables and Kruskal–Wallis tests for continuous variables).
CMV D+/R–, cytomegalovirus donor positive/recipient negative; ECD, expanded criteria donor.

Immunosuppression

The cyclosporine, tacrolimus, and sirolimus trough concentrations, respectively, were broadly similar between the overall study population and between the country subsets, with generally similar changes in concentration over the 52-week study period (Fig. 1a–d).

Mean daily doses of mycophenolate mofetil were usually higher (across all treatment groups) in patients from Turkey than those in the overall population, whereas these values were usually lower in the German and Spanish subsets than those in the overall population (Fig. 2a–d). There was a significant difference among these countries in all treatment groups ($P < 0.001$).

Efficacy

In the overall study, renal function was significantly ($P < 0.001$) superior in the low-dose tacrolimus group than that in the other treatment groups [1]. Likewise, renal function was consistently better in the low-dose tacrolimus group across all three country subsets (Fig. 3a), although across treatment groups, the GFR was lower in Spain and Germany, and higher in Turkey, than that in the overall study. There were differences among groups and among countries in GFR in an analysis of variance model ($P < 0.001$ for both factors and $P = 0.83$ for the interaction, but with the effect in countries obtained individually being significant only in Germany, with $P = 0.038$).

The incidence of BPAR at 12 months in the overall study was significantly ($P < 0.001$) lower in the low-dose tacrolimus group than that in the other treatment groups, while the rate in the low-dose sirolimus group was considerably higher than that in all other groups (Fig. 3b). Likewise, the low-dose tacrolimus group showed the lowest incidence of BPAR compared with that of the other treatment groups in all three countries (Fig. 3b). In Spain, the trend was the same as overall, but with lower rates of BPAR than that in the overall study. In Germany, although the trend was similar to that seen in the overall study, rates in the low-dose tacrolimus and low-dose sirolimus groups were considerably higher than those seen in the overall study. In Turkey, BPAR rates were considerably lower than those in the overall study, and the rates were similar between the low-dose cyclosporine and low-dose sirolimus groups in this subset (Fig. 3b). There was a significant between-group difference in BPAR when controlled for the country effect ($P < 0.001$, Cochran–Mantel–Haenszel test, with Germany being the only country that, taken alone, displayed a significant effect) and a significant between-country difference ($P < 0.001$).

Graft survival (uncensored or death-censored) at 12 months in the overall study was significantly ($P < 0.05$) higher in the low-dose tacrolimus group than that in the standard-dose cyclosporine and low-dose sirolimus groups in the overall study (Table 2). Graft survival censored for death was also highest in the low-dose tacrolimus groups in all countries, although in Germany

