Study protocol: the TRAnsplant BIOpsies (TRABIO) study – a prospective, observational, multicentre cohort study to assess the treatment of kidney graft rejections

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ABSTRACT

Introduction Despite continued efforts, long-term outcomes of kidney transplantation remain unsatisfactory. Kidney graft rejections are independent risk factors for graft failure. At the participating centres of the TRAnsplant BIOpsies study group, a common therapeutic standard has previously been defined for the treatment of graft rejections. The outcomes of this strategy will be assessed in a prospective, observational cohort study.

Methods and analysis A total of 800 kidney transplantation patients will be enrolled who undergo a graft biopsy because of deteriorating kidney function. Patients will be stratified according to the Banff classification, and the influence of the treatment strategy on end points will be assessed using regression analysis. Primary end points will be all-cause mortality and graft survival. Secondary end points will be worsening of kidney function (≥30% decline of estimated Glomerular Filtration Rate [eGFR] or new-onset large proteinuria), recurrence of graft rejection and treatment response. Baseline data and detailed histopathology data will be entered into an electronic database on enrolment. During a first follow-up period (within 14 days) and subsequent yearly follow-ups (for 5 years), treatment strategies and clinical course will be recorded. Recruitment at the four participating centres started in September 2016. As of August 2020, 495 patients have been included.

Ethics and dissemination Ethical approval for the study has been obtained from the ethics committee of Kiel (AZ B 278/16) and was confirmed by the committees of Munich, Mainz and Stuttgart. The results will be reported in a peer-reviewed journal, according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria.

Trial registration number ISRCTN78772632; Pre-results.

Strengths and limitations of this study

► The multicentre, prospective study design and the large sample size will yield high-quality data related to diagnostic, prognostic and therapeutic features of kidney graft rejections.

► High internal and external validity are expected since los to follow-up will be minimal and multiple participating centres across Germany are involved.

► The study may be limited by its observational design, which cannot show causation but only association, and is potentially prone to confounders.

of choice. It offers higher overall life expectancy and better quality of life than treatment with dialysis.[1] The increasing pool of immunosuppressant drugs has markedly improved patient and graft survival after kidney transplantation.[2 3] Short-term outcomes are quite good, with the unadjusted 1-year patient and graft survival rates of deceased-donor-organ-transplantations being 96.3% and 91.4 %, respectively, according to the latest data from the European Renal Association-European Dialysis and Transplant Association registry.[4] However, 5-year patient and graft survival rates were only 87.3% and 78.6 %, respectively, for those who received kidney transplants between 2008 and 2012, indicating considerable room for improvement.[4] As patient and graft survival rates were 86.6% and 77.5 %, respectively, among those who received transplants between 1998 and 2002, it is obvious that little progress has been made over the past decade.[5] The US Scientific Registry of Transplant Recipients annual report of 2018 reveals similarly unsatisfactory

INTRODUCTION

For patients with end-stage renal disease (ESRD), kidney transplantation is the therapy

advances in 10-year outcomes: unadjusted, non-death-censored graft survival rates at 10 years after transplantation were approximately 52.0% for deceased-donor kidney transplantations conducted in 2008 vs 45.0% for transplantations conducted in 1998.[6] The impacts of several recently Food and Drug Administration (FDA)-approved maintenance immunosuppressants such as everolimus (in 2010) and belatacept (in 2011) remain a matter of ongoing debate. In any case, there is an urgent need for further investigation.

A possible explanation for the persistently poor long-term outcomes lies in the detrimental effect of acute and chronic allograft rejections.[7] Both, antibody-mediated rejections (AMR) and T cell-mediated rejections (TCMR), adversely affect patient and graft survival,[8 9] but prognosis is worse when features of AMR such as donor-specific antibodies (DSA) are present. Thus, chronic AMR is suspected to be one of the major drivers of late graft failure.[10 11] The impact of borderline and subclinical TCMR-associated histological changes on long-term outcomes is a subject of longstanding debate, but such pathologies are increasingly being recognised as additional risk factors for late graft failure.[12] Chronic active TCMR has recently been introduced to the Banff classification as a new entity of graft rejection, and there are signs that it could be a strong predictor of poor prognosis.[13]

