CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

# Off-Label Use of Intravenous Immunoglobulin for Solid Organ Transplant Rejection: A Review of Clinical Effectiveness


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**Authors:** Sara D. Khangura, Sarah Visintini

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## Abbreviations

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| AMR | Antibody-mediated rejection |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| DSA | Donor-specific antibodies |
| eGFR | Estimated glomerular filtration rate |
| GFR | Glomerular filtration rate |
| IgG | Immunoglobulin G |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| MDRD | Modified Diet in Renal Disease |
| MFI | Mean fluorescence intensity |
| MP | Methylprednisolone |
| RCT | Randomized controlled trial |
| RTX | Rituximab |
| SCID | Subcutaneous immunoglobulin |

## Context and Policy Issues

The transplantation of solid organs — including heart, kidney, liver, lungs, and pancreas[1] — has advanced significantly since the middle of the 20th century, with important and often life-saving benefits to patients with a variety of conditions.[2] In 2016, the Canadian Institute for Health Information estimates that 2,906 solid organ transplants occurred in Canada.[3]

Despite important advances in the success of solid organ transplantation, rejection of transplanted organs remains an important barrier. Organ transplant rejection occurs when a patient's immune system recognizes and attacks cells and tissues from the donor organ.[4] Risk factors for organ transplant rejection include prior pregnancy, blood transfusion, and past transplants.[5] Organ transplant rejection can be experienced by the patient as a feeling ill (e.g., malaise, nausea, fever) and can result in loss of the transplanted organ.[4] Rejection can occur at various points in time, manifesting as either acute (i.e., from during the procedure, up to three months afterward) or chronic (i.e., more than three months following the procedure) conditions.[6]

Treatment for acute transplant rejection has focused on the use of immunosuppressant therapy to reduce the immune system's rejection response to the donor tissue and avoid loss of the transplanted organ — though, this approach is less effective in cases of chronic organ transplant rejection.[7] In cases of antibody-mediated rejection, current treatments include plasmapheresis, proteasome inhibitors, complement inhibition, rituximab, and intravenous immunoglobulin (IVIG), though research evaluating these treatments to-date remains scarce and consists mostly of case reports and small case series of retrospective cohort studies.[5] While significant advances have been realized, particularly over the past 30 years,[2] long-term benefits of existing treatments have not been consistently demonstrated.[8]

Immunoglobulin (also referred to as immune globulin or gamma globulin) is a purified blood product pooled from the plasma of healthy blood donors.[9] Immunoglobulin may be administered as IVIG or as subcutaneous immunoglobulin (SCIG). In Canada, various preparations of immunoglobulin are approved specifically for use in patients with one or more of the following six conditions: primary immune deficiency, immune thrombocytopenic purpura, secondary immune deficiency states, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, and multifocal motor neuropathy.[10] The products approved for use are ANTHRASIL, Flebogamma, Octagam, Cutaquig (subcutaneous), and WinRho SDF.[10,11] Others approved for marketing are Atgam, Cytogam, Gammagard, Gamunex, Hepagam B, Igivnex, Panzyga, Privigen, and Varizig.[10,11]

Between 1998 and 2006, Canada's per capita use of IVIG grew 115%, which makes Canada one of the highest consumers of IVIG per capita worldwide.[12-14] The belief is that much of this growth is attributable to an increase in off-label use of IVIG.[12,13,15] A three month audit in 2007 conducted by the Ontario Regional Blood Coordinating Network found that: 50% of IVIG use was on-label; 40% was off-label, but potentially clinically effective, and; 10% was off-label and possibly not clinically effective.[16] In Canada (except Quebec), Canadian Blood Services supplies IVIG to hospitals at no charge; however, there is no formal mechanism for oversight regarding IVIG use.[13,15,16] Each dose of IVIG can cost between $550 and $2,200 CAD per child and between $2,000 and $8,000 CAD per adult; this does not include other associated costs of treatment.[12] From April 2005 to March 2006, this IVIG use cost Canadian Blood Services $196.1 million CAD.[13]

IVIG has been identified as a potentially beneficial therapy for patients experiencing solid organ transplant rejection.[17] The purpose of this report is to provide a synthesis of the available evidence on the clinical effectiveness of off-label use of IVIG for solid organ transplant rejection. This report is complementary to a 2017 CADTH Rapid Response, Summary of Abstracts report: "Off-Label Use of Intravenous Immunoglobulin for Solid Organ Transplant Rejection, Paraneoplastic Disorders, or Recurrent Miscarriage: Clinical Effectiveness".[18]

## Research Questions

What is the clinical effectiveness of off-label use of intravenous or subcutaneous immunoglobulin for the treatment of solid organ transplant rejection?

