Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis

Florian G Scurt, Lara Ewert, Peter R Mertens, Hermann Haller, Bernhard M W Schmidt, Christos Chatzikyrkou

Summary

Background ABO-incompatible renal transplantation (ABOi-rTx) is increasingly used to overcome organ shortage. Evidence about its non-inferiority in comparison with ABO-compatible renal transplantation (ABOc-rTx) needs to be analysed at early and late timepoints. We aimed to investigate differences in outcome after ABOi-rTx and ABOc-rTx.

Methods We did a systematic review and meta-analysis of observational studies published up until Dec 31, 2017, that reported outcome data (±1 year of follow-up) after ABOi-rTx and included an ABO-compatible control group, by searching the Cochrane Central Register of Controlled Trials (CENTRAL), Embase Ovid, MEDLINE Ovid, and PubMed. Trials on recipients of ABOi-rTx were assessed, if an ABO-compatible control group was included and if outcome data on at least graft or recipient survival with 1 year or more of follow-up were available. Exclusion criteria included case reports, editorials, reviews and letters, animal studies, meeting papers, studies unable to extract data, non-renal solid organ and bone-marrow transplant studies, and deceased donor ABOc-rTx. Data were extracted from published reports. Primary endpoints were all-cause mortality and graft survival at 1, 3, 5, and more than 8 years after transplantation. In the meta-analysis, we used a fixed-effects model if the P value was 0, and both a fixed-effects and random-effects model if P was more than 0. This study is registered with PROSPERO, number CRD42018094550.

Findings 1264 studies were screened and 40 studies including 49 patient groups were identified. 65,063 patients were eligible for analysis, 7098 of whom had undergone ABOi-rTx. Compared with ABOc-rTx, ABOi-rTx was associated with significantly higher 1-year mortality (odds ratio[OR] 2·17 [95% CI 1·63–2·90], p<0·0001; P=29%), and 5 years (OR 1·89 [1·46–2·45], p<0·0001; P=29%), and 5 years (OR 1·47 [1·08–2·00], p=0·01; P=68%) following transplantation. Death-censored graft survival was lower with ABOi-rTx than with ABOc-rTx at 1 year (OR 2·52 [1·80–3·54], p<0·0001; P=61%) and 3 years (OR 1·59 [1·15–2·18], p=0·0040; P=58%) only. Graft losses were equivalent to that of ABOc-rTx after 5 years and patient survival after 8 years. No publication bias was detected and the results were robust to trial sequential analysis until 5 years after transplantation; thereafter, data became futile or inconclusive.

Interpretation Despite progress in desensitisation protocols and optimisation of ABOi-rTx procedures, excess mortality and loss of kidney grafts was found compared with ABOc-rTx within the first 3 years after transplantation. Only long-term outcomes after 5 years yielded equivalent survival rates and organ function. Awareness of the increased risks of infection, organ rejection, and bleeding could improve care of patients and promote efforts towards paired kidney exchange programmes.

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Introduction

Kidney transplantation is the renal replacement therapy option with the greatest benefit for most patients with end-stage renal disease.1 However, most patients have to endure many years on dialysis because of constantly growing kidney transplant waiting lists and the scarcity of organs from deceased donors. Among the strategies developed to overcome the problem of organ shortage, particular attention has been paid to expanding the living donor pool, and many efforts have been made to facilitate renal transplantation in the setting of ABO blood group incompatibility.