Unfortunately, the lack of clear evidence from randomised controlled trials (RCTs) regarding the best treatment of kidney graft rejections forces physicians to rely on expert opinion, case series and retrospective studies. For active AMR, standard of care at most centres consists of corticosteroids, plasmapheresis and intravenous immunoglobulins. The long-term benefits of this strategy are uncertain because the results from underpowered RCTs have been inconsistent. The benefits of newer agents such as rituximab, bortezomib and complement inhibitors are similarly uncertain. In case of chronic active AMR, the ideal treatment strategy remains equally unclear, but current recommendations favour a conservative approach.[14 15] Standard of care for acute TCMR is usually based on corticosteroid treatment, with addition of lymphocyte-depleting agents such as rabbit antithymocyte globulins or alemtuzumab for severe episodes. Interpretation of earlier trials evaluating the efficacy of this strategy is difficult because most trial designs did not exclude mixed AMR-TCMR episodes, which might have influenced results. A few trials have evaluated pure TCMR, but they used heterogeneous treatment protocols.[16] All in all, long-term treatment outcomes of acute TCMR have not been well studied, a limitation which extends to the question of whether to treat all borderline and subclinical TCMRs with high-dose corticosteroids.[12] While there is some preliminary data indicating that a subgroup of patients with chronic active TCMR might benefit from an immunosuppressive burst therapy, currently no clear consensus exists on how to approach this entity.[17] Further assessment of long-term outcomes after kidney graft rejections is needed, which we aim to address with this prospective, observational, multicentre study of TRAnsplant BIOpsies (TRABIO) in suspected kidney graft rejections.

STUDY PURPOSE

The objectives of this study are:
1. To analyse the association of different treatment strategies with clinical outcomes after rejection episodes diagnosed through indication biopsies.
2. To describe the prognostic and histopathological features of kidney graft rejections in Germany.

METHODS AND ANALYSIS
Study population and enrolment

All patients who undergo an indication biopsy for suspected kidney graft rejection due to deteriorating kidney function at the participating transplant centres will be screened for participation in the study. Graft rejection can either be suspected by the primary care physician with a subsequent referral for an indication biopsy at the transplant centre or suspicion can be raised directly at the transplant centre during a regularly scheduled appointment. Deterioration of graft function with graft rejection is suspected when acute kidney injury as defined by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines is present in the absence of another highly suggestive cause of kidney injury, for example, hypovolaemic shock or ureteric obstruction, or when new-onset high proteinuria (>300 mg/dL in urine dipstick test) is detected.[18] Figure 1 lists the inclusion and exclusion criteria. Adult patients (≥18 years) of both sexes and any ethnicity will be eligible. Patients with a history of retransplantation and patients that have received a combination-organ transplantation such as kidney/pancreas or kidney/liver will also be eligible. Patients will be excluded, if they have previously had a biopsy-proven kidney graft rejection. Patients with a previous biopsy for delayed graft function can be included, if the biopsy did not show signs of rejection. Any kidney transplant patient that is scheduled to undergo a graft biopsy at a participating centre will automatically be screened and

Inclusion criteria:

    Kidney graft recipient
    18 years or older
    Medical indication for kidney biopsy
    Written and informed consent

Exclusion criteria:

    Current participation in a clinical trial
    Previously documented problems with patient compliance
    Pregnancy
    Previous biopsy-proven kidney graft rejection

Figure 1 Inclusion and exclusion criteria for enrolment of kidney transplant patients with suspected graft rejections.

