Rituximab and hypogammaglobulinemia in the setting of ABO-incompatible kidney transplantation

Hamza Naciri Bennani1, Zhyiar Abdulraham1, Bénédicte Puissant-Lubrano2, Asma Allal1, Lionel Rostaing1,3,4*

1Département de Néphrologie et Transplantation de Organs, CHU Toulouse, France
2Laboratoire d’Immunologie, CHU Toulouse, France
3Service de Néphrologie, Hémodialyse, Aphereses et Transplantation, CHU Grenoble-Alpes, France
4Université Joseph Fourier, Grenoble Alpes, France

ABSTRACT

Background: ABO-incompatible (ABOi) kidney transplantation can be achieved by desensitizing the recipient using apheresis plus rituximab-based immunosuppression.

Objectives: We sought to ascertain the factors that contributed to low immunoglobulin levels at post-ABOi kidney transplantation.

Patients and Methods: This single-center study included 43 ABO-i kidney-transplant recipients desensitized with rituximab-based therapy. Posttransplant immunoglobulin levels (IgG, IgA, and IgM) were prospectively monitored within 2 years. If severe hypogammaglobulinemia occurred, i.e., IgG levels <4 g/L, patients received polyvalent immunoglobulin (IVIg substitution).

Results: Within 1-year posttransplantation, 25% of patients experienced at least once severe hypogammaglobulinemia. On D –30 (pre-transplantation), IgG, IgA, and IgM levels were within normal ranges: 10 ± 4.4, 1.9 ± 1.2, and 0.8± 0.5 g/L, respectively. IgG levels were significantly decreased at D0 (4.2 ± 3.8 g/L) compared to D–30. At D15, IgG levels did not significantly differ from those on D0 or D–30. Conversely, beyond month-1 posttransplant IgG levels were within normal ranges and were significantly higher than levels measured on D0. Within three months posttransplantation, 11 patients required IVIg because IgG levels were <4 g/L (IVIg+ group). When these patients were compared with those that did not receive IVIg within 3 months posttransplantation (IVIg– group), IgG levels were similar at D –30 in both groups. Conversely, at D0, IgG levels were significantly lower in the Ig+ group (2.4 ± 2 vs. 5.5± 4.2 g/L; P = 0.009); the difference remained significant until D15 posttransplantation (Ig+ : 3.4 ± 1.7, Ig–: 6.6 ± 2 g/L; P = 0.0002). There was no statistical difference between the two groups after D15. Infectious complications did not significantly vary between patients with or without hypogammaglobulinemia.

Conclusions: We conclude that hypogammaglobulinemia occurred frequently after ABO-incompatible kidney transplantation but did not cause more infectious complications.

Implication for health policy/practice/research/medical education: ABO incompatible kidney transplantation is widely accepted, and results in very good long-term results provided pretransplant desensitization. The latter relies on rituximab therapy that might result in hypogammaglobulinemia. Herein, we demonstrate that hypogammaglobulinemia is frequent after ABO incompatible kidney transplantation, i.e. in 25% of patients. However, immunoglobulin substitution, i.e. by infusing IVIg in cases of severe hypogammaglobulinemia (< 4 g/L) prevents posttransplant infectious complications.

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*Corresponding author: Lionel Rostaing, MD, PhD, Email: lrostaing@chu-grenoble.fr
1. Background
Many patients worldwide develop end-stage renal disease (ESRD). The best possible treatment option for ESRD is kidney transplantation (1,2). However, due to the shortage of deceased kidney donors, live-kidney transplantation is now common (3). In this setting, ABO-incompatible (ABOi) kidney transplantation can occur where the potential recipient has isoagglutinins directed against the potential donor. Transplantation can be done provided the recipient undergoes pretransplant desensitization, which includes rituximab therapy (that has now replaced splenectomy) and conventional immunosuppression (tacrolimus, steroids, mycophenolic acid) (4,5).