## Key Findings

One randomized controlled trial and one non-randomized, retrospective, observational study were identified describing the clinical effectiveness of off-label use of intravenous immunoglobulin for the treatment of solid organ transplant rejection. Evidence of moderate quality from one randomized controlled trial investigating intravenous immunoglobulin combined with rituximab versus placebo in 25 renal transplant patients with chronic antibody mediated rejection indicated that there was no important effect on renal function. Evidence of limited quality from one non-randomized, retrospective observational study investigating intravenous immunoglobulin versus methylprednisolone in 39 renal transplant patients with antibody mediated rejection indicated that there was a significant improvement in renal function. Further evidence from larger, long-term studies, including investigating other types of organ transplants, is necessary to reduce uncertainty.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and October 26, 2017.

### Selection Criteria and Methods

One reviewer screened all citations returned from the literature searches. In the first phase of screening, titles and abstracts were reviewed for relevance and those deemed to be potentially relevant were then retrieved[18] and later assessed for eligibility by another reviewer using full-text.

The inclusion of sources at the full-text level of screening was based on the eligibility criteria outlined in Table 1.

## Table 1: Selection Criteria

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| **Population** | Patients any age with acute rejection and antibody-mediated rejection after solid organ transplantation |
| **Intervention** | Human IVIG or SCIG products, including but not limited to those available in Canada, alone or in combination with corticosteroids or other immunomodulation therapy. |
| **Comparator** | Treatment as usual, placebo, or no treatment |
| **Outcomes** | Clinical benefits and harms |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies |

IVIG = Intravenous immunoglobulin; SCIG = Subcutaneous immunoglobulin.

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, did not use a comparative design, were duplicate publications, or were published prior to 2012.

### Critical Appraisal of Individual Studies

The included studies were critically appraised by one reviewer using the Downs and Black checklist, which is applied using 26 items across five sub-scales to assess reporting, external validity, bias, confounding, and power.[19] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 456 citations were identified in the literature search. Following screening of titles and abstracts, 432 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 22 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one RCT and one non-randomized clinical trial. Appendix 1 presents the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

### Summary of Study Characteristics

#### *Study Design*

One multi-centre, double-blind randomized controlled trial (RCT)[20] and one single-centre, non-randomized, retrospective, comparative observational study[21] were identified.

#### *Country of Origin*

The RCT was conducted in Spain[20] and the non-randomized study was conducted in Poland.[21]

### *Patient Population*

Patients participating in the RCT[20] were 25 kidney transplant recipients with chronic, antibody-mediated rejection (AMR). The mean age in the intervention arm was 47 (± 13) years and in the comparison arm was 49 (± 15) years. Ten of the 25 patients (40%) participating in the RCT were female.

Patients evaluated in the non-randomized study[21] were 39 kidney transplant recipients with AMR. The mean age in the intervention arm was 40.64 (± 11.23) years and in the comparison arm was 37.45 (± 11.61) years. Eighteen of the 39 patients (46%) participating in the non-randomized study were female.

### *Interventions and Comparators*

The RCT compared IVIG plus rituximab (RTX) versus placebo. Patients randomized to receive IVIG plus RTX were administered IVIG at a dose of 0.5 grams (g)/ kilogram (kg) once every three weeks for a total of four doses, as well as a single dose of RTX at a dose of 375 milligrams (mg)/ metre$^2$ (m) one week following the last dose of IVIG. Patients randomized to placebo received an isovolumetric saline solution using the same schedule as patients randomized to IVIG plus RTX.[20]

The non-randomized study compared IVIG versus methylprednisolone (MP). Patients receiving IVIG were administered between one and three g/kg for two consecutive days, as well as intravenous (IV) MP, antihistamine, and basic immunosuppression. Patients receiving MP were administered IV MP at a dose of 500 mg for three consecutive days, as well as prednisone and basic immunosuppression.[21]