	Banff category	Therapy
1	No histological changes	No modification of immunosuppressive therapy
2	Acute AMR	**Acute-phase:** plasmapheresis for 5 days <u>and</u> prednisolone (i.v.; 250 mg/d) for 3 days <u>and</u> rATG (i.v; 4.5 - 6 mg/kg BW) over course of 3 - 10 days <u>and possibly</u> IgG (10 mg/d) for 5 days **Maintenance:** prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d)
	Chronic active AMR	<u>Possibly</u> IgG (i.v.; 20 g/d) for 3 days, repeat after one month
3	Borderline	**Acute-phase:** prednisolone (i.v.; 250 mg/d) for 3 days, <u>if no response:</u> continue on day 4 + 5 <u>if no response after day 5:</u> rATG (i.v; 4.5 - 6 mg/kg BW) over course of 3 - 10 days **Maintenance:** increase tacrolimus trough level to 6 - 9 ng/ml for 3 months, then 5 - 8 ng/ml prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d) MMF = 1.5 g/d <u>or</u> myfortic = 1080 mg/d
4	Acute TCMR type IA, IB, IIA	**Acute-phase:** prednisolone (i.v.; 250 mg/d) for 3 days, <u>if no response:</u> continue on day 4 + 5 <u>if no response after day 5:</u> rATG (i.v; 4.5 - 6 mg/kg BW) over course of 3 - 10 days **Maintenance:** increase tacrolimus trough level to 6 - 9 ng/ml for 3 months, then 5 - 8 ng/ml prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d) MMF = 1.5 g/d <u>or</u> myfortic = 1080 mg/d
	Acute TCMR type IIB, III	**Acute-phase:** prednisolone (i.v.; 250 mg/d) for 3 days, <u>if no response:</u> continue on day 4 + 5 <u>and</u> rATG (i.v; 4.5 - 6 mg/kg BW) over course of 3 - 10 days **Maintenance:** increase tacrolimus trough level to 6 - 9 ng/ml for 3 months, then 5 - 8 ng/ml prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d) MMF = 1.5 g/d <u>or</u> myfortic = 1080 mg/d
	Chronic active TCMR type IA, IB, II	**Maintenance:** <u>possibly</u> increase tacrolimus trough level to 6 - 9 ng/ml for 3 months, then 5 - 8 ng/ml <u>and/or</u> prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d)
5	IFTA grade II, III	No modification of immunosuppressive therapy
6	BK-Virus	**Maintenance:** reduce MMF or myfortic reduce tacrolimus trough level <u>and possibly</u> IgG (i.v.; 20 g/d) for 3 days
	HUS	Eculizumab No modification of maintenance therapy
---	Mixed acute AMR and acute TCMR	**Acute-phase:** plasmapheresis for 5 days <u>and</u> prednisolone (i.v.; 250 mg/d) for 3 days <u>and</u> rATG (i.v; 4.5 - 6 mg/kg BW) over course of 3 - 10 days **Maintenance:** increase tacrolimus trough level to 6 - 9 ng/ml for 3 months, then 5 - 8 ng/ml prednisolone (p.o.; =7.5 mg/d for 6 months, then 5 mg/d)

Figure 2 Standard operating procedures for the treatment of kidney graft rejections, as applied by the participating centres. AMR, antibody-mediated rejection; BW, body wt; HUS, haemolytic uraemic syndrome; IFTA, interstitial fibrosis and tubular atrophy; IS, immunosuppression; MMF, mycophenolate mofetil acid; rATG, rabbit anti-thymocyte globulins; TCMR, T cell-mediated rejection.

approached for enrolment prior to biopsy. Before enrolment, each patient will be informed by a physician about the risks and benefits of the study, and of his/her rights. Only patients who provide written and informed consent will be enrolled. All patients will be followed up for 5 years, regardless of the kidney biopsy result.

Rejection treatment
The TRABIO Trial Group participants have previously agreed on a common standard of care, which is currently being applied in the treatment of kidney graft rejections at the respective centres (figure 2). In this standard of care, diagnostic classification according to the Banff criteria determines the suggested therapeutic approach.[19] Importantly, since this is a non-interventional trial, the treatment and diagnostic procedures previously agreed on will

not be modified for any study-related purpose. Treating physicians are allowed to modify the proposed treatment strategy in the best interest of the individual patient. This will lead to a cohort of patients in which treatment has deviated from standard treatment. Treatment strategy and outcomes after deviation from treatment standards will be closely monitored and will be a focal point of the analysis.

Study design
This study was designed as a prospective, observational, multicentre cohort study. Recruitment started in September 2016 and will last until 800 patients have been enrolled. As of August 2020, 495 patients have been recruited from four participating transplantation centres across Germany. Figure 3 presents a scheme of the study
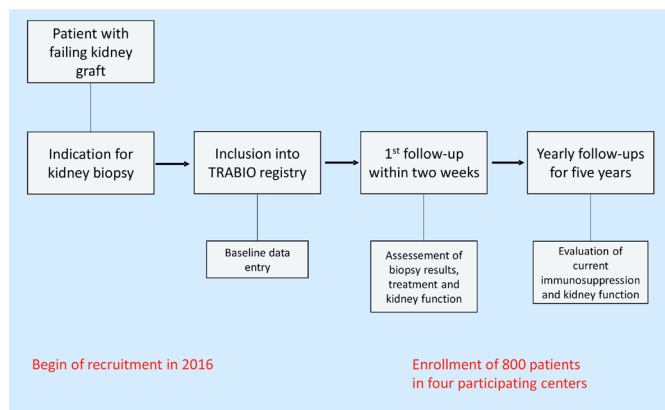
Figure 3 A total of 800 patients who undergo indication biopsy for suspected kidney graft rejection at one of four German transplantation centres will be included in the study after obtaining their written informed consent. Data will be collected and recorded at enrolment and then at yearly follow-ups for 5 years.

design. After the initial biopsy, baseline data will be recorded. The first follow-up will be within 14 days after enrolment for evaluation of the biopsy results. After that, patients will be followed up yearly for a total of 5 years; at each follow-up, details of treatment, maintenance immunosuppression, kidney function and outcomes will be recorded. If a patient is lost to follow-up because he/she is not available for a scheduled follow-up appointment, the patient's primary care physician will be contacted to inquire about whether the patient is deceased. If the patient is alive, another appointment will be scheduled or, when this is not possible, the data required for follow-up will be directly obtained from the primary care physician.