Rituximab is a chimeric monoclonal antibody that binds CD20. It is used to treat B-cell lymphomas and autoimmune diseases, such as systemic lupus erythematosus (6), rheumatoid arthritis (7), autoimmune cytopenia (8), and ANCA-associated vasculitis (9). Rituximab causes rapid depletion of CD20-expressing B-cell precursors and mature B-cells, which then remain at very low or undetectable levels for 6--9 months before slowly returning to pretreatment levels (10). Rituximab therapy has also been associated with late-onset neutropenia (11) and hypogammaglobulinemia (12). Patients with rheumatoid arthritis and that receive rituximab have higher infection rates if they develop hypogammaglobulinemia (12). Similarly, ANCA-associated vasculitis that is treated with rituximab, and where subsequent immunoglobulin-G (IgG) levels are <4 g/L, is an independent factor predictive for severe infection (13).

Following standard kidney transplantation, hypogammaglobulinemia is rarely a matter of concern as most immunosuppressive drugs target T-cells, and not B-cells. Nonetheless, a meta-analysis reported posttransplant IgG levels of <7 g/L in 40% of patients; in the same study, when severe hypogammaglobulinemia was observed, i.e., a level of <4 g/L, this was significantly associated with mortality (14). Conversely, a recent single-center study did not find a high prevalence of hypogammaglobulinemia or that a level of <4 g/L was associated with mortality (15).

In the setting of pretransplant desensitization, where rituximab is widely used, it is important to monitor immunoglobulin levels so that, if they become low (e.g., <4 g/L), polyvalent immunoglobulins can be substituted. As of today, no study has examined immunoglobulin levels in the setting of ABO-incompatible kidney transplantation.

In this study, we prospectively monitored pre- and post-ABOi kidney transplantation immunoglobulin levels: if hypogammaglobulinemia occurred, i.e., if IgG levels decreased to <4 g/L, patients were given immunoglobulin (IVIg) substitution.

2. Objectives
We want to ascertain the factors that contributed to low immunoglobulin levels at post-ABOi kidney transplantation.

3. Patients and Methods
3.1. Study population
This is single-center study was conducted between March 2011 and May 2015. Forty-three patients underwent ABOi live-kidney transplantation; of these, 10 also had one or more donor-specific anti-HLA alloantibody (ies) (DSA). The desensitization protocol has already been published (16). Briefly, in the setting of ABOi/HLAi, patients received 40 days of pretransplant IV-Ig at 1 g/kg, followed by rituximab 375 mg/m² at days (D) –30 and –15 pretransplantation. Tacrolimus, mycophenolic acid, and steroids were started at D –10 (before transplantation). In addition, apheresis sessions (semi-specific immunoabsorption or double-filtration plasmapheresis) were scheduled to decrease DSA mean fluorescence intensity to <3000 at transplantation. In the setting of ABOi, patients received one rituximab injection (375 mg/m²) at D --30 pretransplant; tacrolimus, mycophenolic acid, and steroids were started at D –10 pretransplantation. According to the pre-desensitization level of isoagglutinins, apheresis was based on either plasmapheresis, double-filtration plasmapheresis, or specific immunoabsorption, i.e., using an anti-A or anti-B column. Posttransplant immunosuppression relied on an induction therapy (basiliximab for ABOi, thymoglobulin for cases of ABOi/HLAi) in addition to tacrolimus, mycophenolic acid, and steroids. For some ABOi patients, mycophenolic acid was replaced with everolimus at D15 posttransplantation to decrease the risk of BKV infection.

Anti-infection prophylaxis was (i) sulfamethoxazole/trimethoprim 400 mg/80 mg every other day for 1 year, and (ii) valganciclovir 900 mg/d adapted to eGFR for either 3 months (when recipient was CMV seropositive) or 6 months (donor was CMV seropositive and recipient was CMV seronegative).