The ABO blood group barrier has long been considered a contraindication to renal transplantation because of the increased risk for humoral rejection and early graft loss.2 However, pretransplant desensitisation strategies, such as the removal of isoagglutinins by plasmapheresis or immunoadsorption and the depletion of antibody-producing cells with rituximab, have enabled ABO-incompatible renal transplantation (ABOi-rTx).3

Although smaller studies evaluating patient and graft outcome after ABOi-rTx did not show any striking differences compared with living donor ABO-compatible renal transplantation (ABOc-rTx), larger registry data have showed conflicting results.4 Therefore, uncertainty about safety and efficacy still exists and ABOi-rTx has not been universally adopted by all transplant centres running renal transplantation programmes.5

We sought to further investigate the potential of ABOi-rTx as a meaningful, safe, and successful alternative for patients with end-stage renal disease presenting with a living donor with an unsuitable blood group.
This systematic review and meta-analysis was done in accordance with the PRospective Studies Collaboration (PROSPERO) protocol. We followed the recommendations by the Cochrane Collaboration, the PRISMA statement, and the GRADE guidelines.

We identified studies using Medline Ovid, Embase Ovid, MEDLINE Ovid, and PubMed. We also searched CENTRAL in The Cochrane Library, with the following keywords and combinations: “ABO-incompatible” OR “ABOi” OR “AB0i” OR “AB0i” OR “ABO-incompatible” OR “ABOI” OR “AB0i” OR “AB0i” OR “ABO-incompatible” AND “renal” OR “kidney” AND “ABOi-rTx” OR “AB0i-rTx”. We included studies published from database inception to Dec 31, 2017, were included. The following electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Embase, Medline, PubMed. We also searched for all studies that were identified and did screening, selection, and data extraction. Summary estimates and patient data from the publication were extracted. We did not seek individual patient data and used only data provided in the published studies. Disagreements were resolved by discussion with a consensus decision or by the decision of another author (PRM or BMWS). In case of duplicates, companion publications, or multiple reports of a primary study, the most complete dataset combined across all known publications was used. All full texts of all trials that fulfilled the eligibility criteria were included.

Search strategy and selection criteria

Three of the authors (FGS, LE, and CC) independently identified studies and did screening, selection, and data extraction. Summary estimates and patient data from the publication were extracted. We did not seek individual patient data and used only data provided in the published studies. Disagreements were resolved by discussion with a consensus decision or by the decision of another author (PRM or BMWS). In case of duplicates, companion publications, or multiple reports of a primary study, the most complete dataset combined across all known publications was used. All full texts of all trials that fulfilled the eligibility criteria were included.

Methods

Evidence before this study

ABO-incompatible renal transplantation (ABOi-rTx) has long been used to overcome the problem of organ shortage. However, the data for its non-inferiority in comparison to ABO-compatible renal transplantation (ABOc-rTx) is equivocal. Although smaller single centre studies did not show any striking differences in graft and patient survival, registry analyses have raised safety issues and highlighted conflicting results. We searched PubMed, MEDLINE, Embase, and the Cochrane Central Register for systematic review and meta-analyses in English published using the search term “ABO” or “AB0” in combination with “incompatible” and “renal” or “kidney”. “ABOi” or “AB0i” in combination with “renal” or “kidney”. 1264 references were identified and 40 studies could be used for the analysis. All studies were published between Jan 27, 1998, and Sept 1, 2012. The existing evidence might not help with optimal clinical decision making and to adequately counsel patients considering an ABOi-rTx.

Added value of this study

To the best of our knowledge, our systematic review and meta-analysis is the most extensive synthesis of available evidence assessing clinical outcomes of ABOi-rTx in comparison with ABOc-rTx. 40 eligible studies, comprising more than 650,000 patients, 7000 of whom had undergone ABOi-rTx, were identified. Our findings showed inferior outcomes of ABOi-rTx for nearly all relevant clinical endpoints: patient and graft survival, infectious and non-infectious complications, and graft rejection episodes. The refinement in the desensitisation protocols and the implementation of less intensive immunosuppressive regimens improved patient and graft survival, but both outcomes still remained worse in the first years after ABOi-rTx than after ABOc-rTx. Randomised controlled trials are of course not feasible in the case of ABOi-rTx, and the evidence we provide has the inherent drawbacks of observational studies. Taking these issues into consideration, the meta-analysis was planned and done according to the most accepted practices regarding assessment of study quality and risk of bias.