### *Outcomes*

Renal function was the primary outcome of interest in both the RCT[20] and the non-randomized study.[21] In the RCT, renal function was measured primarily by the estimated glomerular filtration rate (GFR) which was calculated using the Modified Diet in Renal Disease (MDRD) equation in mL/min per 1.73 m$^2$. Serum creatinine was also measured using mg/decilitre (dL). Secondary measures of renal function included proteinuria (g/day), renal lesions characterized (using Banff criteria), donor-specific antibodies (DSA) reported as mean fluorescence intensity (MFI) and adverse events, including graft loss and/or death. The duration of follow-up was one year.

Measures of renal function reported in the non-randomized study[21] included the change in estimated glomerular filtration rate (GFR) across time using the MDRD formula and modeled using a mixed, generalized linear method. Serum creatinine was also reported as a measure of interest using mg/dL. Adverse events were neither pre-specified as an outcome of interest nor reported in the results, however, mention was made of side effects in the discussion section of the paper. Duration of follow-up varied across patients — from 1.88 to 34.11 months in the IVIG group and 4.7 to 75.76 months in the control group — due to the retrospective design of the study.

The beneficial direction of effect for the primary outcome was implied in both papers as being a reduction in GFR.[20,21] While a minimally important clinical difference was not explicitly reported *a priori*, authors of the RCT[20] described in the paper's discussion that the planned sample size was based, in part, on identifying a 10 ±10 millilitre (mL)/ minute (min) per 1.73 m$^2$ difference between groups (which implicates a minimally important clinical difference). Minimally important clinical difference was not addressed in the non-

randomized study; though the authors did make it clear that a reduction in the linear slope of GFR across time was evidence of a benefit to patients.[21]

Additional details regarding the characteristics of included publications are provided in Appendix 2.

## Summary of Critical Appraisal

Both studies in this review clearly reported their objectives, patient characteristics, interventions and outcomes of interest.[20,21] However, while the RCT[20] clearly reported the main findings, random variability in the data, losses to follow-up, and actual probability values, the non-randomized study[21] did not clearly report on these items. For both studies in this review, neither a list of confounders nor a list of adverse events was reported. Clarity of reporting is critical to a transparent assessment of the strengths and limitations of studies. Because some information was lacking from the reports of the studies included in this review, they could not be assessed in their entirety.

It was not possible to assess any of the items addressing external validity for the included RCT[20] as details about the representativeness of subjects asked to participate, patients who consented to participate and the interventions administered were not reported. Similarly, the non-randomized study did not report information on the representativeness of the subjects included in the study, nor the interventions administered, but whereas the RCT reported a patient flow diagram (but failed to validate representativeness), the non-randomized study did not describe any relevant details concerning the selection of patients. In order to understand whether and how the findings of a study may apply to other, similar patients, an assessment of external validity is essential. Because external validity could not be ascertained for either study, it remains unclear whether their findings can appropriately be applied to other, similar patients.

The risk of bias was assessed as low in the RCT,[20] with subjects and outcome assessors blinded to the intervention received, no apparent unplanned analyses reported, consistent follow-up duration across patients, ostensibly appropriate statistical analyses, reasonable compliance and transparent reporting of losses to follow-up (as well as the use of intention-to-treat analyses) and the use of apparently appropriate outcome measures. While the non-randomized study likewise reported no apparently unplanned analyses, statistical adjustment for inconsistent follow-up duration across patients, and otherwise apparently appropriate statistical analyses, it is unlikely that patients and outcome assessors were blinded to the interventions due to the investigators' use of a retrospective method. Further, there was nothing reported concerning compliance with the intervention and the outcome measures were not clearly described. In this review, the retrospective design used in the non-randomized study is an important consideration when weighing the internal validity of its reported findings; thus, it should be interpreted with caution as bias may have had an impact on the effects reported.