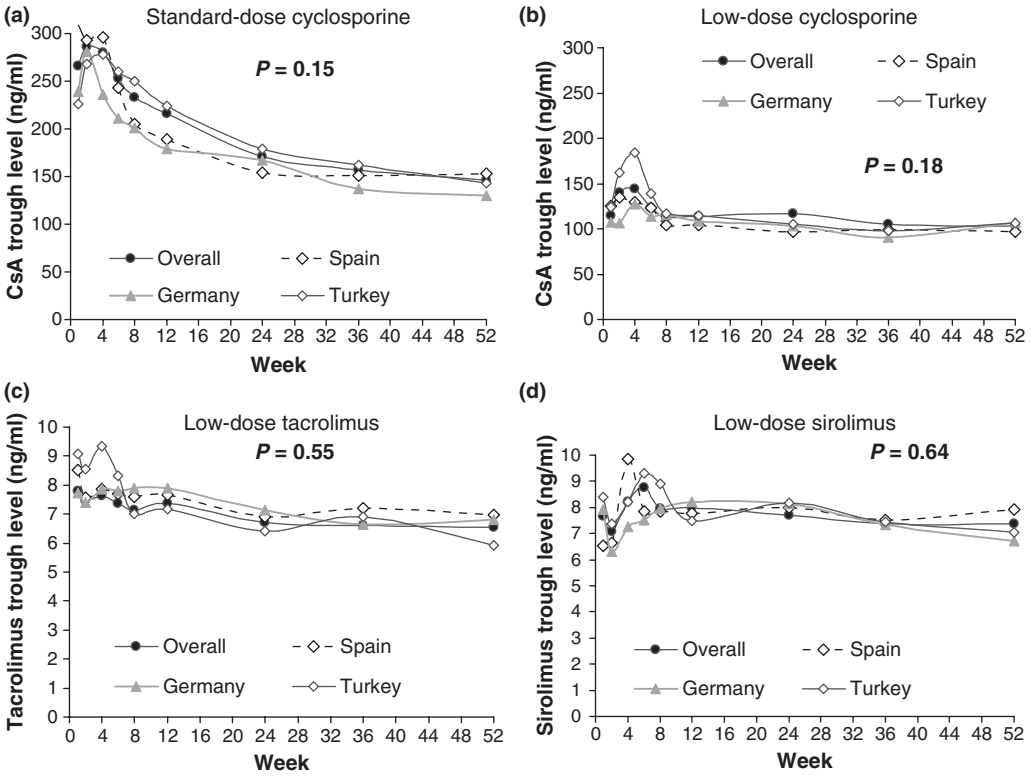

Figure 1 Immunosuppressive drug trough concentrations in the overall Symphony study, and in the Spain, Germany, and Turkey subsets in the (a) standard-dose cyclosporine, (b) low-dose cyclosporine, (c) low-dose tacrolimus, and (d) low-dose sirolimus treatment groups (intent-to-treat population). *P*-values are from a comparison over the three countries of the average exposure to the different drugs during the study period (Kruskal–Wallis tests). CsA, cyclosporine.

it was at the same level as that of low-dose sirolimus (97.2 and 97.3%, respectively). This latter group of patients in Germany had the best uncensored graft survival (96%), followed by standard-dose cyclosporine treated patients in Turkey. Graft survival rates across all treatments were consistently lower (1.5–6.1% lower) in Spain than that in the overall study, but there was no significant difference among the three countries for uncensored ($P = 0.12$) or death-censored ($P = 0.11$) graft survival. There was no significant between-group difference in death-censored graft survival when controlled for country effect ($P = 0.33$; Cochran–Mantel–Haenszal test).

In the overall study, 12-month patient survival rates did not differ significantly between the treatment groups (Table 2); there was no significant relationship between patient survival and country ($P = 0.88$). The survival rate was 100% in both cyclosporine groups in Turkey and the low-dose sirolimus in Spain.

Safety

Generally, the between-group differences in the incidence of selected adverse events were broadly similar in the overall patient population and country subsets. Serious adverse events were more common in the low-dose sirolimus group than that in the other groups in the overall patient population (Table 3). The Turkish subset had the lowest incidence of serious adverse events reported (13.0–27.6% across the four treatment groups) compared with that of the Spain and Germany (50.7% vs. 68.6%) subsets. New-onset diabetes after transplantation was consistently more common in Germany across the four treatment groups relative to that in Spain and Turkey. Interestingly, the incidence of new-onset diabetes after transplantation, diarrhea, and lymphocele was highest in the German low-dose sirolimus group, occurring at >8%, >6%, and >8%, respectively, relative to that in any other treatment group in the three countries assessed. Diarrhea was generally more common in Spain, except in the low-dose sirolimus group as highlighted above, and occurred at greater than twofold lower rate in each treatment group in Turkey relative to that in Spain and Germany. Likewise, opportunistic infections were consistently greater than twofold lower in Turkey relative to that in Spain and Germany. CMV infection was consistently lower in the low-dose sirolimus group than that in the other treatment