Implications of the available evidence

ABOi-rTx is a valuable option for a kidney transplant candidate presenting with an ABO-incompatible living donor, considering the alternative treatment approaches: remaining on the waiting list and waiting for an ABO-compatible deceased donor or not having a transplant and staying on dialysis. Our study suggests that, compared with an ABO-compatible living donor, ABOi-rTx is disadvantageous and has worse results in nearly all patient-relevant clinical outcome metrics. Our findings favour kidney paired donation instead of proceeding with an ABOi-rTx and are a call for action to expand the networks and improve the usage of kidney exchange programmes.

Particularly, we assessed whether the effects of ABOi-rTx in terms of graft survival, patient survival, and infectious and non-infectious complications are similar overall to that of ABOc-rTx, and whether the effects were similar after taking different desensitisation strategies into consideration, such as the incorporation of rituximab-based protocols. For this purpose, we did a systematic review and meta-analysis of the available published evidence.
after transplantation. Secondary outcomes were infectious and non-infectious complications, and graft rejections. Infectious complications included sepsis, urinary tract infections, cytomegalovirus infection, BK polyomavirus infection, and Pneumocystis jirovecii pneumonia. Non-infectious complications included surgical revisions, haematomas, lymphoceles, and ureteral complications. Surgical revisions were defined as unscheduled operative procedures mostly required to address serious bleeding complications in the kidney transplant anatomical location or elsewhere, surgical wound dehiscence, symptomatic lymphoceles, and urine leak. Graft rejections encompassed overall, borderline, cellular, and humoral rejections. Subgroup analysis for the main outcomes were stratification by older (ie, splenectomy) and newer (ie, rituximab) desensitisation protocols.

Because of the absence of randomised controlled studies identified in the search, the risk of bias was assessed by the use of the Newcastle-Ottawa Scale and included the following items: representativeness of the exposed population, appropriate election and comparison of the study groups, adequate ascertainment of exposure (preconditioning therapies), and accuracy of outcome assessment. A point value of less than five points indicates a reduced study quality. Two authors (FGS and LE) allotted the point scores independently of one another. Disagreements were resolved by discussion and consensus or by the decision of a third author (CC). The study quality and the risk of bias in the study results were not used as exclusion criteria.

We calculated the summary estimates using Review Manager (RevMan, version 5.3) and trial sequential analysis program version 0.9 beta. We used a p value of 0.033 (calculated by dividing 0.05 by (2 + 1)/2) or less as statistically significant in the analyses of the primary outcomes, and a p value of 0.025 (ie, 0.05/(3 + 1)/2) or less as statistically significant in the analyses of the secondary outcomes. To avoid false confirmations of intervention effects induced by multiple outcome comparisons, we changed the traditional 95% confidence interval. We divided the probability 0.05 by the value halfway between 1 (no adjustment) and the number of primary outcome comparisons (the Bonferroni adjustment). This results in a multiplicity adjusted p value threshold using one primary outcome that equals 0.05 (corresponding to the 95% CI), two primary outcomes that equals 0.033 (corresponding to a 96.7% CI), and three outcomes that equals 0.025 (corresponding to a 97.5% CI). The 2 in the equation indicates two primary outcomes (graft and patient survival) and the 3 indicates three secondary endpoints (infectious and non-infectious complications, and graft rejections). Publication bias was examined by funnel plots and Egger’s and Begg’s tests.

We identified statistical heterogeneity by inspecting the forest plots and the estimates of the diversity (I²) and inconsistency (I²) statistics. I² is a different heterogeneity measure to P and accounts for the total relative reduction in variance, when changing the model from a random-effects model to a fixed-effects model.