For the purpose of this study, we prospectively monitored IgG, IgA, and IgM levels, as well as total lymphocyte counts, and CD4, CD8, and CD19 subsets at the following time-points: D –30, D0, D15, month (M)1, M3, M6, M12, M18, and M24 posttransplantation. At posttransplant D15, and thereafter at any time-point, if IgG levels decreased to <4 g/L, the patient received one dose of IVIg at 1 g/kg, over a 4-hour period (Clairyg® or Privigen®).
3.2. Ethical considerations

The research followed the tenets of the Declaration of Helsinki; the study protocol was approved by the ethics committee of CHU Toulouse (France) and all participants gave written informed consent before enrolling into the study.

3.4. Statistical analysis

Results are expressed as means (±standard deviation) or median (ranges) where appropriate. Comparisons between groups were done by using student t test. A P value of <0.05 was considered statistically significant.

4. Results

Of the 43 patients, two had early graft failure: one patient presented with immediate posttransplant allograft-vein thrombosis and underwent allograft removal, the other patient developed acute renal failure at three months posttransplant, which was related to secondary oxalosis: he lost his graft despite intensive hemodialysis therapy.

4.1. Overall population

Within the first year posttransplant 25% of patients experienced at least one severe case of hypogammaglobulinemia, i.e., IgG levels <4 g/L. On D –30, IgG, IgA, and IgM levels were within normal ranges at 10 ± 4.4, 1-9 ± 1.2, and 0.8 ± 0.5 g/L, respectively (Table 1). IgG levels were significantly decreased at D0 (4.2 ± 3.8 g/L) compared to D –30. At D15, IgG levels did not significantly differ from those on D0 or D –30. Conversely, IgG levels at posttransplant M1, M3, M6, M12, M18, and M24 were within normal ranges and were significantly higher than levels measured on D0 (Table 1).

IgA levels were significantly decreased on D0 (1.1 ± 1.1 g/L) compared to those on D –30 (1.9 ± 1.2 g/L). After transplantation, they progressively increased and, at the last follow-up (M24), they were similar to those on D –30: i.e., 1.7 ± 0.9 g/L. In addition, IgM levels on D0 were significantly decreased compared to those on D –30 (0.3 ± 0.3 vs. 0.8 ± 0.5 g/L; P < 0.001). Thereafter, they progressively increased to reach pre-desensitization levels at M24 (0.7 ± 0.4 vs. 0.8 ± 0.5 g/L) (Table 2).

Within the first three months posttransplantation, 11 patients required IVIg therapy because their immunoglobulin levels were <4 g/L (IVIg group). When we compared these patients with those that did not receive IVIg within the first three months posttransplantation (IVIg group), IgG levels were similar at D –30 in both groups. Conversely, at D0, IgG levels were significantly lower in the Ig ± group (2.4 ± 2.0 g/L vs. 5.5 ± 4.2 g/L; P = 0.009); the difference remained statistically significant until D15 posttransplantation (Ig ±: 3.4 ± 1.7 g/L and Ig+: 6.6 ± 2 g/L; P = 0.0002), whereas there was no statistical difference between the two groups afterwards, except at M6 (Ig+: 6.2 ± 2.3 vs. Ig±: 9.2 ± 2 g/L; P = 0.001).

Table 3 shows the results for total lymphocytes, and T-cell and B-cell lymphocytes after ABOi kidney transplantation. At D0, D15, M1, and M3 there were significant decreases in total lymphocyte counts as well as T-CD3’, T-CD4’, T-CD8, and B cells, when compared to D-30 pretransplantation. Because patients that were

