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ABSTRACT

Background. Few studies have evaluated the effect of different immunosuppressive strategies on long-term kidney transplant outcomes. Moreover, as they were usually based on historical data, it was not possible to account for the presence of pretransplant donor-specific human-leukocyte antigen antibodies (DSA), a currently recognized risk marker for impaired graft survival. The aim of this study was to evaluate to what extent frequently used initial immunosuppressive therapies increase graft survival in immunological low-risk patients.

Methods. We performed an analysis on the PROCARE cohort, a Dutch multicentre study including all transplantations performed in the Netherlands between 1995 and 2005 with available pretransplant serum ($n = 4724$). All sera were assessed for the presence of DSA by a luminex single-antigen bead assay. Patients with a previous kidney transplantation, pretransplant DSA or receiving induction therapy were excluded from the analysis.

Results. Three regimes were used in over 200 patients: cyclosporine (CsA)/prednisolone (Pred) ($n = 542$), CsA/mycophenolate mofetil (MMF)/Pred ($n = 857$) and tacrolimus (TAC)/MMF/Pred ($n = 811$). Covariate-adjusted analysis revealed no significant differences in 10-year death-censored graft survival between patients on TAC/MMF/Pred therapy (79%) compared with patients on CsA/MMF/Pred (82%, $P = 0.88$) or CsA/Pred (79%, $P = 0.21$). However, 1-year rejection-free survival censored for death and failure unrelated to rejection was significantly higher for TAC/MMF/Pred (81%) when compared with

CsA/MMF/Pred (67%, $P < 0.0001$) and CsA/Pred (64%, $P < 0.0001$).

Conclusion. These results suggest that in immunological low-risk patients excellent long-term kidney graft survival can be achieved irrespective of the type of initial immunosuppressive therapy (CsA or TAC; with or without MMF), despite differences in 1-year rejection-free survival.

Keywords: anti-HLA antibodies, graft survival, immunological low-risk, immunosuppression, kidney transplantation

INTRODUCTION

Different immunosuppressive regimes are used to prevent rejection and to maintain long-term graft function in kidney transplant recipients [1]. Standard therapy in most transplant centres nowadays consists of a combination of induction therapy with an interleukin-2 receptor antagonist (IL2RA) and tacrolimus (TAC), mycophenolate mofetil (MMF) plus prednisolone (Pred) [2, 3]. A hallmark study that played an important role in the widespread implementation of this strategy was the Efficacy Limiting Toxicity Elimination (ELITE)-Symphony trial [4]. In this large randomized clinical trial, standard-dose cyclosporine (CsA) was compared with low-dose CsA, low-dose TAC and low-dose sirolimus. Additional treatment for all patients consisted of MMF, Pred, and patients treated with a low-dose prescription also received daclizumab, an IL2RA, during the first 2 months. Intention-to-treat analyses indicated that a low-dose TAC regime was superior to all other regimes regarding renal function, acute rejection and graft-survival at 1-year follow-up [4]. After 3-year follow-up, at the end of the study, no significant difference in graft survival for both CsA regimes compared with TAC was observed anymore, whereas renal function and freedom from biopsy-proven rejection remained superior in the TAC arm [5]. Only a limited number of studies evaluated the effect of different immunosuppressive regimes on long-term outcomes [6–9]. None of these studies took the presence of pretransplant donor-specific anti-human-leukocyte antigen (HLA) antibodies (DSA), a well-known risk factor for graft loss [10, 11], into account as they were primarily based on historical data. Patients at low risk of rejection, that is, those with a first transplantation and no DSA, may require a less intensive immunosuppressive treatment compared with patients with DSA or other immunological risk markers such as retransplantation [12]. The aim of this study was therefore to assess to what extent frequently used initial immunosuppressive therapies increase graft survival in first kidney transplants without DSA in the absence of induction therapy.

MATERIALS AND METHODS

Study population

We performed an analysis on the prospective Profiling Consortium of Antibody Repertoire and Effector (PROCARE) cohort, a Dutch multicentre study evaluating all transplantations performed in the Netherlands between January 1995 and December 2005 with available pretransplant serum. Detailed methods on the cohort were previously published [11]. Of note, the T-cell-dependent complement-mediated cytotoxicity test was negative in all transplantations. Pretransplant sera were only recently (*post hoc*) tested for the presence of luminex-defined anti-HLA antibodies. DSA were assigned for HLA-A/-B/-DQ/-DR by comparing bead specificities of the positive beads with the HLA type of the donor on the split antigen level. Clinical data were obtained from the Netherlands Organ Transplant Registry. Data on cold ischaemia time were missing in 226 patients, historic peak panel reactive antibody (PRA) in 42 and number of HLA-A/-B/-DR mismatches in 39. We used Markov chain Monte Carlo single imputation to impute these missing values.

