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Marginal Impact of Tocilizumab Monotherapy on Anti-HLA Alloantibodies in Highly Sensitized Kidney Transplant Candidates

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Background. Highly HLA–sensitized kidney transplant candidates are difficult to desensitize, which reduces their chances of receiving a transplant. **Methods.** We administered tocilizumab as a monotherapy (8 mg/kg once a mo) to 14 highly sensitized kidney transplant candidates. Highest mean fluorescence intensities of anti-HLA antibodies obtained before and after tocilizumab administration were compared from raw and diluted sera. **Results.** The administration of tocilizumab significantly reduced dominant anti-HLA antibody sensitization. However, this decrease in mean fluorescence intensities was minor compared with the initial values. **Conclusions.** Tocilizumab as a monotherapy was not sufficient to allow highly sensitized kidney–transplant candidates to undergo transplantation and, therefore, was not an effective desensitization method.

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INTRODUCTION

Kidney transplantation remains the best option for patients with end-stage kidney disease for various reasons; for example, it provides better survival and quality of life compared with those receiving dialysis.[1-4] However, many patients cannot readily undergo kidney transplantation because they are broadly sensitized against HLA antigens as a result of previous blood transfusions, pregnancies, and

a previously failed kidney transplant(s). HLA sensitization then often precludes finding a suitable HLA-compatible kidney transplant. To circumvent this obstacle, for some HLA highly sensitized kidney transplant candidates, pre-transplant desensitization can be attempted.[5]

Desensitization programs rely on plasmapheresis plus high doses of intravenous polyvalent immunoglobulins (IVIg),[6] on rituximab and IVIg,[7] or by using semi-specific immunoadsorption plus rituximab,[8-10] tocilizumab,[11] or imlifidase.[12] However, despite pretransplant desensitization some patients might be kidney transplanted whereas they present donor-specific anti-HLA alloantibodies (DSAs) defining HLA incompatible (HLAi) kidney transplantation.

Among the therapies used to desensitize kidney transplant candidates, tocilizumab (TCZ) has been used only once.[11] Vo et al included 10 kidney transplant candidates unresponsive to desensitization using IVIg + rituximab and so were treated with IVIg+tocilizumab (IVIg on days 0 and 30 at 2 g/kg and tocilizumab 8 mg/kg on day 15 and then monthly for 6 mo). This allowed 5 of them to receive a transplant.

Tocilizumab is a humanized anti-interleukin-6-receptor monoclonal antibody (IgG1 subclass) against the alpha-chain of IL-6R and prevents binding of IL-6 to the membrane and soluble interleukin-6-receptors (IL-6R). Tocilizumab is licensed to treat rheumatoid arthritis and systemic juvenile idiopathic arthritis. The recommended posology is 8 mg/kg intravenous every 4 weeks.[13]

Indeed, in the setting of HLA desensitization, interleukin (IL)-6 is an attractive target. IL-6 is a multifunctional pleiotropic cytokine that stimulates B- and T-cell functions. It is produced by various cells in the innate immune system; for example, macrophages, dendritic cells, mast cells, neutrophils,

B cells, and, to some extent, CD4 effector T-helper cells. IL-6 is also indispensable for Tfh differentiation[14] and is a late-acting B cell–differentiation factor that is involved in the in vitro differentiation of B cells into antibody-forming cells and germinal-center reactions. It also regulates the acute phase response and inflammation.[15] In lupus patients with mild-to-moderate disease, tocilizumab decreases (1) disease activity, (2) levels of antidouble-stranded DNA antibodies, and (3) frequency of circulating plasma cells.[16] In addition, tocilizumab decreases preswitch and postswitch memory B-cell subsets[17] and interferes with plasmablasts thereby inducing a reduction in the number of circulating T-helper cells and IL-21 production.[18] In a rat-antimouse IL-6R (mMR16-1) model, it was found that donor-specific antibody (DSA) responses were attenuated, that is, reduced DSA IgM, IgG2a, and IgG1 responses model.[19]

Based on these data, we conducted a trial to examine whether tocilizumab as a monotherapy could modulate (ie, decrease the expression of anti-HLA alloantibodies) in kidney transplant candidates that had not otherwise undergone attempted desensitization. To the best of our knowledge, this hypothesis has not been explored until now.