### Table 1. Immunoglobulin levels (IgG, IgA, and IgM) after ABOi kidney transplantation

|                | IgG (g/L) | IgA (g/L) | IgM (g/L) |
|----------------|-----------|-----------|-----------|
| D –30          | 10 ± 4.4  | 1.9 ± 1.2 | 0.8 ± 0.5 |
| D0             | 4.3 ± 3.8 | 1.1 ± 1.1 | 0.3 ± 0.3 |
| D15            | 5.3 ± 2.4 | 1.3 ± 0.7 | 0.4 ± 0.2 |
| M1             | 6.8 ± 2.6 | 1.4 ± 0.9 | 0.5 ± 0.3 |
| M3             | 7.6 ± 2.7 | 1.5 ± 1.1 | 0.5 ± 0.3 |
| M6             | 8.3 ± 2.3 | 1.7 ± 1.1 | 0.6 ± 0.3 |
| M12            | 8.8 ± 2.4 | 1.6 ± 0.9 | 0.7 ± 0.4 |
| M18            | 8.4 ± 2.5 | 1.7 ± 0.9 | 0.6 ± 0.4 |
| M24            | 9.1 ± 2   | 1.7 ± 0.9 | 0.7 ± 0.4 |

Abbreviations: D, day; M, month; Ig, immunoglobulin; ABOi, ABO incompatible.

| Denotes P value D0 vs. D –30 <0.001; b denotes P<0.001 for the comparison between Mn vs. D0; c denotes P=0.02 vs. D0; d denotes P<0.05 vs. D0. |

### Table 2. T- and B-cells after ABOi kidney transplantation

|                | TCD3’ (/mm³) | TCD4’ (/mm³) | TCD8’ (/mm³) | CD19’ (/mm³) | Total lymphocytes (/mm³) |
|----------------|--------------|--------------|--------------|--------------|-------------------------|
| D –30          | 1255 ± 683   | 774 ± 374    | 488 ± 339    | 131 ± 71     | 1630 ± 722              |
| D0             | 992 ± 952    | 630 ± 645    | 342 ± 323    | 0.8 ± 2.9    | 1094 ± 1002             |
| D15            | 366 ± 414    | 222 ± 297    | 139 ± 121    | 0.6 ± 1.6    | 416 ± 463               |
| M1             | 1004 ± 1052  | 512 ± 582    | 445 ± 647    | ND           | 1166 ± 1200             |
| M3             | 812 ± 720    | 469 ± 437    | 306 ± 339    | 0.5 ± 1.6    | 965 ± 806               |
| M6             | 851 ± 663    | 438 ± 450    | 314 ± 258    | 15 ± 28      | 1053 ± 693              |
| M12            | 1022 ± 620   | 518 ± 401    | 453 ± 337    | 45 ± 57      | 1306 ± 665              |
| M18            | 1068 ± 653   | 505 ± 328    | 410 ± 269    | 64 ± 65      | 1345 ± 646              |
| M24            | 1317 ± 950   | 563 ± 305    | 663 ± 727    | 84 ± 77      | 1647 ± 973              |

Abbreviations: D, day; M, month; T, T lymphocytes; B, B lymphocytes; CD, cluster of differentiation; ABOi, ABO incompatible.
Table 3. Immunoglobulin G levels after ABOi kidney transplantation according to the need for IVIg at posttransplantation.

| IVIg (+) (n = 31) | IVIg (-) (n=32) | P value |
|------------------|----------------|---------|
| IgG (g/L)        | IgG (g/L)      |         |
| D --30           | 10.5 ± 5.2     | 9.8 ± 4 | ns             |
| D0               | 2.4 ± 2        | 5.5 ± 4.2 | 0.009 |
| D15              | 3.4 ± 1.7      | 6.6 ± 2 | 0.0002 |
| M1               | 6.2 ± 3.5      | 7.2 ± 2.2 | ns          |
| M3               | 7.5 ± 3        | 7.8 ± 2.5 | ns          |
| M6               | 6.2 ± 2.3      | 9.2 ± 2 | 0.001 |
| M12              | 7.8 ± 2.6      | 9.5 ± 2.2 | ns          |
| M18              | 7.7 ± 2.8      | 8.8 ± 2.2 | ns          |
| M24              | 8.9 ± 2.2      | 9.2 ± 2 | ns          |

Abbreviations: ABOi, ABO incompatible; IVIg, intravenous immunoglobulins; D, day; M, month; ns, not significant.

