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Impact of ABO Compatibility/Incompatibility on the Perioperative Anti-SARS-CoV-2 Immunoglobulin G Levels in 2 Preoperatively Vaccinated Patients Undergoing Kidney Transplant: A Case Report

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ABSTRACT

Herein, we monitored the perioperative anti-SARS-CoV-2 spike immunoglobulin G titers in patients who were preoperatively vaccinated with 2 doses of a COVID-19 messenger RNA vaccine. Additionally, we compared the clinical settings between ABO-incompatible and ABO-compatible pre-emptive kidney transplant (KTx). Case 1 was of a 45-year-old man who was an ABO-incompatible KTx recipient. Before transplant, his serum antibody titers decreased from 278 U/mL at baseline to 41.9 U/mL after desensitization therapy (84.9% lower) and 54.7 U/mL (80.3% lower) at day 8; it is now maintained at 4.1 U/mL at 6 months posttransplant (98.5% lower). Case 2 was of a 50-year-old man who was an ABO-compatible KTx recipient. His serum antibody titer level decreased from 786 U/mL at baseline to 386 U/mL on day 8 (50.8% lower) and is now maintained at 156 U/mL at 6 months posttransplant (80.1% lower). We suggest that anti-SARS-CoV-2 spike immunoglobulin G titers should be monitored during the perioperative period to determine the optimal timing of COVID-19 vaccine booster doses for the maintenance of protective immunity, particularly in ABO-incompatible KTx recipients who require desensitization therapy.

DATA AVAILABILITY

The data that has been used is confidential.

THE immune response to COVID-19 vaccination of patients with chronic kidney disease (CKD) receiving renal replacement therapy was significantly lower than that of the general population, particularly in patients undergoing kidney transplant (KTx) [1−3]. Recent studies have shown immune responses to posttransplant COVID-19 vaccination in unvaccinated KTx recipients [4−7] and not highlighted the importance of preoperative vaccination in patients undergoing KTx. Although it is recommended that vaccination should be prioritized during the pretransplant period, there are no reports regarding the monitoring of anti-SARS-CoV-2 spike antibody titers.

Herein, we report 2 cases of patients who were preoperatively vaccinated with 2 doses of the Comirnaty COVID-19 vaccine (BioNTech-Pfizer BNT162b2) in whom the anti-SARS-CoV-2 S immunoglobulin (Ig) G titers were monitored before undergoing ABO-incompatible (Case 1) and ABO-compatible (Case 2) pre-emptive KTx. Additionally, the clinical settings between the 2 cases were compared.

CASE REPORT

Case 1

The patient was a 45-year-old Japanese man who was diagnosed with end-stage kidney disease (ESKD) due to diabetic

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nephropathy. At 41 years old, he was diagnosed with diabetes mellitus and began treatment with diet modification and medication. At this point, proteinuria was already noted, and his serum creatinine level gradually increased to 1.36 mg/dL. Thereafter, his kidney function gradually declined, ultimately leading to ESKD. At 45 years old, he was referred to our hospital for further evaluation and treatment, including pre-emptive living donor KTx.

The 2-dose COVID-19 messenger RNA (mRNA) vaccination was completed 3 months before transplant, and the preoperative antibody titer against the SARS-CoV-2 spike protein was 278 U/mL (Elecsys Anti-SARS-CoV-2 S RUO, Roche Diagnostics, Basel, Switzerland; positive threshold, ≥0.8 U/mL).

The proposed transplant was ABO-incompatible because the donor had type B blood, while the recipient had type A blood. The ABO titer for anti-B before desensitization therapy was 1:16.

Tacrolimus (TAC), mycophenolate mofetil (MMF) (2000 mg/d), and methylprednisolone (mPSL) were administered 1 week before transplant (Fig 1). Additionally, the anti-CD20 monoclonal antibody rituximab (100 mg) was also administered at 1 week and 3 days before transplant, according to our pre-transplant regimen (Fig 1). TAC was started at a dose of 0.1 mg/kg/d, and the trough level was maintained at 8 to 12 ng/mL for the first few weeks after transplant. After 1 week of oral immunosuppressant therapy, the patient underwent 3 sessions of hemodialysis with 2 sessions of double filtration plasmapheresis and 1 session of plasma exchange using fresh frozen plasma as desensitization therapy before transplant. Induction therapy with intravenous mPSL (500 mg) and basiliximab (20 mg), which was also administered 4 days after transplant, was administered on the day of transplant. The dose of mPSL was gradually tapered to 40 mg and switched to an oral formulation at the end of the first posttransplant week. The patients' anti-B titers remained below the target value.

