STROBE checklist

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement:guidelines for reporting observational studies. Lancet 2007; 370: 1453

Title

Mycophenolate Mofetil use is associated with prolonged graft survival after kidney transplantation

Type of study

Closed cohort study

Abstract

See manuscript

Introduction

Background

Azathioprine (AZA) was replaced for mycophenolate mofetil (MMF) in many transplant centers but data on graft and patient survival are lacking. The three large registration trials showed less biopsy confirmed rejection when used together with cyclosporine (CSA).

Objectives

Evaluation of the outcome of MMF in transplant and patient survival of transplant patients at the Medical University of Vienna, Austria.

Methods

Study design

Population used for case: patients with AZA therapy.

Population used for control: patients with MMF therapy.

Setting and Participants

We made use of the patients recorded in the Austrian (OEsterreichisches) Dialysis and Transplant Registry (OEDTR) and EUROTRANSPLANT database that received a renal allograft between January 1st 1996 and January 1st 2005.

Only the first transplant was analyzed in the study population. Follow up data of the patients used were available until 2007.

Variables

See supplement of article (webtable 1).

Data source / measurement

The Austrian Dialysis and Transplant Registry (OEDTR) was used as data source.

Study size

The number of transplantations during the study period determined the sample size.

Quantitative variables

All variable are listed in the supplement of the paper. Biopsy confirmed acute rejection (BCAR) and chronic allograft nephropathy (CAN) were defined according to Banff 93 and 97 criteria, respectively. BCAR was defined as Banff borderline and higher grades/types of cellular rejection. Diagnosis and grading of lesions of native kidney biopsies and of the donor kidney before transplantation was performed according to the WHO classification.

Arterial hypertension was defined as mean arterial BP of 107 mmHg or at least one antihypertensive drug in 50% of the time at risk. Patients were classified as having coronary heart disease when they had unstable angina or a myocardial infarction or when coronary stenosis was documented by angiography or radioisotopic technique.

Heart failure, vascular disease, and diabetes status were defined on physicians' discretion (1).

Actual and functional graft survival as well as patient survival was used as outcome. Functional graft loss was defined as permanent return to dialysis or retransplantation. Death was considered a competing risk for graft failure (2, 3).

Statistical methods

Continuous variables are described as mean and standard deviation or median and interquartile range and were compared by t-test or Wilcoxon rank-sum tests when appropriate. Categorical variables are described by frequencies and percentages and were analyzed by chi-square test.

Kaplan-Meier (KM) plots were used to visualize the time to event in the MMF and AZA groups. Differences between the groups were analyzed by the log-rank test.

We used time to graft failure (functional graft survival), time to death (patient survival) with functioning graft and time to either death or graft failure (whichever was first; actual graft survival) as endpoints. To address the competing risk situation in our analyses, we did not withdraw patients who experienced the respective competing risk from risk sets until the last recorded event. For multivariable analysis we applied the Cox proportional hazards model (4). We considered the number of blood pressure lowering drugs, cardiovascular disease, peripheral vascular disease, coronary heart disease, cardiomyopathy, mean arterial pressure, cholesterol level, diabetes, age at transplantation, year of transplantation, time on dialysis, cold ischemia time, donor age, sum of HLA mismatches, serum hemoglobin, and CNI and steroid co-immunosuppression as potential confounding variables. All variables entered the analyses with their values measured at time of transplantation. We used the purposeful selection algorithm as proposed by Hosmer and colleagues to obtain a set of variables that control confounding (5). This algorithm guarantees that no important confounding variables and no important independent predictors of survival are missed in the final model.

Since verifying the proportional hazards assumption by inspecting Schoenfeld residual plots revealed a more pronounced effect during the first year than afterwards, we repeated Cox regression analysis including only patients that were alive with functioning graft at one year after transplantation (MI1YR) (see supplemental data webfigure 9). Furthermore, using logistic regression of received immunosuppressive treatment (AZA or MMF) on the selected variables, we computed propensity scores (probability of AZA treatment). Subsequently, another confounder-adjusted Cox analysis was performed, which equalizes the distribution of confounding variables between patients treated by AZA or MMF by using the inverse

probabilities of each patient's actually received treatment as weights. This approach is also known as marginal structural modelling (MSM).

Since some patients had missing entries for some of the potential confounding variables, we contrasted results from complete-cases-only analysis (CCO) to those from multiple imputation analysis (MI) following Van Buuren et al. where we used all potential confounding variables, survival time and censoring indicator in the imputation model (6). We obtained initial imputations for missing values from an imputation model that involved only completely recorded variables. Subsequently, we drew new imputations for each variable in turn based on all other variables. The imputation process was iterated such that final imputations were independent from initial imputations. For imputation we used logistic and linear models when appropriate. The results of five independently imputed data sets were combined using Rubin's rules (7). Since the information gain by applying multiple imputation is considerable, the purposeful selection algorithm applied after multiple imputation selected more variables as confounders or important predictors than were obtained by a complete cases only analysis.

A p-value <0.05 was considered statistically significant.

Results

Participants

1219 patients and first allografts were analysed. For number of patients per analysis in detail see the table below.