HLAi (in addition to being ABOi) received two doses of rituximab (375 mg/m²) at pretransplant instead of one dose in the ABOI group, we assessed immunoglobulin subclass levels and lymphocyte subsets, excluding the 10 HLA/ABOi patients (Table 4). The levels of IgG, IgA, IgM and lymphocyte subsets were very similar to those of the entire population (Tables 1 and 3) for each time-point; values were always non-significant. There was no significant difference between patients that had hypogammaglobulinemia and those that did not regarding the risk of posttransplant infections, e.g., bacterial infections, cytomegalovirus, BK-virus infections, or parasitic/fungal infections. (Table 5).

Table 6 summarizes the studies reporting on prevalence of hypogammaglobulinemia in rituximab-related non-transplant patients.

5. Discussion
This is the first large series to report on posttransplant hypogammaglobulinemia in the setting of ABOI kidney transplantation where rituximab induction therapy was given at pretransplant to desensitize recipients. We found that within the first year posttransplant, 25% of recipients presented with at least one severe case of hypogammaglobulinemia (<4 g/L).

Rituximab-related hypogammaglobulinemia has been reported in non-organ transplant patients. Twenty-three percent of patients that received a rituximab-based therapy for non-Hodgkin’s lymphoma had severe hypogammaglobulinemia, as defined by IgG levels <5.8 g/L. However, in this British study, the total dose of rituximab was not mentioned nor was the number of infectious complications (19).

Conversely, in the setting of rituximab-treated autoimmune disorders, the prevalence of severe hypogammaglobulinemia is much lower. Cortazar et al reported on a series of 239 patients with ANCA-associated vasculitis and where the median rituximab dose was 7 g (range: 5–10); over a mean period of 2.4 years, the prevalence of severe hypogammaglobulinemia (IgG <4 g/L) was only 4.6%. The likelihood of developing an infectious complication was linked to baseline IgG levels. Receiving rituximab therapy when IgG levels were <4 g/L increased the risk of an infectious complication by 2.13 (range 1.04–4.36) (13). Similarly, Roberts et al reported on a series of 243 patients that had systemic lupus erythematosus, granulomatosis with polyangiitis, or microscopic polyangiitis, and had received rituximab (median dose: 6 g [range: 1–23]). Thirty-five percent of patients developed hypogammaglobulinemia, defined as IgG levels <7 g/L; however, it was only severe in 4%, i.e., IgG <3 g/L. The study did not report the number of infectious complications (17).

Marco et al reported on 177 patients affected with primary systemic vasculitis, including systemic lupus erythematosus. The patients received a median dose of rituximab of 6 g [range: 1.0–20.2]; 40% developed hypogammaglobulinemia (<6 g/L) at some point, but it was only severe (<3 g/L) in 4% of this cohort. Nonetheless, 40% of the cohort develop severe infections (18). In addition, Besada et al reported on 29 patients with granulomatosis and polyangiitis that received 9 gr (range: 5–13) of rituximab: 40% developed hypogammaglobulinemia (<4 g/L).

Table 4. IgG, IgA, and IgM levels and lymphocyte counts in ABOi kidney-transplant recipients (excluding patients that were ABOi/HLAi)