To construct a homogenous low-risk population, we included only recipients of a first transplantation without pretransplant DSA and who received no induction therapy. Within this low-risk population, we focussed on initial immunosuppressive regimes that were used in more than 200 patients. Immunosuppressive treatment was per centre's discretion, but in general target trough levels during the first months of 150–300 ng/mL for CsA and 10–20 a ng/mL for TAC were pursued. If administered, then patients on CsA received twice daily 1000 mg MMF and patients on TAC twice daily 750 mg. Pred was tapered off to zero after 3 months or continued in a low dose (∼0.1 mg/kg). The primary outcome was 10-year death-censored graft survival and the secondary outcome was 1-year rejection-free survival censored for death and graft failure unrelated to rejection. Rejection was defined as treatment for rejection, which in the majority of cases were biopsy-proven according to standard practice in the participating centres. Patients who were lost to follow-up over time (4.6%) were censored from survival analyses based on the recorded last date seen.

Statistical analysis

We performed an intention-to-treat analysis, evaluating the initially prescribed immunosuppressive regime without taking medication changes and adherence into account. Baseline characteristics were compared with the Chi-square test and unpaired *t*-test or Mann–Whitney U test as appropriate. Death-censored graft survival was compared among regimes by constructing a Kaplan–Meier curve and tested for significance with the log-rank test. In addition to restricting to immunological low-risk patients, we also adjusted for several covariates with a Cox proportional hazard model in order to limit confounding by indication [13]. The following covariates were included: recipient and donor age (both normal and quadratic), transplant centre, number of HLA-A/-B/-DR mismatches on broad antigen level, historic peak PRA level, donor type and cold ischaemia time for donation after brain death and donation after circulatory death donors. Except for transplant centre, these covariates were selected because they were previously identified as risk markers for graft loss in the PROCARE cohort [11]. As the immunosuppressive treatment strategies within this observational cohort was per centre's discretion, we also included transplant centre. For rejection-free survival, we additionally included delayed graft function (DGF) as a covariate since

patients with DGF usually undergo a surveillance biopsy 7 days after transplantation. These biopsies frequently showed borderline or type IA rejection that may not have been detected otherwise [14, 15]. Statistical analyses were performed with R 3.5.1 and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 4724 transplantations with available pretransplant DSA status, 1961 were excluded because they were retransplantations, patients had pretransplant DSA and/or received induction therapy (Figure 1). Within the immunological low-risk patients, three initial regimes were identified that were used in more than 200 patients: CsA/Pred ($n = 542$), CsA/MMF/Pred ($n = 857$) and TAC/MMF/Pred ($n = 811$). Baseline characteristics are provided in Table 1. Patients on TAC/MMF/Pred were more recently transplanted and were older. Moreover, their donors were older and the mean number of HLA-A/-B/-DR mismatches was higher. On the other hand, cold ischaemia time for deceased donor transplantations was markedly lower, and there were more living donors in the TAC/MMF/Pred group.

The crude 10-year death-censored graft survival was 79% in patients receiving the reference therapy (TAC/MMF/Pred) as well as in patients on CsA/Pred ($P = 0.69$) and 82% in patients receiving CsA/MMF/Pred ($P = 0.08$; Table 2). After adjustment for several covariates in Cox multiple regression, still no significant difference in graft survival between the patients on either one of the CsA-based therapies and the TAC/MMF/Pred group was observed (Figure 2A and Table 2). The distribution of graft failure causes did not significantly differ between patients being treated with TAC/MMF/Pred and CsA/MMF/Pred or CsA/Pred (Supplementary data, Figure S1). However, 1-year rejection-free survival was markedly lower in patients receiving either CsA/MMF/Pred [67%, adjusted hazard ratio (HR) for acute rejection 1.65, 95% confidence interval (CI) 1.29–2.09] or CsA/Pred (64%, adjusted HR = 1.89, 95% CI 1.47–2.42) compared with patients on the TAC-based regime (81%). The majority of the rejection episodes occurred within the first 3 months after transplantation and the difference between the regimes also emerged within this time frame (Figure 2B). The percentage of patients requiring rejection treatment between Month 3 and Year 1, regardless of whether they received rejection treatment within the first 3 months or not, did not significantly differ among the groups (CsA/MMF/Pred = 5%, CsA/Pred = 6%, TAC/MMF/Pred = 7%; overall $P = 0.13$).