In this way, D² can adjust for the required increase in information size due to heterogeneity. If we found substantial clinical, methodological, and statistical heterogeneity, we would not report the results as pooled effect estimates in a meta-analysis. If I² was 0, we would use and report a fixed-effects model, and if I² was more than 0, we would use both a fixed-effects and random-effects model. If the intervention effects differed in the two models, we would emphasise the most conservative estimate (point estimate closest to the null effect), and if the intervention effects were approximately equal in the two models, we would emphasise the result with the widest CI.

Because cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data, we used trial sequential analysis to assess this risk. The calculated required information size takes into account the event proportion in the control group, the assumption of a plausible relative
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risk (RR) reduction and the anticipated heterogeneity variance (D²) of the meta-analysis. This calculation enables the statistical inference concerning a cumulative meta-analysis that has not yet reached the required information size to be determined.

We used a family-wise error rate of 5% leading to a statistical significance level of 3-3% for each of the two co-primary outcomes and 2-5% for the anticipated four co-secondary outcomes, a β of 20%, and a D² value suggested by the trials in the meta-analysis or a D² value of 20% if the actual measured heterogeneity was in fact 0, because in this case heterogeneity would most probably increase when further trials are added until the required information size is reached. To calculate anticipated intervention effects for the primary and secondary outcomes in the trial sequential analysis, we used realistic a-priori RR reductions or RR increases based on the confidence limits in the traditional naive meta-analysis. We present naive 95% confidence limits (CIs) for all estimates. This study is registered with PROSPERO, number CRD42018094550.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table: Characteristics of included studies

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*Only graft survival of the first era was analysed, because of a lack of information in the publication. †Population consisted of children only.

Results

Of the 1264 citations identified from electronic and hand searches, 51 full-text articles were identified for possible eligibility, and after exclusion of incomplete reports, 40 studies were included in the meta-analysis (figure 1; appendix p 1). Details of the studies are summarised in the table. All studies were published between Jan 27, 1998, and Sept 1, 2017, and included 65063 patients in total. The number of paediatric and adult recipients of ABOi-rTx ranged between ten and 1878 for the included studies, and the number of ABOc-rTx recipients ranged between 21 and 26504. The mean age of the adult study participants was 44-9 years (range 34-56) in the ABOi-rTx group and 43-1 years (31-53) in the ABOc-rTx group. Because some studies described outcome data of subgroups (living donors vs deceased donors, adult vs pediatric recipients, use or not of rituximab, cross match positive vs cross match negative, and transplantation at different time periods, 49 different patient groups were available for analysis. All studies had a Newcastle-Ottawa Scale score of 5 or more (table).

37 (65063 participants) for 1 year, 27 (44213 participants) for 3 years, 15 (56640 participants) for 5 years, and three studies (11039 participants) for more than 8 years were included in the analysis of mortality after transplantation (figure 2). Compared with ABOc-rTX, ABOi-rTx was associated with a higher risk of 1-year mortality (D²=65%), 3-year mortality (D²=58%), 5-year mortality (D²=83%), but not of 8-years or more mortality (D²=0%). Overall numbers
of events and patients, ORs, and heterogeneity data are presented in figure 2. No publication bias with regard to the mortality outcome was evident (appendix pp 2–3). Trial sequential analysis confirmed that the meta-analysis was conclusive regarding the anticipated intervention effect leading to the required information size for mortality at 1 year, 5 years, and inconclusive for mortality at more than 8 years (appendix).

36 studies (59,970 participants) were included in the analysis of death-censored graft survival (figure 3A) and 37 studies (60,085 participants) in the analysis of death-uncensored graft survival (appendix p 7) at 1 year. Overall numbers of events and patients, ORs, and heterogeneity data for graft survival are presented in figure 3 and the appendix. At 1 year, death-censored graft survival was lower after ABOi-rTx than after ABOc-rTx ($D^*=79\%$), as was death-uncensored graft survival (appendix). No publication bias with regard to the graft survival outcome was evident (appendix). Trial sequential analysis showed that the meta-analysis was conclusive regarding the anticipated intervention effect leading to the required information size (appendix).