MATERIALS AND METHODS

Population: Description

We enrolled 14 active waitlisted kidney transplant candidates for whom some (or all) anti-HLA antibodies have mean fluorescence intensities (MFIs) of ≥10 000. Above an MFI of 10 000, antibodies can fix C3d and are difficult to attenuate by other desensitization therapies, thus justifying the choice of this threshold.[20] HLA sensitization had developed after a previous transplantation ($n = 12$), a blood transfusion ($n = 1$), or after multiple pregnancies ($n = 1$). Median calculated panel-reactive antibody level was 97% (62–100). Median historical rate of incompatible grafts over the last 5 years (historical TGI provided by French Biomedicine Agency) was 94% (48–100). One patient with a past TGI of 48% had a potential living HLA incompatible donor; the other patients that were waiting for a deceased donor had historical TGIs of >92%. The time between previous transplant failure and beginning tocilizumab therapy was 94 (12–204) months; in addition, none of the patients were receiving immunosuppressive therapy for at least 3 years before be included in this study.

There were 9 males; overall mean age was 49 ± 12 years. Their cumulative time on dialysis was 182 ± 87 months, and the median time waiting for a kidney transplant was 94 (12–204) months. Because all patients were on an active waiting-list, their medical conditions were assessed regularly, that is, none had an ongoing condition that would preclude kidney transplantation.

None had undergone previously attempted desensitization. We scheduled at least 6 tocilizumab infusions per patient (8 mg/kg after a hemodialysis session over 30 min) every 4 weeks; on average, the median number of doses was 7 (4–12). Only 1 patient has had <6 tocilizumab injections, that is, 4 because she eventually got a living kidney transplant from her husband. The aim of tocilizumab therapy was to decrease the highest MFI values to <10 000.

All the patients were willing to be desensitized to obtain access to transplantation and gave their written informed consent (CNIL [French National committee for data protection] approval number 1987785v0).

Data Acquisition

Sera from these patients were collected before each tocilizumab injection, and all were monitored in a single histocompatibility laboratory (HLA Laboratory, EFS La Tronche, France). Anti-HLA antibody identification was performed using Luminex technology and a Lifecodes Single Antigen (LSA; Immucor, Norcross, GA) bead automated system with batches of beads containing 96 antigen beads for both HLA classes. Evaluation of LSA results was done by Immucor Lifecodes MatchIt Antibody Software (United States) V4.2. For this study, MFI refers to background corrected MFI or to the "raw value" provided by MatchIt.

Patients were considered to be sensitized to a specific antigen class if at least 1 MFI was ≥2000. The LSA technology MFI limit is around 20 000, that is above this value the results may be subject to a prozone effect that distorts the results. Highly sensitized patients may have antibody MFIs >20 000 but exact MFIs over 20 000 cannot be measured on raw serum due to the prozone effect. In cases where a prozone effect was suspected, the serum was diluted before the very first tocilizumab injection using an adapted dilution factor for each patient from 1:5 to 1:20. If prozone was confirmed, serum retrieved on the last day of tocilizumab administration was studied with the same dilution factor as previously used.

Historical sera collected at least 6 months before starting tocilizumab monotherapy were termed "6 months Before TCZ." Three patients have no historical serum due to center transfer ($n = 2$) or absence of anti-HLA alloantibody follow-up ($n = 1$). Sera collected before the very first tocilizumab administration were termed the "Days Before TCZ" sera. Sera collected on the day of last tocilizumab administration were termed "After TCZ." Sera collected after the last administration of tocilizumab were not used because posttocilizumab treatments varied from patient to patient.

Statistical Analyses

Data treatment and statistical analyses were conducted using RStudio V1.2 and R V3.6.2. MFI values from all beads of each class were used to calculate different variables. Mean, median, and highest MFIs were calculated for sensitized patients and for each class. The number of beads where MFI ≥10 000 was also recorded.

The previously described calculated variables per serum were then compared between the "Before TCZ" and "After TCZ" raw sera data. The mean of the deltas and the standard deviations (SD) were calculated, and the P value from a paired Wilcoxon test was determined. The results of the variable "Bead number with MFI ≥10 000" were then detailed on a boxplot figure. This was repeated for the "Highest MFI" variable; however, the raw sera from patients without a prozone effect were separated from the data for diluted sera from patients with a prozone effect. Differences between before and after tocilizumab administration were statistically evaluated using a paired Wilcoxon test. P values of <0.05 were considered statistically significant. Finally, a linear-mixed effects models (LME) was performed on the MFIs of all antibodies of the raw sera "After TCZ." Patients were taken as random effects and "Before TCZ" MFIs values, HLA class, and

number of tocilizumab injections administered as fixed effects without interaction.