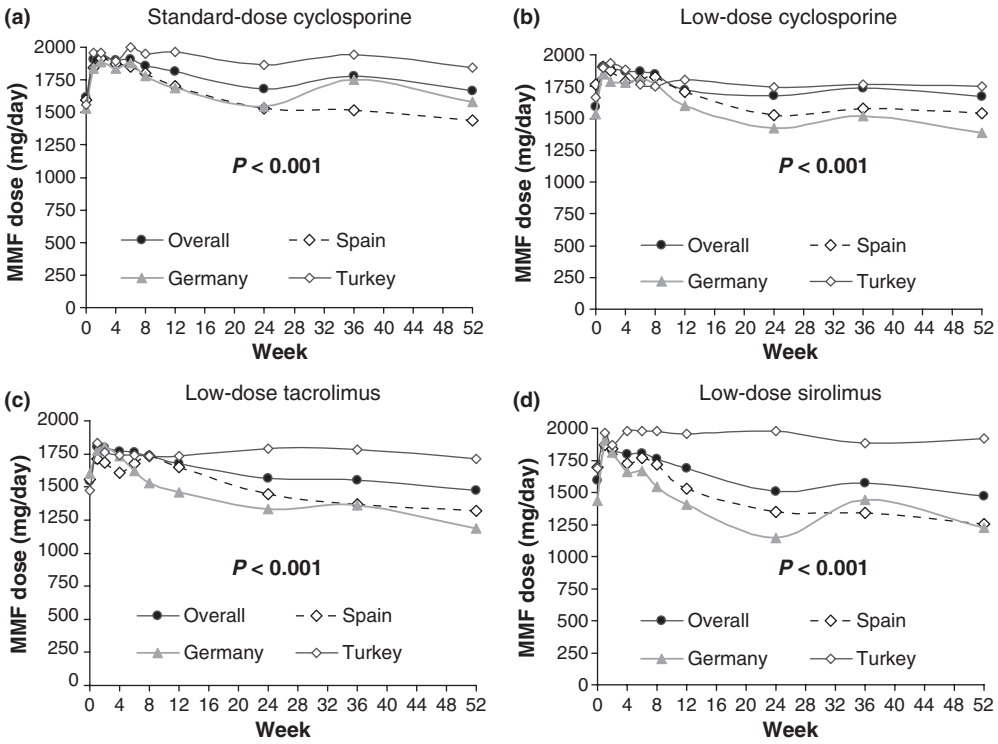

Figure 2 Mycophenolate mofetil (MMF) corrected mean daily doses (mg) in the overall Symphony study, and in the Spain, Germany, and Turkey study populations in the (a) standard-dose cyclosporine, (b) low-dose cyclosporine, (c) low-dose tacrolimus, and (d) low-dose sirolimus treatment groups over 52 weeks (intent-to-treat population). *P*-values are from a comparison over the three countries of the average MMF dose during the study period (Kruskal–Wallis tests).

groups in all countries, and occurred at a lower rate in each treatment group in Turkey.

Discussion

The results of this sub-analysis of data from three countries with differing donor populations and transplant practices show that, as in the overall study, GFR was highest and BPAR lowest in patients receiving a regimen of daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose tacrolimus. However, there were some notable differences in efficacy outcomes between the overall study and the three participating countries.

Overall results in GFR, graft survival, and BPAR across treatments observed in Spanish patients were broadly similar to those observed in the overall patient population. GFR and graft survival were, however, lower than that in the overall study, possibly because in Spain, patients were at higher risk of inferior renal function and poorer graft survival – twofold more patients received kidneys from ECD, there were no living donors, and patients were slightly older. The lower graft survival in the Spanish subset is consistent with that reported in the Campbell *et al.* study [6] and a study by Krieger *et al.* [7]; both studies showed that graft survival tended to be lower in cadaveric renal transplant recipients. In addition, the inferior quality of marginal and elderly donor kidneys may account for the reduced graft function and survival. Despite this, BPAR rates were lower in Spanish patients than that in the overall population. There is no obvious explanation, but these results are consistent with other studies showing that cadaveric renal transplant recipients had lower rates (or a trend toward lower rates) of acute rejection compared with that of live-donor kidney transplant recipients [6,8,9]. However, this is in contrast to the Turkish BPAR rate with predominantly live donors showing even lower acute rejections rates across all four treatment groups compared with the Spanish subset.

In German patients, the mean GFR was lower in each treatment group than that in the corresponding group in the overall study. Again, this is likely to be the result of differences in the recipients and the donor pool. The German patients had fewer living donors than the overall study group, with almost twice as many ECDs. The pattern of between-group differences in BPAR rates was the same as that in the overall study.