The serum antibody titers are shown in Fig 1. The antibody titers markedly decreased after the first and second double filtration plasmapheresis sessions, first session of plasma exchange,

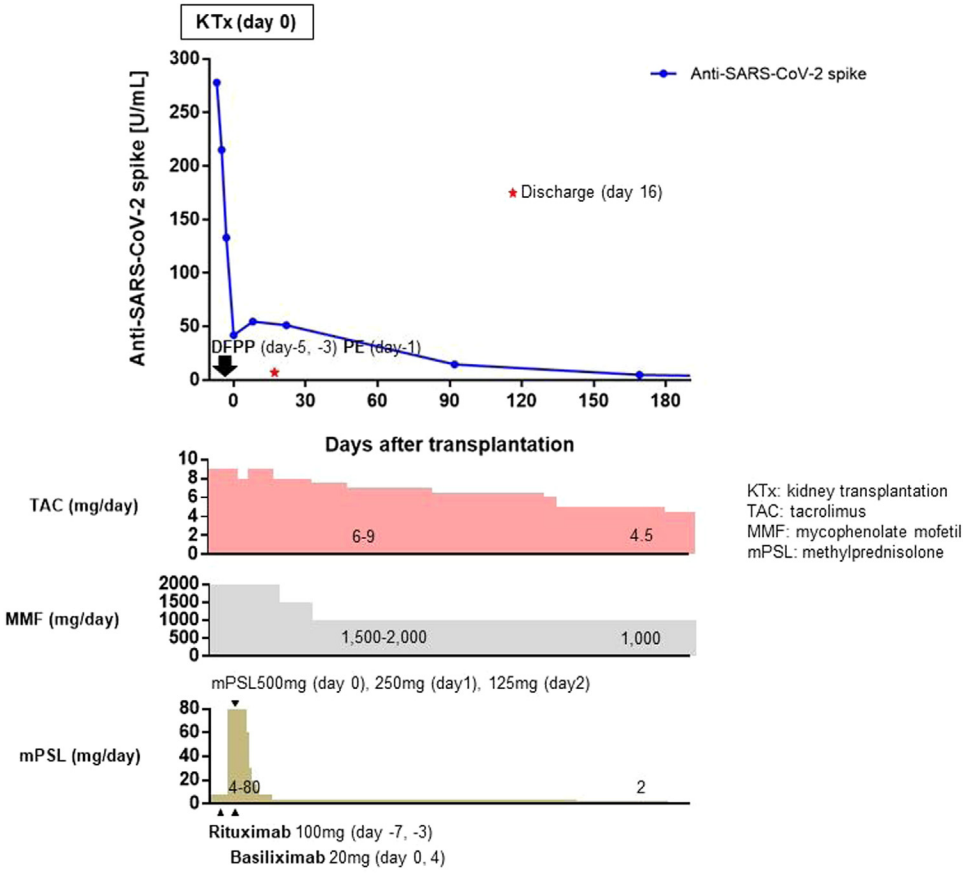

Fig 1. Antibody titers after preoperative desensitization therapy and tapering of triple immunosuppression in posttransplant patients. Anti-SARS-CoV-2 spike antibody titers markedly decreased before transplant after the first and second sessions of double filtration plasmapheresis, first session of plasma exchange, and 2 doses of rituximab. At days −5, −3, and −1, antibody titers were 215 U/mL, 133 U/mL, and 41.9 U/mL, respectively. Six months after transplant, the antibody titers did not decrease below the sensitivity level (<0.8 U/mL) and were maintained at 4.1 U/mL.

KTx, kidney transplant; MMF, mycophenolate mofetil; mPSL, methylprednisolone; TAC, tacrolimus.

and administration of 2 doses of rituximab (215 U/mL, 133 U/mL, and 41.9 U/mL on days −5, −3, and −1, respectively). The antibody titers on days −5, −3, and −1 were 22.6%, 52.1%, and 84.9% lower than the titer before desensitization therapy, respectively. After transplant, the antibody titer gradually declined; however, it did not decrease below the sensitivity level and was maintained at 4.1 U/mL (98.5% lower than preoperative titer) at 6 months postoperatively.