26 studies (43,945 participants) were included in the analysis of death-censored graft survival at 3 years (figure 3B) and 27 studies (44,060 participants) were included in the analysis of death-uncensored graft survival at 3 years (appendix). At 3 years, death-censored and death-uncensored graft survival was lower after ABOi-rTx than after ABOc-rTx (death-censored $D^*=78\%$ and death-uncensored $D^*=72\%$). No publication bias was evident and trial sequential analysis confirmed that the meta-analysis was conclusive (appendix).

15 studies with 51,160 participants and 16 studies with 51,275 participants were included in the analysis of death-censored (figure 3C) and death-uncensored (appendix) graft survival, respectively, at 5 years. Death-uncensored
Figure 2: All-cause mortality after ABOi-rTx versus ABOc-rTx at 1 year (A), 3 years (B), 5 years (C), and more than 8 years (D) after transplantation.

ABOi-rTx=ABOi-compatible renal transplantation. ABOc-rTx=ABO-incompatible renal transplantation.
(p=0·02, D²=84%) but not death-censored graft survival (p=0·09, D²=85%) was lower after ABOi-rTx than after ABOc-rTx. No publication bias was evident with regard to this outcome and trial sequential analysis supported futility of the intervention (appendix).

Three studies (8617 participants) were included in the analyses of graft survival (death-censored and death-uncensored) at 8 years or more (figure 3D; appendix). Death-censored (p=0·79, D²=86%), and death-uncensored graft survival (p=0·74, D²=88%), were not lower after ABOi-rTx than after ABOc-rTx. Trial sequential analysis supported futility of the intervention regarding the anticipated effect leading to the required information size (appendix).

Nine studies (2093 participants) were included in the analyses of sepsis, ten (2964 participants) in the analyses of urinary tract infections, 24 (15703 participants) in the analyses of cytomegalovirus infection, and eight (1983 participants) in the analyses of BK polyomavirus infection, and eight (1983 participants) in the analyses of P. jirovecii pneumonia (appendix). Overall numbers of events and patients, ORs, and heterogeneity data for infectious complications are presented in the appendix.

The proportion of patients with sepsis was higher after ABOi-rTx than after ABOc-rTx (D²=0%). No statistically significant difference was observed in the risk of urinary tract infections (D²=48%), cytomegalovirus infection (D²=71%), BK polyomavirus infection (D²=0%), and P. jirovecii pneumonia (D²=0%).

Six studies (3800 participants) were included in the analyses of surgical revisions, ten studies (2479 participants) were included in the analyses of bleeding or haematoma, ten studies (5179 participants) were included in the analyses of lymphoceles overall, four studies (838 participants) were included in the analyses of ureteral complications, and four studies (527 participants) were included in the analyses of detailed complications (appendix). Overall numbers of events and patients, ORs,
Figure 3: Graft failure (death censored) of ABOi-rTx versus ABOc-rTx 1 year (A), 3 years (B), 5 years (C), and more than 8 years (D) after transplantation. ABOi-rTx=ABO-incompatible renal transplantation. ABOc-rTx=ABO-compatible renal transplantation.
and heterogeneity data for non-infectious complications are presented in the appendix. A greater proportion of patients who had ABOi-rTx had surgical revision than those who had ABOc-rTx (D=0.0%), bleeds or haematomas (D=0.2%), and lymphoedema (D=8.2%). We found no significant difference in the proportion of patients with surgically treated lymphoedema (D=6.1%) or ureteral complications (D=0.0%) between patients who had ABOi-rTx and those who had ABOc-rTx.

20 studies (6569 participants) were included in the analysis of overall rejections, eight (1338 participants) in the analysis of borderline rejections, 26 (4648 participants) in the analysis of acute antibody-mediated rejections (ABMR), and 22 (3251 participants) in the analysis of T-cell mediated transplant rejections (appendix). Overall numbers of events and patients, ORs, and heterogeneity data for non-infectious complications are presented in the appendix.