In Turkey, results in terms of renal function and BPAR were consistently better in all four treatment groups

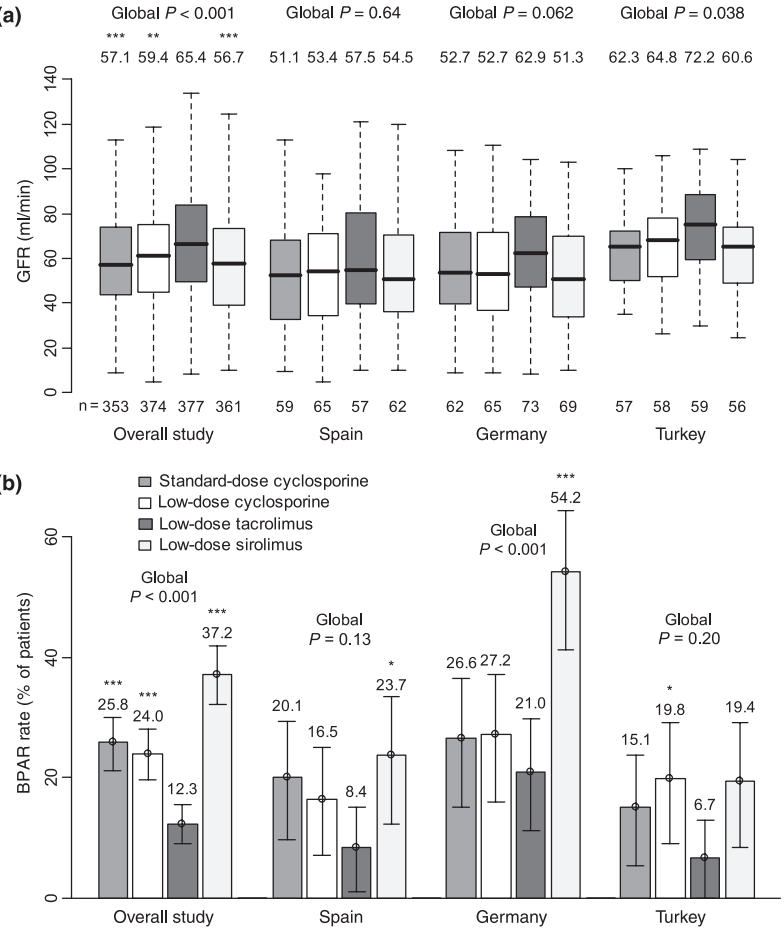

Figure 3 (a) Calculated glomerular filtration rate (GFR) at 12 months after transplantation in single-organ renal transplant recipients in the Symphony overall patient population, and in the Spain, Germany, and Turkey country subsets (intent-to-treat analysis). GFR was calculated from serum creatinine using the Cockcroft–Gault formula. The mean GFR in each subgroup is indicated above the box-plots, and the number of patients providing a measurement (without imputation) is displayed under the box-plots. (b) Biopsy-proven acute rejection (BPAR) at 12 months after transplantation in single-organ renal transplant recipients in the Symphony overall patient population, Spain, Germany, and Turkey subsets (excluding patients with borderline biopsy-proven acute rejection values). There was a strong association between BPAR and country ($P < 0.0001$). Data are Kaplan–Meier estimates (height of the columns and figure above them) with 95% confidence intervals for the intent-to-treat population. In both plots, 'Global P' refers to results of the global (i.e., over the four treatments) significance test within each country. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ versus low-dose tacrolimus.

compared with that in the overall study population, probably in part because fewer patients were infected with CMV; some studies have demonstrated a link between CMV infection and acute rejection [10]. In the interpretation of these figures, one should take into account that the definition of CMV infection was left to the discretion of the investigators and may have varied among countries. However, the mean recipient age in the Turkish subset was also >12 years younger than that in the overall or the other country subsets, which could have been a potential risk factor for increased acute rejection. A decreased risk for the occurrence of acute rejection was noted in older (>50 years) compared with younger renal transplant recipients (18–49 years) [11], and is widely presumed to be because of lower immunological activity with increasing age. Moreover, the Turkish subset had more than twice the incidence of patients with PRA values of >5% compared with that of the overall study, and more than fourfold compared with that of the other country subsets.