Case 2

A 50-year-old Japanese man was diagnosed with ESKD secondary to IgA nephropathy. At 44 years old, he presented with hematuria and proteinuria and was treated with diet modification and medication; however, his outpatient follow-ups were irregular. At 46 years old, his estimated glomerular filtration rate decreased to 41 mL/min/1.73 m^2 and proteinuria increased to 3.3 g/g creatinine. Kidney biopsy was performed and revealed IgA nephropathy. Although CKD was adequately managed, his kidney function gradually declined, ultimately leading to ESKD. At 50 years old, he was referred to our hospital for further evaluation and treatment, including for pre-emptive living donor KTx.

Two doses of COVID-19 mRNA vaccination were administered 5 months before transplant, and the preoperative serum antibody titer against the SARS-CoV-2 spike protein was 786 U/mL.

The proposed transplant was ABO-compatible because both the donor and recipient had type A blood. Administration of TAC, MMF (2000 mg/d), and mPSL was initiated 1 week before transplant (Fig 2). TAC was started at a dose of 0.1 mg/kg/d, and the trough level was maintained at 8 to 12 ng/mL for the first few weeks after transplant.

Induction with intravenous mPSL (500 mg) and basiliximab (20 mg) was initiated on the day of transplant. Basiliximab was administered for 4 days after transplant, while mPSL was gradually tapered to 40 mg and switched to an oral formulation at the end of the first posttransplant week.

The serum antibody titers are shown in Fig 2. The antibody titer on day 8 was 386 U/mL, which is 50.8% lower from the preoperative titer. After transplant, the antibody titer gradually

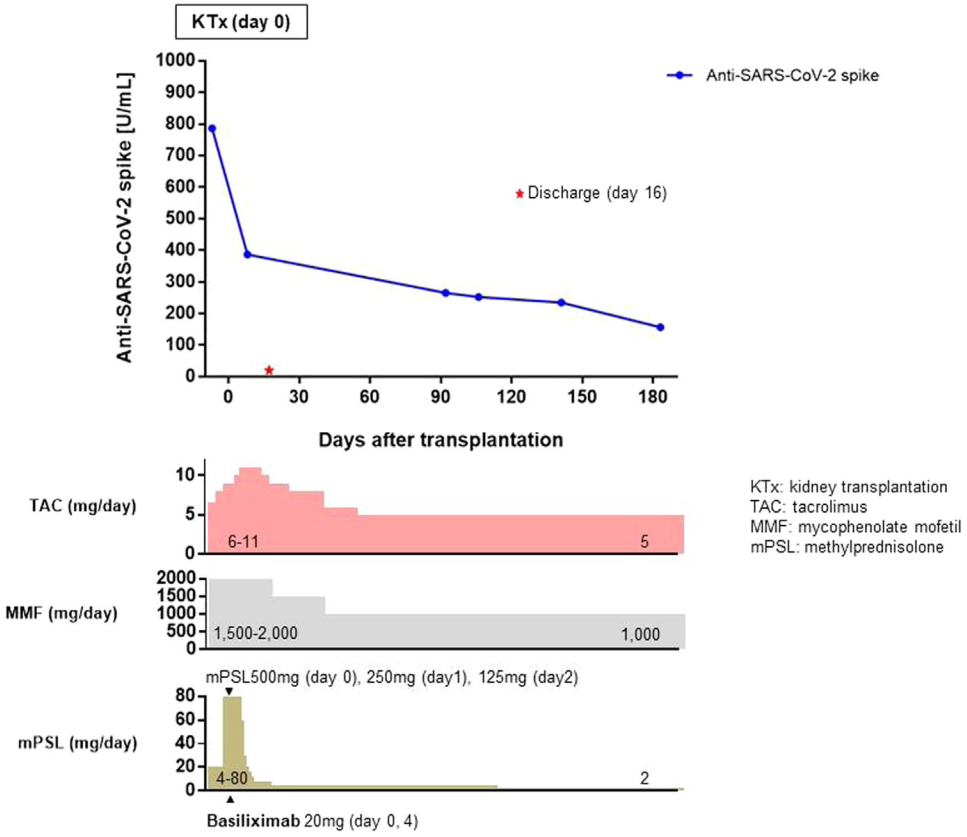

Fig 2. Antibody titers after transplant with tapering of triple immunosuppression. Anti-SARS-CoV-2 spike antibody titers decreased from the preoperative level of 786 U/mL to 386 U/mL on postoperative day 8. Six months after transplant, the antibody titers did not decrease below the sensitivity level (<0.8 U/mL) and were maintained at 156 U/mL.