Data

Figure 4 shows the data that will be recorded at enrolment and follow-up. On enrolment, demographic data (age, sex); transplantation date; bloodtype AB0 compatibility; underlying kidney disease; comorbidities; induction and maintenance immunosuppressive treatment

	Day of biopsy	1st follow-up	Yearly follow-up
Demographic data	X		
Comorbidities	X		
Transplantation date	X		
AB0-compatibility	X		
Cause of native kidney loss	X		
Induction IS	X		
Previous biopsies	X		
DSA status	X		
Kidney function	X	X	X
Current IS-regimen	X	X	X
Detailed biopsy results		X	
Acute IS-treatment		X	

Figure 4 Categories of data that will be recorded at enrolment and during follow-up visits. AB0, blood types A/B/0; DSA, donor-specific antibodies; IS, immunosuppression

(drug classes and doses as well as calcineurin inhibitor and mechanistic Target of Rapamycin [mTOR] inhibitor trough levels); DSA status (presence, type, titre); previous biopsy results and kidney function (proteinuria and best serum creatinine level in previous 2 weeks, 3 months and 1 year) will be acquired and entered into an electronic database created specifically for this study by *NITEFLITE,* Munich, Germany. Additionally, at the first follow-up, detailed biopsy findings (quality of biopsy sample, Banff lesion scores, Banff categories,[19] presence of polyomavirus and acute-phase treatment strategies (drug classes and doses, number of plasmapheresis sessions) will be recorded. At each subsequent follow-up, patient survival; kidney function (proteinuria, serum creatinine, need for dialysis) and current immunosuppressive treatment (drug classes and doses as well as calcineurin inhibitor and mTOR inhibitor trough levels) will be recorded. Presence of polyoma virus infection will be detected by PCR testing of serum and urine. If a patient has to undergo a rebiopsy for graft deterioration of any cause, the findings of that biopsy will be recorded.

Biopsies

Biopsies will be performed by experienced nephrologists under sterile conditions. The biopsy specimen will be stored in 4% formaldehyde and sent for histopathological analysis at the responsible nephropathology laboratory of the clinic performing the biopsy. Biopsies will be performed and read locally using a standardised protocol. All biopsies will be diagnosed and interpreted according to the Banff-classification.[19] The following Banff-lesion scores and additional findings will be graded routinely:

> number of glomeruli, number of sclerosed glomeruli, number of arteries, Banff i, Banff t, Banff v, Banff g, Banff ptc, Banff C4d, Banff ci, Banff ct, Banff cv, Banff cg, Banff mm, Banff ah, Banff ti, Banff i-IFTA, segmental arterial intima fibrosis without hyperelastosis, segmental arterial intima fibrosis with lymphatic infiltrates, thrombotic microangiopathy, glomerulonephritis, focal and segmental glomerulosclerosis, pyelonephritis, polyomavirusnephritis, posttransplant lymphoproliferative disease

Outcomes

The primary outcomes of this study will be all-cause mortality and dialysis-free graft survival, which will be assessed at each follow-up. Dialysis-free graft survival at the time of follow-up is defined as complete independence from haemodialysis, peritoneal dialysis and absence of retransplantation or death from graft failure. The secondary outcomes will be worsening of kidney function (defined as >30% decrease in the Chronic Kidney Disease-Epidemiology Collaboration-Glomerular Filtration Rate (CKD-EPI-GFR) from the best GFR up to 12 weeks prior to rejection), new-onset large proteinuria (defined as >300 mg/dL in urine dipstick test) and biopsy-proven second episode of acute graft rejection. If

there is no resolution of graft dysfunction, this will count as a persistent rejection. If graft function has recovered at any point and subsequently deteriorates again, a second rejection episode will be suspected. A complete resolution of a treated rejection episode is determined by presence of patient and graft survival at follow-up 2, a≥90% recovery of CKD-EPI-GFR back to baseline CKD-EPI-GFR, and resolution of new-onset large proteinuria. A partial response is defined as a 50%–89% recovery of CKD-EPI-GFR back to baseline CKD-EPI-GFR. These outcomes were chosen because they are objectively measurable and patient centred.