No significant difference between treatment groups was observed in overall (D=68.0%), borderline (D=74.0%), or T-cell mediated rejections (D=0.0%). By contrast, the proportion of patients with ABMR was higher after ABOi-rTx than after ABOc-rTx (D=51.5%).

Subgroup analyses of rituximab-based versus non-rituximab-based desensitisation protocols revealed higher 1-year and 3-year mortality after ABOi-rTx than after ABOc-rTx (appendix) regardless of the initial desensitisation protocol (1 year mortality: OR 2.70 [95% CI 1.74–4.18], I²=27%, p=0.03; p=0.03). p=0.02 with rituximab, 3-year mortality: OR 2.37 [1.04–5.42], p=0.07, p=0.01 without rituximab and OR 1.77 [1.20–2.60], p=0.001. p=0.02 with rituximab, 5-year survival, ABOi-rTx was not associated with significantly higher mortality than was ABOc-rTx in the rituximab group (OR 0.68 [0.34–1.36], p=0.28, I²=21%, p=0.03), compared with the group without rituximab (OR 1.82 [95% CI 1.47–2.24], p<0.001, I²=60%, p=0.47).

Data-censored graft survival at 1 year was equal in the ABOi-rTx and the ABOc-rTx group (appendix), if the initial desensitisation protocol included rituximab (OR 1.72 [95% CI 1.01–2.94], I²=39%, p=0.07) and was worse in the ABOi-rTx group than the ABOc-rTx group if the initial desensitisation protocol did not include rituximab (OR 3.56 [95% CI 1.84–6.87], I²=71%, p=0.001). Data-censored graft survival at 3 years was worse in the ABOi-rTx group given non-rituximab-based desensitisation protocols than in the ABOc-rTx group (OR 2.46 [95% CI 1.12–5.39], I²=71%, p=0.001), but was similar to the ABOc-rTx group in those who received rituximab-based desensitisation protocols (OR 1.19 [0.76–1.86], I²=27%, p=0.001). Studies reporting graft survival data after 5 years did not show significant differences between treatment groups when groups were analysed according to whether or not they received a rituximab desensitisation protocol (appendix).

The risk of sepsis and cytomegalovirus infections after ABOi-rTx was significantly higher than after ABOc-rTx in patients who received non-rituximab-based desensitisation protocols, but no difference was seen between treatment groups in those who received rituximab-based desensitisation protocols (appendix). The risk for polyclonal nephropathy was not lower after ABOi-rTx than after ABOc-rTx in patients who received non-rituximab-based desensitisation protocols (OR 0.37, 95% CI 0.09–1.45; p=0.15), but there were only two studies reporting such data (appendix). A trend for a higher risk for polyclonal nephropathy was observed after ABOi-rTx than after ABOc-rTx in patients who received rituximab-based desensitisation protocols (p=0.03). Regarding P. jirovecii pneumonia and urinary tract infections, no significant differences between ABOi-rTx and ABOc-rTx were found with any of the initial desensitisation protocols (appendix).

In patients who received either rituximab or non-rituximab-based desensitisation protocols, ABOi-rTx was not associated with significantly more overall rejections, borderline rejections, or T-cell mediated transplant rejections than was ABOc-rTx (appendix). There was a trend for a higher risk of ABMR after ABOi-rTx than after ABOc-rTx with both desensitisation protocols (p=0.03). Nevertheless, the risk of ABMR was significantly lower if an initial rituximab-based desensitisation protocol was used (appendix).