The RCT addressed confounding by recruiting patients within the same timeframe, employing a randomized design that was concealed from patients and care providers, and accounting for loss to follow-up.[20] However, it was unclear whether the RCT recruited patients for the intervention and comparison groups from the same or different centres, and there was no explicit description of confounding variables. In the non-randomized study,[21] it was clear that patients in both groups were selected from a single centre; however, there was no clear description of confounding variables or loss to follow-up. Further, it was clear that patients were treated at variable points across time and that there was no

randomization undertaken due to the investigators' use of a retrospective method. The potential for confounding is an important threat to internal validity as well, and is essential for study investigators to consider — particularly when using a non-randomized approach. While the RCT in this review did not explicitly report potential confounders, its use of a randomized design is an important strength that stands in contrast to the method employed in the non-randomized study. The non-randomized study's failure to explicitly discuss potential confounding variables is another important limitation.

Finally, sample sizes in both studies were small and study power was acknowledged as a limitation by the authors of both studies.[20,21] Power calculations are critical as part of considering an adequate sample size — which is a fundamental consideration in weighing the importance of a study's findings and conclusions as it serves as an indicator of the probability of avoiding a Type II error i.e., finding an apparent effect among the sampled patients in a study where no effect actually exists.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

## Summary of Findings

*What is the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of solid organ transplant rejection?*

**Antibody-Mediated Rejection following Kidney Transplant**

**Renal Function**

One RCT[20] and one non-randomized, retrospective observational study[21] were identified describing the comparative effect of off-label use of IVIG versus placebo[20] and methylprednisolone[21] on renal function in patients with antibody-mediated rejection (AMR) following kidney transplant. No information regarding SCIG was identified.

The RCT reported change in mean estimated glomerular filtration rate (GFR) at one year of follow-up in the IVIG + RTX group as −4.2 (±14.4) mL/min per 1.73m$^2$ ($P$ = 0.125) and in the placebo group, −6.6 (±12.0) mL/min per 1.73m$^2$ ($P$ = 0.248). The difference between groups was not statistically significant ($P$ = 0.475).[20] Nonetheless, the authors suggested caution in interpreting the results given the limitations of their sample size.[20] The non-randomized, retrospective observational study reported the change in average, absolute GFR before and after the intervention in the IVIG group as -2.25 mL/min and in the methylprednisolone (MP) group, -5.26 mL/min. The statistical difference between groups was not reported. The non-randomized study also reported the results of a generalized mixed linear model of estimated GFR that found the change in linear slope was significant in patients receiving IVIG i.e., 0.69 mL/min/month ($P$ < 0.001) but not significant in patients receiving MP i.e., 0.01 mL/min/month (difference reported qualitatively as not significant i.e., no $P$-value). The relative change between groups in linear slope before and after the interventions were administered was reported as 0.7 mL/min/mo ($P$ < 0.033), suggesting a significant benefit for the IVIG group.[21]

Change in mean serum creatinine was measured in both studies using mg/dL. The RCT reported a change of 0.2 (± 2.1) in the IVIG + RTX group and 0.6 (± 1.1) in the placebo group — the difference between groups was not statistically significant.[20] The non-randomized study reported only baseline values per group for serum creatinine with no follow-up data.[21]

The RCT also reported on several secondary measures of renal function, none of which demonstrated any statistically significant differences between the IVIG + RTX and placebo groups.[20]

**Adverse Events**

The RCT[20] explored adverse events (AEs), recording 26 in the IVIG + RTX group and 28 in the placebo group — which authors described qualitatively as not different between groups. In the IVIG + RTX group, five patients required hospitalization for AEs, whereas four patients in the placebo group were hospitalized for AEs. Diagnoses among hospitalized patients in the IVIG + RTX group included urinary sepsis, urinary tract infection, fever, and hyponatremia. In patients who received placebo and were hospitalized for AEs, diagnoses included acute diverticulitis, acute gastroenteritis with acute renal failure, and esophageal perforation.[20]

While the non-randomized study did not pre-specify evaluation of AEs, and did not report any AEs in the results, the authors indicated that no serious side effects were observed in patients as a result of receiving IVIG.[21]

Appendix 4 presents a table of the main study findings and authors' conclusions.

## Limitations

There were a number of limitations with the evidence identified in this review describing off-label IVIG for the treatment of solid organ transplant rejection. The comparative evidence in this area was limited, such that two studies were found to be eligible. Additional evidence in this area is of limited methodological rigour, using non-randomized designs, small sample sizes and not employing the use of any comparison group against IVIG interventions.