KTx, kidney transplant; MMF, mycophenolate mofetil; mPSL, methylprednisolone; TAC, tacrolimus.

declined; however, it did not fall below the sensitivity level and was maintained at 156 U/mL (80.1% decrease) at 6 months postoperatively.

DISCUSSION

We describe 2 patients who were vaccinated against COVID-19 before KTx in whom the serum anti-SARS-CoV-2 S IgG titers were monitored. Additionally, we compared the clinical settings between Case 1 (ABO-incompatible) and Case 2 (ABO-compatible) wherein the serum antibody titers decreased by 98.5% and 80.1%, respectively, from pretransplant to 6 months posttransplant.

This case report has 2 important clinical implications. First, ABO-incompatible patients are more likely to have lower postoperative serum antibody titers than ABO-compatible patients because of preoperative desensitization therapy. Second, compared with posttransplant vaccination, COVID-19 vaccination before transplant may allow patients to produce high levels of antibody titers that prevent its decrease to below the sensitivity level (<0.8 U/mL) 6 months after transplant.

Similar to our report, antibody titers in patients who underwent KTx after the second dose of SARS-CoV-2 mRNA vaccine decreased by 54% and 87% on days 28 and 100, respectively, compared with the titer on day 0 [8]. However, this report did not compare ABO-incompatible and ABO-compatible transplant settings.

In ABO-incompatible KTx, desensitization protocols with potent therapeutic apheresis have been used for anti-A/B antibody removal [9,10]. Therapeutic apheresis is not specific for IgG; hence, it reduces the levels of all plasma proteins, with total IgG and IgM and anti-A/B antibody being significantly reduced [10]. Additionally, antibodies against *Pneumococcus* and *Haemophilus* polysaccharide antigens are significantly reduced, whereas those against tetanus and diphtheria protein antigens are not [10]. Our findings confirm that anti-SARS-CoV-2 S IgG titers in ABO-incompatible patients decreased more than that in ABO-compatible patients, which could theoretically be because of the elimination of anti-SARS-CoV-2 S IgG.

Although no optimal threshold has been established for achieving protective immunity, early reports have indicated that higher levels of antibody titers after the second COVID-19 vaccine dose were correlated with a reduced risk of symptomatic infection. A vaccine efficacy of 80% against symptomatic infection with SARS-CoV-2 was achieved with an antispike antibody titer of 264 binding antibody units (BAU)/mL [11]. Note that BAU/mL was converted to U/mL (U/mL = 0.972 × BAU/mL) [12]. In our 2 patients, antibody titers declined throughout the perioperative period, particularly in ABO-incompatible patients, and both antibody titers were below the threshold (256 U/mL) at 6 months postoperatively. Thus, regarding the strategy of booster vaccination for posttransplant patients with low antibody titers, the ABO compatibility/incompatibility should be considered instead of the current conventional vaccination strategy.

We recently reported the evaluation of immune responses to posttransplant COVID-19 vaccination and their possible relationship with other cofactors in KTx recipients; 44.8% of KTx recipients did not develop antibody response (<0.8 U/mL) after receiving the second dose of COVID-19 vaccine. Factors that may significantly affect the inadequacy of response to the COVID-19 vaccine in these patients are older age, shorter duration after KTx, and use of a higher dosage of MMF for maintenance immunosuppression [13].

In our 2 patients, COVID-19 vaccination before transplant may have induced antibody production. Additionally, the antibody titers did not decrease below the sensitivity level (<0.8 U/mL) even at 6 months posttransplant. This result is consistent with that of our another study wherein after the second dose of COVID-19 mRNA vaccine in older patients with late-stage CKD, the antibody titers tended to be lower in patients with CKD stage G5D than in patients with CKD stages G4 and G5 [14]; therefore, CKD progression may cause antibody titers to decline, and administering the COVID-19 vaccine is strongly recommended before the commencement of renal replacement therapy.

CONCLUSIONS

In summary, although our patients had both preoperatively received the second dose of the COVID-19 mRNA vaccine and produced antibodies, continuous and regular monitoring of the SARS-CoV-2 S antibody titers during the perioperative period is important because the titers may decline 6 months posttransplant. We strongly suggest that this strategy be applied for ABO-incompatible transplant recipients, particularly those undergoing desensitization therapy, to determine the optimal timing for COVID-19 booster vaccination to maintain the protective immunity obtained from COVID-19 vaccination.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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