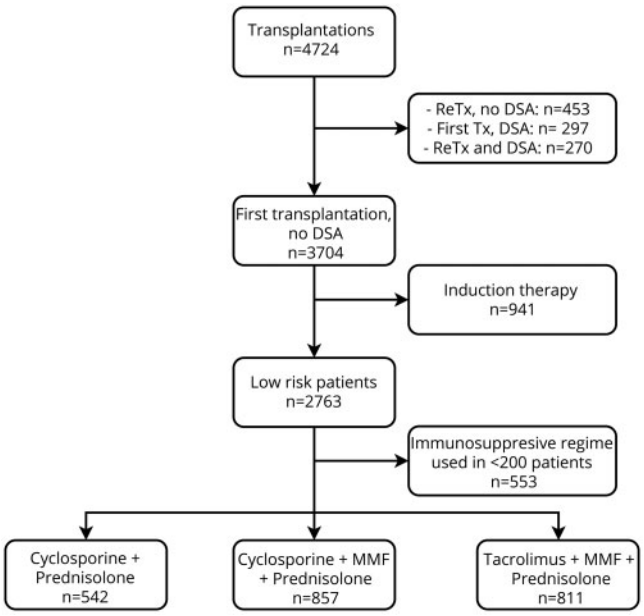

FIGURE 1: Flowchart for the inclusion and exclusion of patients. ReTx, retransplantation; Tx, transplantation.

DISCUSSION

The results of this study show that irrespective of the type of initial immunosuppressive therapies (CsA or TAC; with or without MMF), excellent long-term graft survival can be achieved in immunological low-risk patients compared with the general graft survival of transplantations performed within the same period [16]. Patients who were treated with CsA showed higher incidences of acute rejection, which is consistent with observations from the ELITE-Symphony trial [4] and others [17, 18]. If adequately treated, then early acute rejection is usually reversible and has only limited effect on long-term graft survival [19, 20]. We think that the lack of differences in graft survival despite the higher incidence of acute rejection in the CsA-treated patients can be explained by the fact that the majority of the rejection episodes occurred within the first 3 months. Previous clinical trials comparing TAC and CsA in different combinations mostly had a short follow-up and showed discrepant results, though they generally did not indicate a difference in long-term graft survival [5, 17, 21–23]. Several large observational studies also showed no differential effect of initial immunosuppressive therapies on mid- and long-term graft survival [6–9, 24].

This analysis was conducted on a large multicentre prospective cohort with at least 10 years' follow-up and relatively few missing data. Unique for this analysis is the availability of information on pretransplant DSA status. In this cohort, the choice of immunosuppressive therapy was not influenced by pretransplant DSA status because luminex single-antigen bead testing for anti-HLA antibodies was not being performed at the time of transplantation. We refrained from performing separate analysis on immunological high-risk patients (DSA positive and/or retransplantations) since numbers were too low for precise estimates, and reliable adjustments for potential confounders and thus prevent spurious findings. Induction therapy was not routinely given in the Netherlands at the time of transplantation of this cohort and could thus introduce confounding by indication. We therefore decided to exclude patients receiving induction therapy, leaving a study population as homogenous as possible.

An important limitation of this study is that clinical practice evolved during the study period as reflected by the close relation between immunosuppressive treatments and era-dependent changes in donor and recipients. Patients receiving TAC/MMF/Pred were more recently transplanted and consequently donors were older and the mean number of HLA mismatches was