| Time  | IgG (g/L) | IgA (g/L) | IgM (g/L) | Total lymphocytes (/mm³) | CD3(+) T-cells (/mm³) | CD19(+) B-cells (/mm³) |
|-------|-----------|-----------|-----------|--------------------------|----------------------|------------------------|
| D --30| 10.2 ± 5.5 | 1.9 ± 1.2 | 0.9 ± 0.6 | 1720 ± 680 | 1320 ± 650 | 135 ± 65 |
| D0    | 5.7 ± 3.9  | 1.3 ± 1.4 | 0.35 ± 0.3 | 1240 ± 990 | 1140 ± 970 | 0.4 ± 1.2 |
| D15   | 5.9 ± 2.2  | 1.35 ± 0.75 | 0.45 ± 0.2 | 455 ± 530 | 400 ± 480 | 0.5 ± 1.5 |
| D30   | 7.1 ± 2.5  | 1.35 ± 0.9 | 0.45 ± 0.2 | 1300 ± 1360 | 1100 ± 1190 | ND |
| M3    | 7.6 ± 2.5  | 1.4 ± 1.2 | 0.5 ± 0.3 | 985 ± 820 | 820 ± 730 | 0.6 ± 2 |
| M6    | 8.6 ± 2.2  | 1.6 ± 1.2 | 0.6 ± 0.4 | 1080 ± 740 | 875 ± 710 | 11 ± 18 |
| M12   | 9.1 ± 2.3  | 1.4 ± 0.6 | 0.7 ± 0.4 | 1380 ± 710 | 1090 ± 660 | 39 ± 40 |
| M18   | 8.3 ± 2.1  | 1.4 ± 0.8 | 0.6 ± 0.4 | 1430 ± 690 | 1140 ± 710 | 67 ± 68 |
| M24   | 9 ± 1.9    | 1.6 ± 0.8 | 0.75 ± 0.45 | 1800 ± 1060 | 1430 ± 1060 | 100 ± 80 |

Abbreviations: D, day; M, month; ND, not determined; Ig, immunoglobulin; CD, cluster of differentiation.
hypogammaglobulinemia (<7 g/L); the rate of infectious complications was not reported (20).

Very few studies have reported on hypogammaglobulinemia in the setting of organ transplantation. Florescu et al’s meta-analysis included data on 1756 solid-organ transplant patients that were evaluated for hypogammaglobulinemia and subsequent posttransplant infections. Within the first year posttransplantation, the rate of hypogammaglobulinemia (IgG <7 g/L) was 45% (95% CI: 0.34–0.55), the rate of mild hypogammaglobulinemia (IgG = 4–7 g/L) was 39% (95% CI: 0.22–0.56), and severe hypogammaglobulinemia (IgG <4 g/L) developed in 15% (95% CI: 0.08–0.22). Hypogammaglobulinemia occurred in 40% of kidney-transplant recipients (14). In addition, the odds ratio of a respiratory infection (OR = 4.83; 95% CI: 1.66–14.05; P = 0.004), cytomegalovirus (OR = 2.40; 95% CI: 1.16–4.96; P = 0.02), Aspergillus (OR = 8.19; 95% CI: 2.38–28.21; P = 0.0009) or other fungal infections (OR = 3.69; 95% CI: 1.11–12.33; p = 0.03) for patients with IgG <4 g/L were higher than for patients with IgG >4 g/L. In addition, the odds ratio for 1-year all-cause mortality for those with severe hypogammaglobulinemia was 21.91 times greater than those with IgG >4 g/L (95% CI: 2.49–192.55; P = 0.005). Severe hypogammaglobulinemia during the first year posttransplantation significantly increased the risk of CMV, and fungal and respiratory infections, and was associated with a higher rate of 1-year all-cause mortality (14).

Augusto et al, reported on a single-center retrospective study that included 318 kidney-transplant recipients. Immunoglobulins were measured prospectively on D15, M6, M12, and M24 posttransplant (15). The prevalence of IgG hypogammaglobulinemia was 56% and 36.8% at D15 and M6, respectively. Age was the sole identified risk factors for IgG hypogammaglobulinemia on D15 (OR: 1.02, P = 0.019). Risk factors at M6 for IgG hypogammaglobulinemia were the presence of IgG hypogammaglobulinemia on D15 (OR 6.41, P <0.001) and treatment of acute rejection (OR: 2.63, P = 0.014). Most infections occurred between D15 and M6 posttransplant. However, times of survival-free infection did not differ significantly between patients with or without IgG hypogammaglobulinemia on D15. Only septicemia that occurred between M6 and M12 posttransplant was more frequently observed in patients with hypogammaglobulinemia. The low prevalence of severe hypogammaglobulinemia (<4 g/d) did not allow conclusions on the risk of infections within this subgroup (15).