RESULTS

Tolerability of tocilizumab therapy was very good. Only one patient presented during therapy with an infectious complication, that is, *Staphylococcus aureus*-related spondylodiscitis that might have been facilitated by tocilizumab therapy. As a result, tocilizumab therapy was stopped for that patient.

At the time of the first tocilizumab injection, all patients were sensitized against class I antigens (at least 1 MFI ≥2000); among them, 12 had at least 1 MFI of ≥10 000. Regarding anticlass II antigens, 11 were sensitized and among these, 8 patients had at least 1 MFI ≥10 000.

Effects of Tocilizumab on Overall HLA Sensitization

Means of delta values between "After TCZ" and "Before TCZ" were negative for all tested variables (Table 1), indicating a global decrease of all these parameters during tocilizumab monotherapy. However, the differences between before and last tocilizumab are not all statistically significant. The paired Wilcoxon tests showed significant *P* values for the median MFI, the mean MFI, and the number of beads with a MFI ≥10 000 in both classes (Table 1). This suggests an impact of tocilizumab on overall anti-HLA sensitization and on the number of beads with MFIs ≥10 000.

However, regarding the highest MFI, results between anticlass I and anticlass II alloantibodies were very different with a significant *P* value for anticlass I but not for anticlass II alloantibodies (Table 1). This suggests a questionable impact of tocilizumab on the highest MFI of raw sera. But since these patients were highly immune, taking into account the prozone effect via the study of diluted sera, this shows different and more accurate results.

Effects of Tocilizumab on HLA Alloantibodies With MFI ≥10 000

Tocilizumab was used to reduce alloantibody MFIs to <10 000. This criterion can be studied using the number of beads with a MFI value ≥10 000 on raw serum. This value is not significantly different between sera from the day before the start of tocilizumab monotherapy and historical sera >6 months before tocilizumab therapy (paired Wilcoxon *P* value, class I: *P* = 0.4, class II: *P* = 0.11). Overall, we can observe an

increase in this value over time (Figure 1A and B). However, this value was significantly lower after tocilizumab injections than before (paired Wilcoxon *P* value, class I: *P* = 0.006, class II: *P* = 0.021) (Table 1; Figure 1C and D). No patient had the number of beads with an MFI ≥10 000 increased during tocilizumab therapy (ie, deltas from −14 to 0). After tocilizumab, the mean bead number with MFI ≥10 000 was 18 for class I and 14 for class II, as compared with 22 and 17 before tocilizumab.

The objective to reduce all MFIs to under the threshold of 10 000 (ie, bead number with high MFI ≥10 000 = 0) was reached by only 2 patients with anticlass I alloantibodies (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 010 and patient 011) and another patient with anticlass II alloantibodies (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 004). These patients initially had a low number of targeted antigens with an MFI ≥10 000 (ie, from 1 to 3) (Figure 1). For the other patients, tocilizumab reduced the number of beads with MFIs of ≥10 000 but did not reduce this number to zero; therefore, these patients were still considered too highly sensitized.

Effects of Tocilizumab on HLA Alloantibodies With the Highest MFIs Antibody

Without taking into account the prozone effect, that is on raw sera, the highest MFI significantly differed between "before TCZ" and "after TCZ" for anticlass I antibodies but not for anticlass II (paired Wilcoxon *P* value class I: *P* = 0.017; class II: *P* = 0.52) (Table 1). However, 9 patients with anticlass I and 8 patients with anticlass II alloantibodies had a prozone effect, which induced a biased highest MFI on raw serum and hid the potential tocilizumab effect. Therefore, comparison of sera between "before tocilizumab" and "after tocilizumab" when diluted by the same dilution factor was more informative for patients with a prozone effect.