The Turkish subset had better renal function across all treatment groups in comparison with that of the overall study group, and in particular, in comparison with that of both the Spanish and German groups. This better renal function in the Turkish subset may be explained by the predominant use of living donors.

Interestingly, the incidence of adverse events was generally much lower in Turkey across all treatment groups than that in Spain or Germany, and the overall study population. While the possibility of underreporting of adverse events cannot be completely ruled out, this would at least be consistent with the better GFR and acute rejections rates observed across all treatment groups in Turkey relative to that in the other countries and the overall study population. In addition, patients in Turkey were generally much younger (>15 years younger relative to that in Spain and Germany, and >12 years relative to that in the overall study population) and as a result, it would be reasonable to assume that they were more likely to have fewer underlying concomitant disease or illness that could be exacerbated.

The incidence of adverse events across the different treatment groups observed in the overall study was usually, but not always, similar to those observed in each of the three country subsets. Thus, the mycophenolate mofetil-based immunosuppressive regimen plus low-dose tacrolimus, which was assessed for its ability to provide

Table 2. Graft and patient survival at 12 months after transplantation in single-organ renal transplant recipients, by treatment group in the Symphony study overall patient population and country subsets.†

	Standard-dose cyclosporine	Low-dose cyclosporine	Low-dose tacrolimus	Low-dose sirolimus	Global *P*-value
Graft survival (uncensored)					
Overall study	89.3*	93.1	94.2	89.3*	0.022
95% CI	86.3–92.5	90.6–95.6	91.9–96.5	86.3–92.4	
Spain	86.6	87.0	90.4	87.8	0.91
95% CI	78.8–95.1	79.4–95.3	83.4–98	80.2–96.1	
Germany	87.2	91.7	93.2	96.0	0.24
95% CI	79.6–95.4	85.5–98.3	87.6–99.1	91.6–100	
Turkey	94.9	93.5	93.5	88.4	0.54
95% CI	89.5–100	87.5–99.9	87.5–99.9	80.7–96.9	
Graft survival (death-censored)					
Overall study	91.9**	94.3	96.4	91.7**	0.022
95% CI	89.2–94.7	92.1–96.7	94.6–98.3	89–94.5	
Spain	89.5	89.6	93.6	87.8	0.76
95% CI	82.5–97.2	82.6–97.2	87.8–99.9	80.2–96.1	
Germany	88.5*	93.0	97.2	97.3	0.072
95% CI	81.3–96.3	87.3–99.1	93.3–100	93.6–100	
Turkey	94.9	93.5	95.1	93.1	0.96
95% CI	89.5–100	87.5–99.9	89.8–100	86.7–99.9	
Patient survival					
Overall study	96.5	98.2	97.2	96.8	0.53
95% CI	94.6–98.4	96.9–99.5	95.5–98.8	95.1–98.6	
Spain	96.8	97.1	96.7	100.0	0.57
95% CI	92.6–100	93.1–100	92.2–100	100–100	
Germany	98.5	95.6	96.0	98.7	0.59
95% CI	95.6–100	91.1–100	91.7–100	96.1–100	
Turkey	100.0	100.0	98.4	93.4	0.033
95% CI	100–100	100–100	95.3–100	87.3–99.9	

*$P < 0.05$; **$P < 0.01$, versus low-dose tacrolimus (log-rank test).
†Data are Kaplan–Meier estimates over time for the intent-to-treat population.

good efficacy but reduced nephrotoxic effects, had an acceptable tolerability profile in a wide range of patients.

Although it can provide a large amount of interesting information for further study, a *post hoc* comparison such as this analysis does have certain limitations. For example, as these were subgroup analyses, the patient numbers were smaller, meaning that the results are more prone to being skewed by outliers or by chance. Given the large size of the original Symphony study, however, the patient numbers in each country included in this report were still relatively large (almost 300 per country). Another limitation of the study was that only a limited number of patients with African or Southeast Asian origin were enrolled despite extensive attempts to recruit more. Consequently, the applicability of the overall Symphony results may be limited in transplant populations, where these patients represent a significant proportion of the transplant population – in the USA, African Americans represent about 24% of transplant recipients [12].