In our series, severe hypogammaglobulinemia was relatively frequent after ABOi kidney transplantation; however, when replacement therapy was implemented (when IgG levels were <4 g/L), the risk of an infectious complication was no greater than in patients that did not have (severe) hypogammaglobulinemia.

### Table 5. Infectious complications within 1-year posttransplantation according to IgG levels (< or ≥ 4 g/L) at posttransplant

| Type of infections | IVIG<sup>+</sup> (n = 11) | IVIG (n = 32) | P value |
|--------------------|---------------------------|--------------|--------|
| Bacterial infections | 10 | 15 | 0.2 |
| Viral infections | | | |
| CMV DNAemia | 2 | 0 | 0.09 |
| BKV DNAemia | 3 | 10 | 0.72 |
| BKV-AN | 1 | 1 | 0.54 |
| Parasitic/mycotic infections | 2 | 1 | 0.5 |

Abbreviations: IVIG, intravenous polyvalent immunoglobulins; CMV, cytomegalovirus; BKV, BK virus; BKV-AN, BKV-associated nephropathy.

### Table 6. Prevalence of hypogammaglobulinemia after Rituximab therapy for autoimmune disorders

| Authors | No. of patients | Type of patients | Rituximab dose | Definition of hypogamma | Percentage of patients developing hypogamma | Infectious complications |
|---------|-----------------|-----------------|----------------|------------------------|------------------------------------------|-------------------------|
| Cortazar et al (13) | 239 | AAV | Induction phase: 2 g Maintenance phase: 7 g (5-10) | <4 g/L | 4.6% over a 2.4-year period of Rituximab therapy | Baseline IgG level <4 g/L increased by 2.13 (1.04-4.36) the risk of infection. |
| Roberts et al (17) | 243 | GPA, MPA, SLE | Median: 6 g (1-23) | <7 g/L | 35% (but only in 4% it was <3 g/L) | Not reported |
| Marco et al (18) | 177 | Primary systemic vasculitis/SLE | Median: 6 g (1-20.2) | <6 g/L | 40% (but only in 4% it was <3 g/L) | 40% of patients developed severe infections |
| Makatsori et al (19) | 114 | NHL, autoimmune disorders | NA | <5.8 g/L | 23% | Not reported |
| Besada et al (20) | 29 | GPA | 9 g (5-13) | <7g/L | 40% | Not reported |

Abbreviations: Hypogamma, hypogammaglobulinemia; AAV, ANCA-associated vasculitis; SLE, systemic lupus erythematosus; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin’s lymphoma; NA, not available.
Recently Barmettler and Price addressed the time period during which IVIg should be substituted for hypogammaglobulinemia noted after rituximab therapy (21). They found two subsets of patients, one of which recovers and one with persistent hypogammaglobulinemia with long-lasting low or absent memory B cells. They suggest that the treatment length in patients could be assessed by the trend of B-cell subsets by flow cytometry in addition to immunoglobulin levels.

6. Conclusions
In conclusion, our study is the first one to address hypogammaglobulinemia following ABO incompatible kidney transplantation. It was found to be frequent; however, when severe hypogammaglobulinemia was substituted with IVIg there was not more infectious complications as compared to that observed in patients with mild/moderate hypogammaglobulinemia that was not substituted. We recommend to monitor immunoglobulin levels following ABO incompatible kidney transplantation when rituximab therapy had been used for desensitization.

Study limitations
This is a single-center study with a limited number of patients. Some of them where only ABO incompatible, whereas others were in addition HLA incompatible. Therefore, the total dose of pretransplant rituximab was twice as much in the ABO incompatible/HLA incompatible group as compared to the ABO incompatible group.

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Conflicts of interest
The authors declared no competing interests.

Authors’ contribution
NBH and AZ collected the date. PLB assessed immunoglobulin levels; AA performed the pretransplant apheresis sessions. RL designed the study, recruited the patients, and followed-up the patients. All authors read and signed the final paper.

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