For the 5 patients without a prozone effect for anticlass I and for the 3 without prozone effect for anticlass II alloantibodies, there was no significant decrease in the highest MFIs observed (Figure 2A and B) (paired Wilcoxon *P* value class I: *P* = 0.12; class II: *P* = 0.50). For anticlass I, the mean highest MFI on raw serum was 11 654 ± 3922 for "before TCZ" and 9252 ± 4055 for "after TCZ," thus a delta of −2402. For anticlass II, the mean highest MFI for "before TCZ" was 7321 ± 1407 and 5355 ± 2773 for "after TCZ," thus a delta of −1965. Except for one patient of 5 for anticlass I (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 012) and 1 patient of 3 for anticlass II antibodies (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 010), the highest MFI decreased during tocilizumab monotherapy for all patients without a prozone effect.

For patients with a prozone effect studied with diluted serum, there was a significant decrease in highest MFI between "before TCZ" and "after TCZ" for both classes (Figure 2C and D) (paired Wilcoxon *P* value class I: *P* = 0.0039; class II: *P* = 0.039). For anticlass I alloantibodies, mean highest MFI was 10 500 ± 3886 for "before TCZ" and 7686 ± 3864 for "after TCZ", thus a delta of −2814. For anticlass II alloantibodies, mean highest MFI went from 11 798 ± 6313 for "before TCZ" to 8611 ± 4728 at "after TCZ": thus a delta of −3186. These values were obtained on diluted sera with a dilution factor from 1:5 to 1:20 according to the patient, but the same dilution factor was applied for each individual

TABLE 1.

Effects of tocilizumab therapy on mean delta MFIs of different variables for anticlass I and anticlass II alloantibodies identified on raw sera days before tocilizumab vs raw sera after tocilizumab therapy

Variables	Anticlass I antibodies			Anticlass II antibodies		
	N	Mean delta ± SD	P	n	Mean delta ± SD	P
Median MFI	14	−928.2 ± 1657.1	0.02	11	−254.7 ± 264.5	0.01
Mean MFI	14	−883 ± 1088.4	0.007	11	−423.3 ± 545.3	0.03
Highest MFI	14	−1868.9 ± 2234.3	0.017	11	−1220.3 ± 3944.7	0.52
Bead number with MFI ≥10 000	12	−4.6 ± 4.6	0.006	8	−3.1 ± 3.6	0.02

For different variables, mean delta, SD, and paired Wilcoxon *P* value between raw serum "Before TCZ" and raw serum "After TCZ."
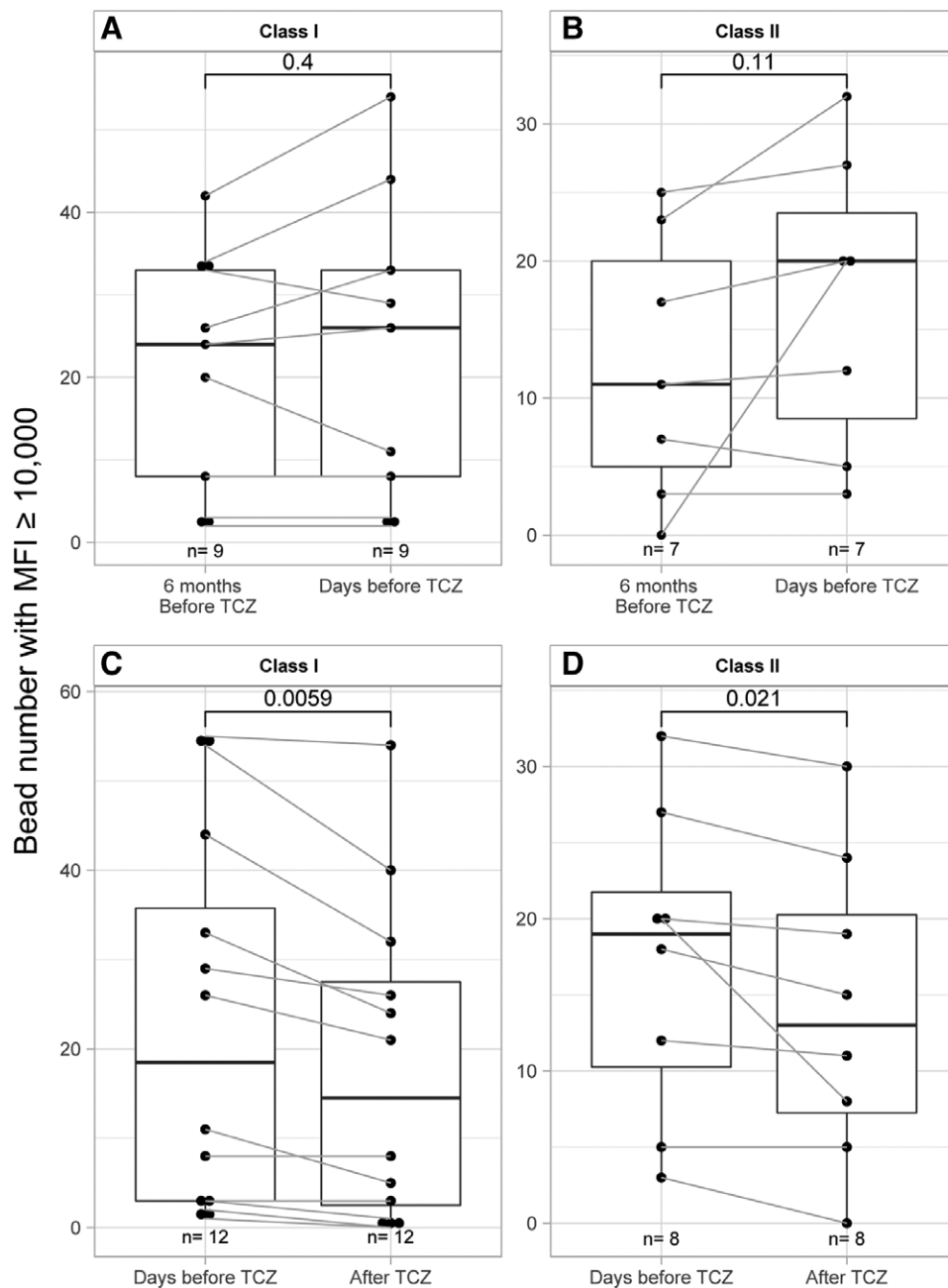MFI, mean fluorescence intensities; TCZ, tocilizumab.