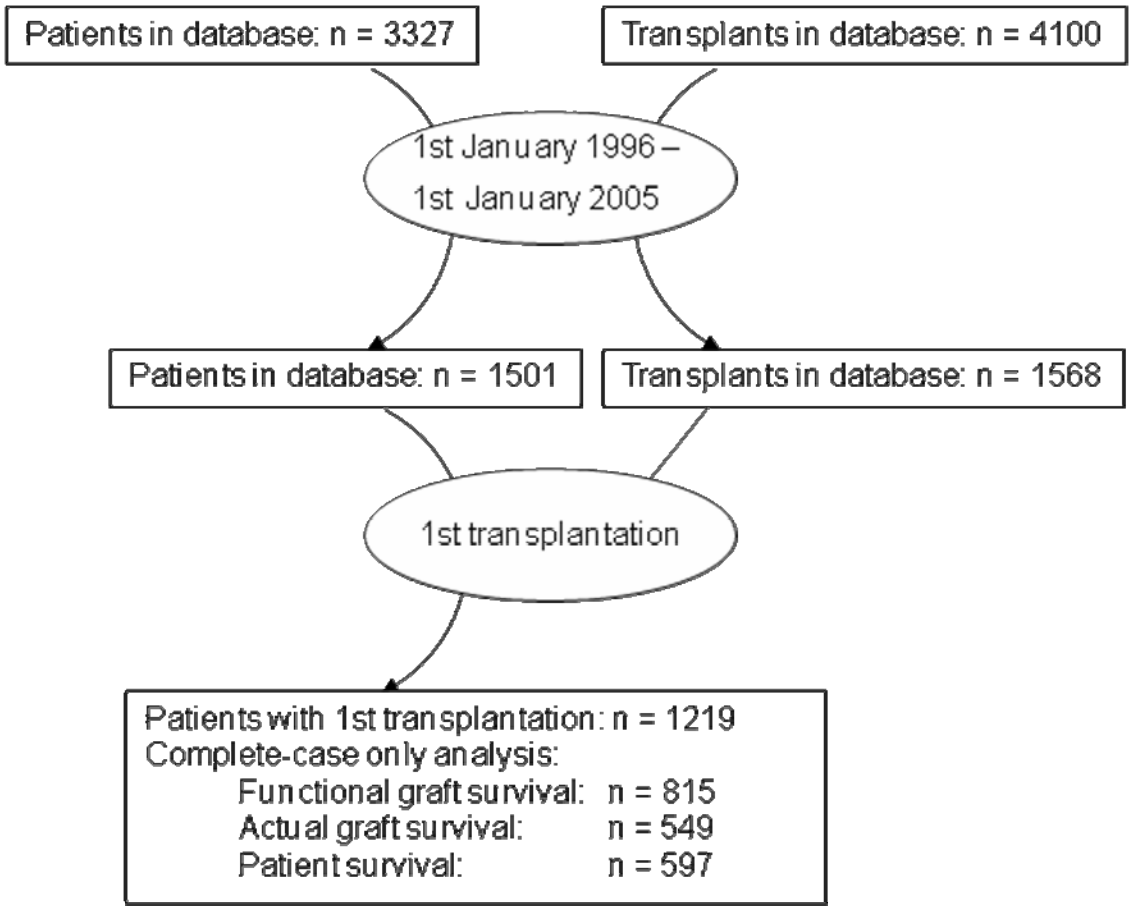
Analysis	CCO		MI		MI > 1 yr	
	Number of Patients	events	Number of Patients	events	Number of Patients	events
Functional graft survival	597	65	1219	131	948	66
Actual graft survival	549	102	1219	247	948	129
Patient survival	815	62	1219	116	948	63

CCO … Complete case only

MI … multiple imputation

MI > 1 yr … multiple imputation, only patients with more than one year of follow up

Flow diagram



Descriptive data

Demographic data

Demographic data as well as data about missing values are listed in table 1 of the article

Follow-up time

The median follow-up time was 4.0 (25^{th}, 75^{th} percentile: 2.0 – 6.1) years.

Outcome data

See KM-plots and number of patients at risk below the x-axis.

Main results

The hazard ratios of AZA use for graft survival and mortality are summarized in webtables 3, 5 and 7 of the article as well as as forest plot in figure 3. Analysis was adjusted for recipient age, donor age, year of transplantation, sum of HLA mismatch, time on dialysis, hemoglobin, mean arterial pressure, cold ischemic time, cholesterol, cardiomyopathy, coronary heart disease, peripheral vascular disease, number of bloodpressure medications, CNI use, steroid use. Confounding variables were included by use of purposeful selection algorithm and when estimates were changed 25 % if variables were included.

Discussion

Key results

Our study showed that use of MMF is associated with a reduced risk of graft loss when compared to an AZA therapy, especially in the first moths after transplantation.

Interpretation

This finding is in line with other studies. Limitations are the confounding by indication which we addressed by propensity and marginal structural models as well as unmeasured confounding which is intrinsic to all observational studies.

Generalisability

Since the data were derived from a national database of a central European country holding predominantly entries from patients of this origin, generalisability to other ethnicities remains unclear.

Other information

Funding

Austrian Science Fund (P-18325 to Rainer Oberbauer), Austrian Academy of Science (OELZELT EST370/04), and Roche Austria GmbH.

References

1. Heinze G, Mitterbauer C, Regele H, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol 2006; 17 (3): 889.

2. Pintilie M. Competing Risks – A practical perspective. Chichester, UK: Wiley, 2006.

3. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer 2004; 91 (7): 1229.

4. Cox DR. Regression Models and Life-tables (with discussion). J Royal Stat Soc B 1972; 34 (2): 187.

5. Hosmer D, Lemeshow S, May S. Applied Survival Analysis. Hoboken, NJ, USA: Wiley, 2008: 133.

6. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999; 18 (6): 681.

7. Rubin DB. Multiple imputation for Nonresponse in Surveys. New York, USA: Wiley, 1987.