Discussion

This systematic review and meta-analysis is based on transplantation data (patient and graft survival) for ABOc-rTx and ABOi-rTx from 40 studies involving more than 65,000 patients originating from the USA, Europe, Asia, and Australia. The statistical analyses reveal a clear benefit of ABOc-rTx over ABOi-rTx in the first 5 years following organ implantation. Only long-term data after 8 years indicate equal performance of the procedures for survivors. With the introduction of a desensitisation strategy that includes rituximab (instead of splenectomy), excess mortality with ABOi-rTx was only seen within the first 3 years, and data-censored graft survival became similar to that of ABOc-rTx within the first year.

The advent of ABOi-rTx provides novel options for patients in need of a transplant organ with a living donor. For most countries, a paired donation programme to circumvent the immunological challenge of ABO incompatibility is precluded by law. Thus, ABOi-rTx remains the only option. Our meta-analysis clearly shows that even with the most advanced desensitisation protocols, patient mortality is higher in the first 5 years after ABOi-rTx than after ABOc-rTx. This higher mortality could be a result of side-effects due to an over-suppressed immune system following desensitisation with emergence of life-threatening infections of bacterial (sepsis) and viral origin (eg, cytomegalovirus).
Higher rates of bleeding events are reported after ABOi-rTx than after ABOc-rTX, probably due to changes of the coagulation system following plasmapheresis or high-volume plasma exchange, or both. Surgical revisions, with more postoperative wound infections, haematomas, and lymphocele formation are more common after ABOi-rTx.

The risk of postoperative bleeding appears to be especially high if immunoadsorption is used. Cytomegalovirus prophylaxis protocols might explain the reduced proportion of patients with early cytomegalovirus infections at present, which obviates viral infections regardless of the cytomegalovirus risk status.

Additionally, the risk of serious infections and infection-related mortality increases considerably if rituximab is used at higher doses or in combination with peritransplant conditioning regimens, or other immunosuppressive agents, in the course of the induction therapy. Despite the abundance of data on rituximab-associated infectious complications, it is not clear whether the prevalence of infectious complications correlates with ABO blood group incompatibility; with the administration of rituximab per se, or if it simply reflects the more intense immunosuppression regimens used in recipients of ABOi-rTx than in those receiving ABOc-rTX.

Our findings suggest that the observed higher early mortality after ABOi-rTx than after ABOc-rTX could be overcome by refining the initial immunosuppressive protocols and individualising the immunosuppressive therapy. Indeed, in smaller studies, selected patients receiving either a reduced dose of rituximab, no rituximab or no plasmapheresis during the induction phase, or lower doses of mycophenolate mofetil during the maintenance phase after ABOi-rTx showed exceptionally good outcomes with less infectious complications and without increased incidence of acute rejection.

The lower (death-censored) graft survival with ABOi-rTx was in line with a high risk of ABMR. Inclusion of rituximab therapy decreased the risk of ABMR 5 years after transplantation; however, the OR for ABMR was still 1.8 in the group that did not receive rituximab. Polyomavirus nephropathy was more common after ABOi-rTx than after ABOc-rTX in patients who received rituximab-based desensitisation protocols, which could be explained by viral escape from the immune surveillance. Polyoma nephropathy is probably another reason for the lower graft survival after ABOi-rTx, although we did not find a statistically significant difference in our analysis. The risk of developing polyomavirus-associates nephropathy in patients who have undergone ABOi-rTx is even significantly higher than in recipients of HLA-incompatible kidney transplants.

The improvement in graft survival at 3 years in the ABOi-rTX group that received rituximab mainly reflects evolution in the preconditioning procedures and immunosuppressive regimens and the transition to more efficient and less toxic treatment protocols. Nevertheless, the proportion of patients with ABMR still remained higher after ABOi-rTX than after ABOc-rTX. Patients undergoing ABOi-rTX are at higher immunological risk because of a re-transplant condition, older age, unrelated donors, more HLA mismatches, or higher panel reactive and donor-specific antibody amounts, than are those undergoing ABOc-rTX. Furthermore, rituximab seems not to be efficient in reducing the concentration of preformed anti-HLA antibodies or preventing the development of de-novo anti-HLA antibodies, both well known and strong risk factors for chronic ABMR and poor graft outcomes.