Proposed statistical methods

After completion of enrolment and follow-up, descriptive analysis will be performed of the study population, histopathological features and treatment strategies. Patients with missing biopsy reports and patients lost to follow-up will be excluded from analysis. Categorical variables (eg, Banff categories) and binary variables (eg, sex, mortality, ESRD) will be summarised as counts and frequencies. Continuous variables (eg, age, CKD-EPI-GFR) will be summarised as means (with SD) or medians (and ranges). Logistic and linear regression analysis will be used to determine how the primary and secondary study outcomes (dependent variables) are related to treatment strategy and adherence to the standard of care (independent variables). ORs (with 95% CIs) will be calculated to quantify the strength of associations. Differences will be considered statistically significant, if CIs do not include 1.0 or if $p<0.05$, as appropriate. Known confounders such as age, time since transplantation, cardiovascular disease, chronic hepatitis, cancer and baseline kidney function as well as history of prior kidney transplantation will be included in the regression models.

Sample size and study duration

As little is known about the frequency and outcomes of kidney transplantations rejections in Germany, a priori power calculation was difficult. A relatively large sample size of 800 was chosen to achieve high power for collection of initial, hypothesis-generating data. The study duration is set to be until 5 years of follow-up have been completed for all patients.

Data safety and patient privacy

Data will be collected by research assistants. All collected data will be entered into the web-based electronic data portal by the principal investigator (PI) of the respective centre. The PIs will have exclusive access to the electronic data portal through individual password-protected accounts. Data will be pseudonymised on entry. To exclude the possibility of incomplete data sets, the electronic data portal is designed such that only complete data sets can be saved. Data validity and quality will be personally verified by the site PIs through comparison with the source files.

Monitoring

Monitoring of the study will be conducted by the GKM, Gesellschaft für Therapieforschung mbH, Munich, Germany. The monitoring organisation will run once-yearly random quality checks of 15% of the patient files. This will be realised through on-site comparison of the source files with the data in the electronic data portal. The monitoring organisation will also verify that only patients who have given informed written consent are included in the database, that the study protocol is being adhered to by all sites, and that all records are adequate and accurate.

Patient involvement

Patients were not directly involved in the development of research questions, outcome measures, study design, or planning of the recruitment process. Patients will be informed of the study results during their routinely scheduled check-ups.

ETHICS AND DISSEMINATION OF STUDY FINDINGS
Ethical approval

The ethics committee of the Christian-Albrechts-University of Kiel approved this study and the ethics committees of the clinics of Munich, Mainz, and Stuttgart confirmed the ethical approval (AZ B 278/16).

Dissemination and data sharing

The first results will be reported in a peer-reviewed journal after 800 patients have completed 1 year of follow-up, using the Strengthening the Reporting of Observational Studies in Epidemiology criteria.[20] Data will be made available to other healthcare professionals after publication and on reasonable request.

Significance, strengths and limitations

Kidney transplantations are associated with high resource costs for all parties involved, but long-term outcomes remain unsatisfactory. More evidence is needed on the long-term prognosis and treatment outcomes of kidney graft rejections, as large RCTs in this field are scarce and often contradictory. Therefore, we expect that this study will provide much needed data. Since kidney transplant patients tend to have very regular appointments with their transplantation centres, lost to follow-up should be minimal. The prospective design and engagement of a monitoring organisation will ensure high-quality data and good internal validity. Furthermore, four separate transplantation centres across Germany will be involved leading to high generalisability of the study findings. However, the study has some limitations. This is an observational study and so can only show associations between potential risk factors and outcomes; causal relationships cannot be established. Additionally, association between two variables may be influenced by confounders; therefore, we will attempt to adjust for the effect of major confounders by including them in regression analyses. Since we do not

conduct surveillance protocol biopsies, we will not be able to detect subclinical rejections. However, we have a strong protocol in place to diagnose and register all episodes of significant graft deterioration. We are confident that through the longitudinal, multicentre design and large cohort size, our study will contribute to the improvement of kidney graft rejection treatment.

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Contributors FAvS-H made substantial contributions to the study design and wrote the paper. GE made substantial contributions to the study design, collected data and wrote the paper. KS made substantial contributions to the study design as well as study management, and substantially revised the paper. BK, MK, VS, JW-M, JM, FS, AP and MB made substantial contributions to the study design, patient recruitment and revised the paper. KA conceptually designed the study, recruited participating centres, is responsible for the majority of histopathological evaluations and revised the paper. TF, UK, LR and UH conceptually designed the study, recruited participating centres, organised funding, and revised the paper. All authors approved this study protocol.

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