FIGURE 1. Numbers of antigen beads with MFI ≥10000 in tocilizumab-treated patients for sera >6 mo before tocilizumab therapy and at tocilizumab therapy initiation for HLA class I (A) and HLA class II (B) then at tocilizumab initiation and after tocilizumab therapy for HLA class I (C) and HLA class II (D). *P* values from a paired Wilcoxon test. MFI, mean fluorescence intensities; TCZ, tocilizumab.

patient (class I, 1:5 $n=1$, 1:10 $n=7$, and 1:20 $n=1$; class II, 1:5 $n=1$, 1:10 $n=6$, 1:20 $n=1$). These adapted dilution factors reduced the MFIs to <20000 but also amplified this decrease and these deltas. All patients with a prozone effect saw their diluted highest MFI decreasing more or less intensely during tocilizumab monotherapy, except 1 patient where anticlass II antibodies had a highest MFI, increasing from 2699 to 4082 with a dilution factor of 1:10 (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 003).

Linear-mixed Model of Individual Posttocilizumab MFIs

Our observations suggest a variable impact of tocilizumab. LME shows a very significant fixed effect of "before TCZ" antigen MFI (LME-fixed effect *P* value $<2\times10^{-16}$, estimate=0.8679), of HLA class (LME-fixed effect $P=4.18\times10^{-6}$, estimate=263.2) on "after TCZ" antigen MFI value. However, the fixed effect of number of tocilizumab administrations was not significant (LME-fixed effect $P=0.528$). These results suggest that posttocilizumab MFI values were highly influenced by the pretocilizumab MFI values but not by the number of tocilizumab administrations. An individual random effect had an important variability (LME random effect SD=539.3) but lesser so than the unaddressed factors (LME random effect SD=1392.0).