In conclusion, similar efficacy trends were observed in the three individual countries as in the overall Symphony study, with the regimen of daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose tacrolimus providing the best efficacy results. Patients in this treatment regimen had superior renal function and a lower BPAR rate than patients in the other treatment groups. Key differences between countries in efficacy outcomes appeared to be the result of differences in transplant characteristics, particularly donor type and recipient age. For this reason, future randomized controlled trials in renal allograft recipients should ideally be conducted at multiple sites in different countries to include patients with a broad range of transplant characteristics, so that results are of relevance to most transplant conditions and are not only based on those in a particular country or part of the world.

This sub-analysis provides evidence for the consistency of the main findings of the Symphony study across transplant populations. Despite slight differences among countries and test results not always being statistically significant, possibly because of much smaller samples and less power, the best efficacy results, in particular as far as acute rejection and renal function are concerned, were obtained with a regimen of daclizumab induction, corticosteroids, low-dose tacrolimus, and mycophenolate mofetil.

Table 3. Incidence of serious adverse events and Kaplan–Meier estimates of the incidence of selected treatment-emergent adverse events (expressed as % patients) during the 12 months after transplantation in the overall Symphony study population and in each country subset. Data are for the safety patient population*.

	Standard-dose CsA	Low-dose CsA	Low-dose tacrolimus	Low-dose sirolimus	Global *P*-value
Any serious adverse event, *n* (%)					
Overall study	170 (44.3)	177 (43.4)	175 (43.4)	201 (52.9)	0.020
Spain	37 (54.4)	44 (62.0)	34 (52.3)	41 (62.1)	0.54
Germany	36 (50.7)	40 (53.3)	53 (68.0)	48 (68.6)	0.044
Turkey	7 (13.0)	7 (10.6)	7 (11.1)	16 (27.6)	0.46
New-onset diabetes after transplantation					
Overall study	6.4	4.7	10.6	7.4	0.020
Spain	0.0	7.1	5.7	5.8	0.34
Germany	6.5	7.3	11.3	19.8	0.39
Turkey	6.1	0.0	10.3	0.0	0.022
Diarrhea					
Overall study	17.5	14.2	27.4	24.0	<0.001
Spain	26.3	14.2	25.7	21.5	0.39
Germany	15.4	10.2	23.6	32.5	0.080
Turkey	6.5	3.4	11.3	6.3	0.49
Lymphocele within 6 months of transplantation					
Overall study	7.0	6.8	3.7	15.5	<0.001
Spain	5.2	11.4	1.7	11.0	0.14
Germany	6.6	14.1	6.8	22.5	0.034
Turkey	2.0	0.0	3.5	13.9	0.0040
Opportunistic infections					
Overall study	33.0	28.1	26.3	26.6	0.025
Spain	32.0	36.6	24.1	24.5	0.51
Germany	32.6	34.3	35.9	32.7	0.87
Turkey	13.5	15.6	8.5	11.2	0.53
Cytomegalovirus infection					
Overall study	15.3	11.5	10.2	6.5	0.033
Spain	16.1	21.3	15.7	4.9	0.070
Germany	16.5	12.9	16.3	12.0	0.83
Turkey	9.6	6.3	6.8	3.7	0.77

*Safety patient population numbers in standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus, and low-dose sirolimus groups were: 384, 408, 403, and 380 in the overall study; 68, 71, 65, and 66 in the Spain subset; 71, 75, 78, and 70 in the Germany subset; and 54, 66, 63, and 58 in the Turkey subset, respectively. CsA, cyclosporine.

Authorship

All authors participated in performing the study, collecting and evaluating the data, and critically reviewing the manuscript. CB: analyzed the data. HE: designed the study, participated in the performance of the study, and prepared the draft of the analyses and the manuscript.

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