Both of the included studies in this review[20,21] examined kidney transplant recipients, limiting any interpretation about the use of off-label IVIG in solid organ transplant rejection patients to renal transplant recipients only. Importantly, both studies employed the use of small sample sizes which necessitates caution in the interpretation of their findings. Extending from this, the conclusions drawn by authors of the two studies are discordant, further suggesting that the evidence addressing the use of off-label IVIG in renal transplant rejection patients remains underdeveloped and that additional, rigourous research is needed to understand its potential effect.

While the included RCT reported a government ministry as its funding source, the non-randomized study did not report their source of funding. In addition to limited generalizability and potential threats to internal and external validity, the lack of a transparent statement of funding warrants further caution. Consequently, the results of this report should be interpreted with caution.

## Conclusions and Implications for Decision or Policy Making

This review identified two comparative studies evaluating the use of IVIG in renal transplant patients with AMR. One study was an RCT examining 25 patients and the other was a non-randomized, retrospective, observational study of 39 patients. Although there is some description of IVIG addressing antibody-mediated rejection (in particular in kidney transplant patients) in related literature, it is acknowledged that the potential mechanism of effect remains uncertain[22] and its effectiveness has not been demonstrated in large, clinical trials.[17] No evidence regarding SCIG was identified.

In this review, limited RCT evidence of moderate quality indicates that the use of IVIG combined with rituximab (RTX) had no statistically significant effect on any study measure of renal function in patients with antibody-mediated rejection (AMR) when compared against placebo.[20] Authors of the study encouraged caution in the interpretation of the results due to its small sample size, in particular. Evidence of limited quality in the non-randomized study indicates that there was no change in absolute average glomerular filtration rate (GFR) in either patients treated with IVIG or those treated with methylprednisolone (MP).[21] Nonetheless, modeled data indicated a statistically significant difference in the post-intervention change in linear slope of the glomerular filtration rate (GFR), favouring patients treated with IVIG. Authors of this study concluded that IVIG improved renal function in patients with AMR.[21]

Most other research evaluating IVIG for solid organ transplantation focuses on kidney transplants in patients with AMR.[23-26] Recent studies examining IVIG in the context of solid organ transplant have been conducted using small samples and single-arm designs examining various treatment regimens that include IVIG.[23-27] This work has similarly demonstrated variable effects, from some apparent effect on measures of organ function in some patients[23,24,27] to no apparent effect in other patients.[25] Consequently, established clinical benefits remain uncertain[25,26] and unrealized.[27]

In conclusion, while one study in this review suggested a benefit of IVIG for patients with AMR of kidney transplant, another study of higher quality found no effect. Both studies had some risk of bias due to uncertain external validity (representativeness) and small sample size (low power). The study that reported a benefit of IVIG had important, additional limitations to internal validity (true effect) and no explicitly stated source of funding. Therefore, results should be interpreted with caution as the clinical effectiveness of IVIG for kidney transplant remains unclear. Further evidence from larger, long-term studies, including investigating other types of organ transplants, is necessary to reduce uncertainty.