Nevertheless, in our analysis, the risk of humoral rejection with rituximab-based desensitisation protocols was clearly reduced (in comparison with splenectomy) and the risk of ABMR in the ABOi-rTX group was similar to that in the ABOc-rTX group 5 years after transplantation if rituximab was initially used. Similar results were obtained in immunologically high-risk recipients of ABOc-rTX given rituximab within the course of induction therapy.

Limitations of this study need to be acknowledged. Our endpoints did not address all consented core outcome domains for studies of kidney transplantation. Only some items of the core outcome sets were encompassed in the primary studies and could be analysed. Other important domains, such as cardiovascular disease, stability of graft function, diabetes, or meaningful patient-reported outcomes, could not be addressed because studies included in the meta-analysis did not report them. Different immunosuppressive protocols were used between studies, making it impossible to assess the effect of a specific induction and desensitisation regimen. Therefore, the effectiveness of the principal isoagglutinin removal technique, starting isoagglutinin thresholds, or the exposure to a specific combination of immunosuppressive drugs could not be assessed. The observational periods were shorter than 5 years in most studies and therefore less data were available for the analyses of clinical outcomes after 5 years. We attempted to exclude studies reporting data for the same patient cohorts when this duplication was indicated in the source files. However, the possibility of patient cohorts included in national registry analyses as well as smaller single-centre studies could not be ruled out. An accurate report of the time after transplantation at which infectious, non-infectious, and immunological complications occurred was not stated. Heterogeneity in the included study cohorts was substantial, with discords in donor and recipient ages and immunological risk factors. Differences in patients' characteristics that might have an effect on transplantation outcomes, such as frailty status, duration of dialysis before transplantation, cardiovascular disease burden, and primary diseases, were not reported in most of the studies.

Although the outcome data for ABOi-rTX within the first 3 years after transplantation are worse than for ABOc-rTX, our results should not be considered conclusive. Further improvements in the immunological tests to combat blood group incompatibility-related complications can be
achieved. A reduction in the dose of the immuno-suppressive drugs applied could be beneficial, given the higher risk of infection than in those who are not taking immunosuppressive drugs. Pre-emptive antibiotic and vistoratic therapy are also options to consider. Furthermore, interest in the coagulation system is warranted and surveillance of bleeding events could be optimised following plasmapheresis and immunosorption. For patients undergoing renal replacement therapy, the option of ABOi-rTx nevertheless holds promise, given its outperformance of continued dialysis procedures. Our analyses do not cover ABOc-rTx from deceased donors. A multipronged comparison of all four modalities (ABOi- rTx vs living ABOC-rTx vs deceased donor ABOc-rTx vs continued dialysis) in the context of a multicentre study or a network meta-analysis could help to further clarify the raised safety and efficacy issues. A similar methodological approach was used in the setting of HLA-incompatible renal transplantation.\(^{49}\)

The alternate option to circumvent ABOi-rTx would be paired kidney exchange, which has been established in numerous centres. Ethical considerations and administrative barriers exist and have to be taken into consideration.\(^{13,14}\) Even more complex scenarios have been successfully managed, such as three-way and multiple-way kidney exchanges. Our results should encourage clinicians, health-care providers, and health policy makers to facilitate and expand the network of kidney exchange programmes.

**Contributors**

BMWS, FGS, and CC conceived and designed the study. FGS, LE, BMWS, and CC collected and evaluated the data. FGS and CC analysed the data and interpreted the results. CC wrote the manuscript and was responsible for the decision to submit for publication. FGS did the statistical analysis, created the tables and figures, prepared the supplementary material, and wrote the appendix. PRM and HH reviewed and edited the manuscript. All authors revised and approved the final manuscript.

**Declaration of interests**

We declare no competing interests.

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**References**