Table 1. Baseline characteristics according to initial immunosuppressive regime

Baseline characteristics	CsA + Pred	CsA + MMF + Pred	TAC + MMF + Pred	P-value[a]	P-value[b]
Number (%)	542 (25)	857 (39)	811 (37)		
Donor characteristics					
Age, mean ± SD (years)	41.7 ± 14.8	42.7 ± 15.1	46.9 ± 14.3	<0.0001	<0.0001
Gender: female, *n* (%)	268 (49)	412 (48)	431 (53)	0.18	0.04
Donor type, *n* (%)				<0.0001	<0.0001
Living	129 (24)	205 (24)	358 (44)		
DBD	384 (71)	559 (65)	260 (32)		
DCD	29 (5)	93 (11)	193 (24)		
Recipient characteristics					
Age mean ± SD (years)	43.8 ± 14.4	44.6 ± 15.0	48.0 ± 13.9	<0.0001	<0.0001
Gender, female, *n* (%)	173 (32)	341 (40)	335 (41)	<0.001	0.53
Peak PRA, median, IQR (%)	2 (0–9)	0 (0–5)	0 (0–4)	<0.0001	0.05
Transplant characteristics					
Cold ischaemia time (h, mean ± SD)[c]	25.0 ± 7.1	21.9 ± 6.9	19.5 ± 7.1	<0.0001	<0.0001
HLA-A, -B, -DR broad mm (mean ± SD)	2.0 ± 1.3	2.1 ± 1.5	2.6 ± 1.5	<0.0001	<0.0001
Transplant mean ± SD (year)	1997 ± 2	1999 ± 2	2002 ± 2	<0.0001	<0.0001

[a]CsA + Pred compared with TAC + MMF + Pred.
[b]CsA + MMF + Pred compared with TAC + MMF + Pred.
[c]For deceased donors only.
mm, mismatches; MMF, mycophenolate mofetil, including mycophenolate sodium; IQR, interquartile range; DBD, donor after brain death; DCD, donor after cardiac death.

Table 2. Transplant outcomes compared among different initial immunosuppressive regimes

Regime	Crude 10-year graft survival (%)	Graft failure—unadjusted HR (95% CI)	Graft failure—adjusted HR[a] (95% CI)	Crude 1-year rejection-free survival (%)	Rejection within year 1—unadjusted HR (95% CI)	Rejection within year 1—adjusted HR[b] (95% CI)
Low risk						
TAC, MMF, Pred	79	Reference therapy		81	Reference therapy	
CsA, MMF, Pred	82	0.81 (0.65–1.02)	1.02 (0.77–1.36)	67	1.89 (1.55–2.30)	1.65 (1.30–2.10)
CsA, Pred	79	1.06 (0.83–1.35)	1.21 (0.90–1.61)	64	2.10 (1.69–2.60)	1.96 (1.53–2.51)

[a]Adjusted for: centre, recipient age [2], donor age [2], donor type, cold ischaemia time for donor after brain death (DBD) and donor after cardiac death (DCD) donors, peak PRA and number of HLA-A/-B/-DR mismatches.
[b]Adjusted for: centre, recipient age [2], donor age [2], donor type, cold ischaemia time for DBD and DCD donors, peak PRA, number of HLA-A/-B/-DR mismatches and DGF.

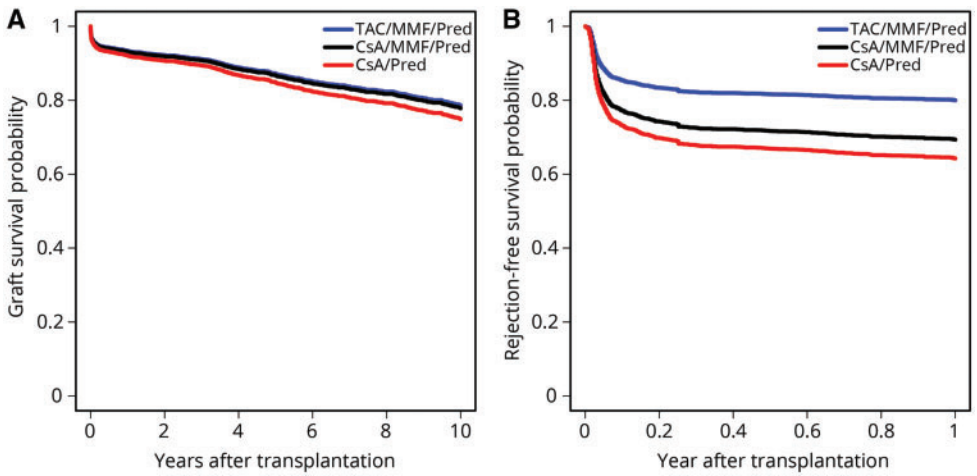

FIGURE 2: Cox proportional hazard estimates for graft and rejection-free survival according to initial treatment. (**A**) Ten-year death-censored graft survival estimates for patients on TAC/MMF/Pred did not significantly differ compared with CsA/MMF/Pred (P = 0.80) or CsA/Pred (P = 0.22). (**B**) One-year rejection-free survival censored for death and failure unrelated to rejection estimates were significantly lower for patients on CsA/MMF/Pred or CsA/Pred compared with TAC/MMF/Pred (P < 0.0001).