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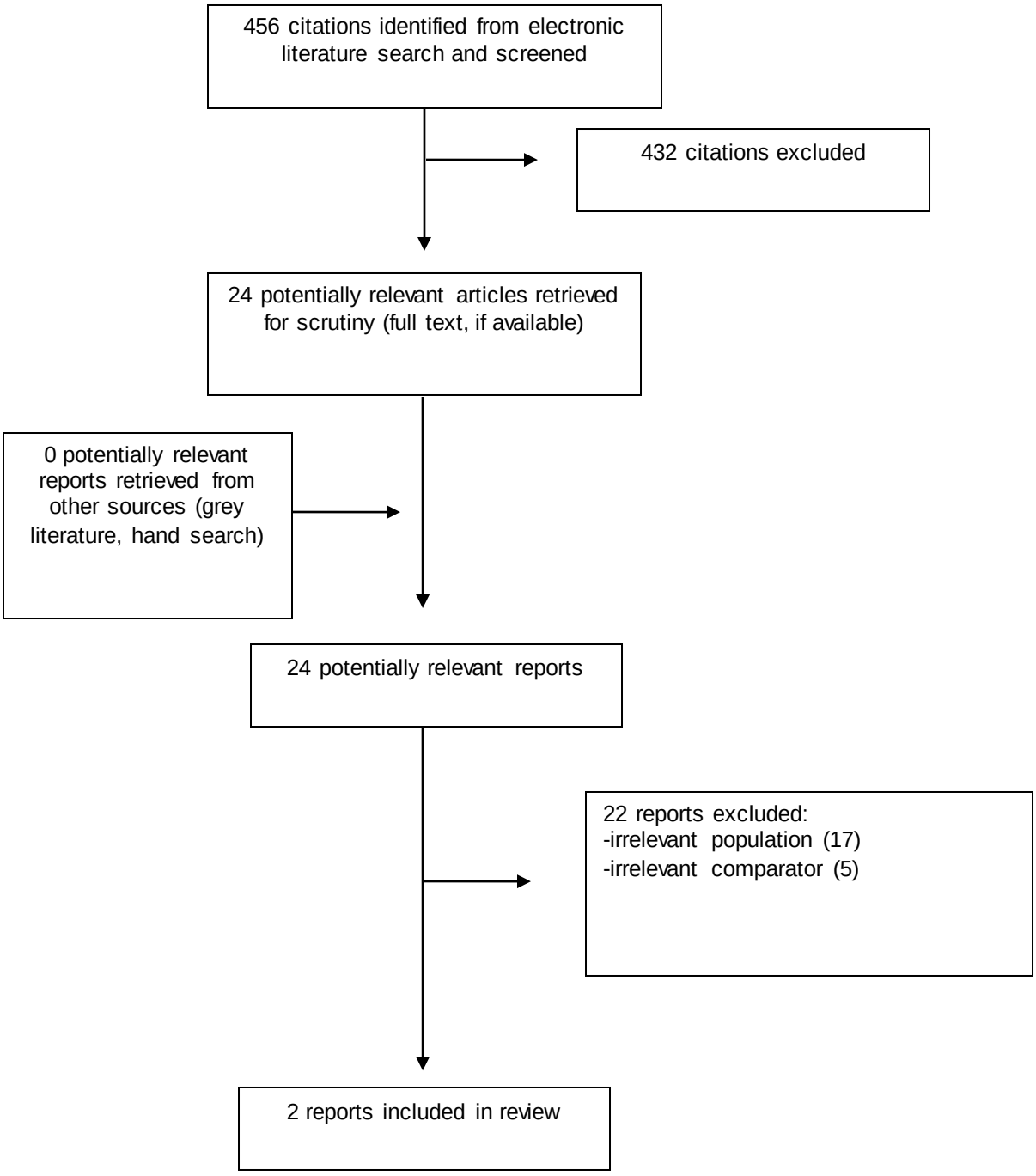
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Measures, Length of Follow-Up |
|---|---|---|---|---|
| Moreso,2017[20]<br><br>Spain | Double-blind RCT | 25 kidney transplant patients with chronic AMR randomized<br><br>Intervention arm:<br>Mean age = 47 (±13)<br>Female/male = 4/8<br><br>Comparison arm:<br>Mean age = 49 (±15)<br>Female/male = 6/7<br><br>Setting was described as multi-centre; additional details NR | IVIG and rituximab (RTX) versus placebo<br><br>Intervention arm:<br>IVIG (0.5 g/kg) every 3 weeks for 4 doses, plus a single dose of rituximab (375 mg/m$^2$) 1 week after the last IVIG dose<br><br>Comparison arm:<br>Isovolumetric saline solution using the same schedule as the intervention arm | Renal function measured by:<br><br>Primarily<br>i. Estimated glomerular filtration rate (GFR) using the Modified Diet in Renal Disease (MDRD) equation (ml/min per 1.73 m$^2$)<br>ii. Serum creatinine (mg/dL)<br><br>Secondarily<br>iii. Proteinuria (g/day)<br>iv. Renal lesions (Banff criteria producing a histological score)<br>v. Donor-specific antibodies (DSA) (reported as mean fluorescence intensity (MFI))<br>vi. Adverse events, including graft loss and/or death<br><br>Follow-up = 1 year |
| Furmanczyk-Zawiska,2016[21]<br><br>Poland | Retrospective observational study | 39 kidney transplant recipients with AMR enrolled<br><br>Intervention arm:<br>Mean age = 40.64 yrs (±11.23)<br>Female/male = 6/11<br><br>Comparison arm:<br>Mean age = 37.45 (±11.61)<br>Female/male = 12/10<br><br>Setting described as single-centre; additional details NR | IVIG versus methylprednisolone (MP)<br><br>Intervention arm:<br>IVIG (1-3 g/kg) for 2 consecutive days plus IV MP, antihistamine and basic immunosuppression<br><br>Control arm:<br>IV MP (500 mg) for 3 consecutive days, plus prednisone and basic immunosuppression | Renal function measured by:<br><br>i. Change in estimated glomerular filtration rate (GFR) over time using the Modified Diet in Renal Disease (MDRD) formula and modeled using a mixed generalized linear method<br>ii. Serum creatinine<br><br>Intervention arm:<br>Mean follow-up = 18.8 mos (range 4.7 to 75.76)<br><br>Comparison arm:<br>Mean follow-up = 10.12 mos (range 1.88 to 34.11) |