Outcome of Tocilizumab as a Monotherapy

Following tocilizumab given as a monotherapy, among these 14 patients, 1 patient could receive a transplant from
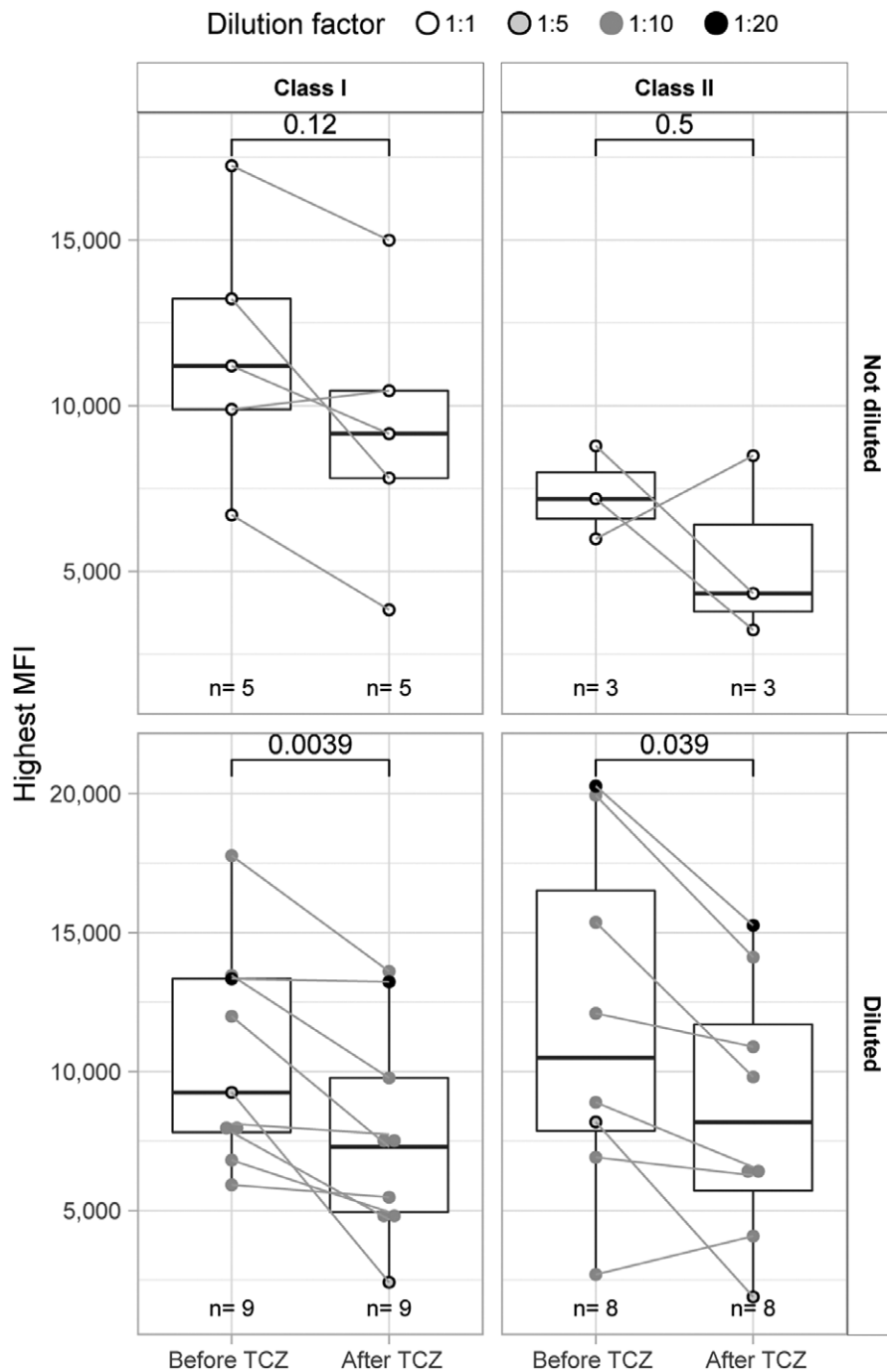
FIGURE 2. Highest MFI value of 14 tocilizumab-treated patients without a prozone effect for anti-HLA class I (A) alloantibodies and anti-HLA class II alloantibodies (B) and with a prozone effect for anti-HLA class I (C) alloantibodies and anti-HLA class II alloantibodies (D). *P* values from a paired Wilcoxon test. MFI, mean fluorescence intensities; TCZ, tocilizumab.

a compatible deceased donor (Figure S1, SDC, http://links.lww.com/TXD/A321; patient 009). For the other patients, 2 stopped desensitization therapy after tocilizumab and are still awaiting a transplant; the other 11 have started another desensitization technique, allowing 8 to now receive a transplant.