higher, both risk markers for graft loss [16, 25]. On the other hand, cold ischaemia time was shorter, and there were more living donors in this group [26]. We adjusted for all these factors and also for historic peak PRA and transplant centre in Cox multiple regression to reduce the potential bias induced by these differences. Transplant year, continuous or stratified, did not influence the relation between initial immunosuppression and graft survival and was therefore not included as a covariate in the Cox multiple regression model. Other limitations of this study are that we could not account for drug dosages and trough levels (if applicable) and had limited follow-up data [26]. For acute rejection, we only had information on whether a patient received treatment for acute rejection. Unfortunately, we do not have information on the type and severity of rejection. In addition, no information on *de novo* DSA development was available. Several lines of data indicate that TAC is associated with a lower risk of *de novo* DSA compared with CsA, whereas the impact of MMF remains controversial [27, 28]. We cannot rule out that patients with CsA/Pred developed more often *de novo* DSA than patients on TAC/MMF/Pred. Lastly, we do not have reliable information on incidence rates of adverse events such as infections and malignancies. Regarding opportunistic infections, other studies suggested that the incidence of BK virus infections is the highest in patients on triple therapy, in particular in patients receiving both TAC and MMF [21, 29, 30]. Moreover, in some studies, treatment with MMF was also associated with increased risk of CMV infections [21, 31, 32]. As screening for and management of BK nephropathy has improved since the early 2000s [33], we cannot rule out that suboptimal management has contributed to the lack of difference in graft survival between patients on TAC/MMF/Pred compared with CsA/Pred.

Taking these limitations into consideration, we suggest that in selected patients at immunological low-risk but at high risk of side effects, minimization of initial immunosuppressive therapy might be a valid alternative. Elderly patients without DSA may particularly benefit from a minimized, age-adapted immunosuppressive therapy. This group is prone to the development of adverse events [34, 35] and is less susceptible to acute rejection because of immunosenescence [36]. We did not analyse other forms of reduced immunosuppression than CsA/Pred because of limited patients numbers. Nonetheless, our data could suggest that a combination of TAC/Pred might also be adequate in these patients. Limited information on this combination as initial therapy is available. A randomized clinical trial including the first and the second deceased donor transplantations indicated a higher incidence of acute rejection in patients on TAC/Pred compared with TAC/MMF/Pred, but no difference in 1-year graft survival [32]. Alternative minimization strategies to reduce the side effect burden in immunological low-risk patients are dosage reduction or initial triple therapy followed by withdrawal of one or two immunosuppressant drugs within the first months post-transplantation [20, 37]. In line with these considerations, a few initiatives are being undertaken to set up prospective clinical trials investigating minimization strategies in elderly transplant recipients (ClinicalTrials.gov: NCT02453867). These clinical trials should not only focus on acute rejection and graft survival, but also include infections and *de novo* DSA development in their outcome measures.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

L.A.M., B.W.W., E.G.K., M.C.V., A.D.v.Z., H.G.O. and L.B.H. were involved in design of the work and interpretation of the data. L.A.M., A.D.v.Z. and L.B.H. analyzed the data. I.J., W.A.A., A.v.d.M., L.B.H., M.C.B., E.S., C.E.H., F.E.v.R., M.L.B., A.C.A.D.D., L.P., M.A.J.S., J.-S.F.S., B.G.H., A.J.L., L.B.B., C.R., M.G.J.T., C.E.V., L.W., E.M.v.D., M.G., M.H.L.C., F.J.v.I., S.A.N., N.M.L., W.S., K.A.v.d.P., N.C.v.d.W., I.J.M.t.B., F.J.B., A.H., P.J.M.v.d.B., J.W.d.F., M.G.H.B., S.H., D.L.R., F.H.C., B.W.W., E.G.K., M.C.V., A.D.v.Z. and H.G.O. were involved in conception of the consortium study and acquisition of the data. All authors were involved in drafting or revising the manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors of this manuscript have conflicts of interests to disclose. L.A.M. is supported by an unrestricted research grant from Astellas pharma unrelated to this manuscript. E.S. is listed as inventor of a patent unrelated to this manuscript. A.D.v.Z. received personal fees from Astellas pharma, Novartis and Chiesi outside the manuscript. None of the other authors has any conflict of interest to disclose.

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