AMR = Antibody-mediated rejection; dL = decilitre; DSA = Donor-specific antibodies; eGFR = Estimated glomerular filtration rate; g = grams; GFR = Glomerular filtration rate; IgG = Immunoglobulin G; IV = Intravenous; IVIG = Intravenous immunoglobulin; kg = kilogram; MDRD = Modified Diet in Renal Disease; MFI = Mean fluorescence intensity; mg = milligram; m = metre; mos = months; MP = methylprednisolone; NR = not reported; RCT = randomized controlled trial; RTX = Rituximab; yrs = years

# Appendix 3: Critical Appraisal of Included Publications

## Table 3: Strengths and Limitations of Clinical Studies using Down's and Black Checklist for measuring study quality[19]

| Strengths | Limitations |
|---|---|
| **Randomized Controlled Trial** | |
| **Moreso, 2017[20]** | |
| ***Reporting***<br>• Aim and objectives, main outcomes, patient characteristics, interventions, main findings, random variability, loss to follow-up and probability values clearly reported<br>***Internal validity – bias***<br>• Study subjects and outcome assessors were blinded<br>• No evidence of unplanned analyses<br>• Follow up duration was standard and consistent<br>• Statistical tests appear appropriate<br>• Compliance with the intervention was reported<br>• Outcome measures clearly reported<br>***Internal validity – confounding***<br>• Study subjects recruited over the same period of time<br>• Study subjects were randomized to treatment<br>• Randomization was concealed<br>• Loss to follow-up accounted for | ***Reporting***<br>• List of principal confounders, distribution of data and adverse events not clearly reported<br>***External validity***<br>• Representativeness of eligible patients, study subjects and treatment setting not clearly reported<br>***Internal validity – confounding***<br>• No information concerning the centre of recruitment per treatment group<br>• No mention of confounding<br>***Power***<br>• Study was underpowered (but this was clearly acknowledged) |
| **Non-Randomized Study** | |
| **Furmanczyk-Zawiska, 2016[21]** | |
| ***Reporting***<br>• Aim and objectives, main outcomes, patient characteristics and interventions clearly reported<br>***Internal validity – bias***<br>• No evidence of unplanned analyses<br>• Variability in follow up duration was adjusted for in the analyses<br>• Statistical tests appear appropriate<br>***Internal validity – confounding***<br>• Patients in both treatment groups recruited from same population | ***Reporting***<br>• List of principal confounders, distribution of data, main findings, random variability and probability values not reported clearly and/or consistently<br>• Adverse events and loss to follow-up not reported<br>***External validity***<br>• Representativeness of eligible patients and treatment setting not clearly reported<br>• Representativeness of study subjects not reported<br>***Internal validity – bias***<br>• Study subjects and outcome assessors not blinded<br>• Outcome measures not clearly reported<br>• Compliance with the intervention not clearly reported<br>***Internal validity – confounding***<br>• Study subjects not recruited over the same period of time<br>• Study subjects not randomized to treatment<br>• Loss to follow-up not explicitly accounted for<br>• Adjustment for confounding not clearly reported<br>***Power***<br>• Study was underpowered (but this was acknowledged) |

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 4: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| Randomized Controlled Trial | |
| Moreso, 2017[20] | |
| i. Change in mean eGFR at 1 year (mL/min per 1.73 $m^2$)<br>• IVIG<br>○ −4.2 ± 14.4 (*P* = 0.125)<br>• Placebo<br>○ −6.6 ± 12.0 (*P* = 0.248)<br>• Difference between groups<br>○ *P* = 0.475<br>ii. Change in serum creatinine at 1 year (mg/dL)<br>• IVIG<br>○ 0.2 ± 2.1<br>• Placebo<br>○ 0.6 ± 1.1<br>• Difference between groups<br>○ *P* = 0.287<br>iii. Change in proteinuria at 1 year (mean g/day)<br>• IVIG<br>○ 0.9 ± 2.1 (*P* = NR)<br>• Placebo<br>○ 0.9 ± 2.1 (*P* = NR)<br>• Difference between groups<br>○ *P* = 0.378<br>iv. Change in renal lesions at 1 year (Banff scores)<br>• IVIG<br>○ Overall score NR (subscale scores only)<br>○ No significant change in severity (*P* = NR)<br>• Placebo<br>○ Overall score NR (subscale scores only)<br>○ No significant change in severity (*P* = NR)<br>• Difference between groups:<br>○ Banff scores = NS (*P* = NR)<br>v. Change in DSA at 1 year (MFI)<br>• IVIG<br>○ No significant change (*P* = NR)<br>• Placebo<br>○ No significant change (*P* = NR)<br>• Difference between groups:<br>○ NS (*P* = NR)<br>vi. Adverse events (AEs)<br>• IVIG<br>○ Total N=26<br>○ Patients with AE requiring hospitalization (N=5)<br>▪ Urinary sepsis (1)<br>▪ Fever with negative cultures (1)<br>▪ Urinary tract infection (2)<br>▪ Hyponatremia (1)<br>• Placebo | *"The primary efficacy variable was the rate of eGFR decline during the first year and it was not different between the treatment and placebo groups, suggesting that the combination of IVIG and RTX does not stabilize renal function in patients with chronic ABMR displaying transplant glomerulopathy."* (p. 932) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| ○ Total N=28<br>○ Patients with AE requiring hospitalization (N=4)<br>▪ Acute diverticulitis (1)<br>▪ Acute gastroenteritis with acute renal failure (2)<br>▪ Esophageal perforation with mediastinal abscess (1)<br>• Difference between groups:<br>○ Reported as "not different" (p. 932) (*P* = NR) | |
| Retrospective Observational Study | |
| Furmanczyk-Zawiska, 2016[21] | |
| i. Change in average absolute estimated GFR (mL/min), pre- and post-intervention<br>• IVIG<br>○ -2.25 (*P* = NS)<br>• MP<br>○ -5.26 (*P* = NS)<br>• Difference between groups NR<br><br>ii. Change in linear slope of estimated GFR (mL/min/month)<br>• IVIG<br>○ Difference at time of intervention<br>▪ 0.69 (*P* < 0.01)<br>• MP<br>○ Difference at time of intervention<br>▪ 0.01 (*P* = NS)<br>• Relative slope change, pre- to post-intervention<br>○ 0.7 (*P* < 0.033) (favours the IVIG group)<br>iii. Serum creatinine<br>• NR | *"IVIG improved graft function in renal recipients diagnosed with biopsy-proven ABMR independently from classic immunologic or nonimmunologic graft function predictors."* (p. 1450) |

AE = adverse event; AMR = Antibody-mediated rejection; dL = deciliter; DSA = Donor-specific antibodies; eGFR = Estimated glomerular filtration rate; g = gram; GFR = Glomerular filtration rate; IgG = Immunoglobulin G; IVIG = Intravenous immunoglobulin; m = metre; MDRD = Modified Diet in Renal Disease; MFI = Mean fluorescence intensity; min = minute; mL = millilitre; MP = methylprednisolone; NR = not reported; NS = not significant; RCT = randomized controlled trial; RTX = Rituximab

# Appendix 5: Additional References of Potential Interest

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