DISCUSSION

In the present study, we demonstrate that tocilizumab as a monotherapy significantly reduced the number and intensity of dominant anti-HLA antibodies in highly HLA–sensitized

kidney transplant candidates that had not attempted previous desensitization. But this effect was marginal compared with initial sensitization. The decrease in MFIs did not allow all MFIs to decrease uniformly below the thresholds set (ie, MFI = 10000). Only one of our patients could benefited from an HLA-compatible transplant after tocilizumab monotherapy.

Wu et al reported on a rat-antimouse IL-6R (mMR16-1) study that focused on attenuating DSA responses.[19] They found that mMR16-1 significantly reduced DSA IgM, IgG2a, and IgG1 responses, whereas normalizing serum amyloid A,

an IL-6-induced acute phase reactant. In addition, mMR16-1 injections increased mononuclear-cell apoptosis in the spleen. Based on these experimental data, it can be hypothesized that targeting the IL-6/IL-6R pathway may serve as a strategy to suppress DSA generation.

Indeed, some years ago, Vo et al reported the results from a phase I/II trial in which 10 highly sensitized kidney transplant candidates failed to be desensitized with rituximab plus IVIg and where the combination of tocilizumab plus IVIg resulted in a decrease in anti-HLA alloantibodies and ultimately allowed 5 of the patients to undergo transplantation.[11]

Recently, the same group reported on the use of tocilizumab (8 mg/kg, monthly, 6 injections) given to 11 kidney transplant recipients presenting with chronic antibody–mediated rejection: they examined the impact of tocilizumab treatment on total IgG, IgG1-4 subclasses, and anti-HLA-IgG.[21] They found that total IgG and IgG1-3 were significantly reduced after tocilizumab therapy, whereas no reduction was seen posttreatment in the control group. In addition, of 11 patients, 8 showed reduced anti-HLA-total IgG and IgG3 at posttocilizumab, but this was not statistically significant.

Lavacca et al reported on 15 kidney transplant recipients presenting with chronic active antibody–mediated rejection where the first-line therapy was tocilizumab.[22] This was associated with histologic improvement and functional stabilization; moreover, gene-expression showed upregulation of 3 genes (*TJP-1*, *AKR1C3*, and *CASK*) involved in podocyte, mesangial, and tubular restoration. In addition, they observed that mean MFI values significantly declined after tocilizumab treatment, that is from 22 600 (21 700–23 700) pre-TCZ to 18 200 (12 650–22 150 post-TCZ; $P = 0.002$), with complete negativation in 1 patient.

When tocilizumab was given to either kidney transplant candidates or kidney transplant recipients, it was always associated with immunosuppressive drugs or immunomodulating agents such as IVIg. Conversely, our patients did not receive any immune modulating/suppressive drug concomitantly: this might explain why tocilizumab had a weak effect on anti-HLA sensitization in our patients.

T-cell response is important for antibody synthesis including HLA alloantibodies. In studies with IL-21 and IL-6 knockout mice, it has been found that these cytokines are indispensable for Tfh differentiation. IL-21 cell intrinsically acts on the naive T cells to differentiate into Tfh through Vav1, whereas IL-6 acts both intrinsically and extrinsically to enhance IL-21 production through c-Maf.[14] Indeed, it has been shown that tocilizumab modulates the T-cell responses. Thus, in a mouse model of fungal keratitis, it has been shown that tocilizumab suppressed disease progression by reducing macrophage infiltration in the cornea and Th1, Th17, and Treg cell infiltration in draining lymph nodes.[23] In humans, Kikuchi et al demonstrated, in 39 rheumatoid arthritis patients that had received tocilizumab therapy over 52 weeks, that there was a significant increase in CD4(+)CD25(+)CD127(low) regulatory T cells (Treg) and HLA-DR(+) activated Treg cells, whereas proportions of CD3(+)CD4(+)CXCR3(−)CCR6(+)CD161(+) T-helper 17 cells did not change. Moreover, the proportion of Treg cells among CD4(+) cells correlated well with clinical response. In addition, the proportions of CD20(+)CD27(+) memory B cells, HLA-DR(+)CD14(+) and CD69(+)CD14(+) activated monocytes, and CD16(+)CD14(+) monocytes was significantly decreased.[24]

Our study has some limitations, such as the small number of patients, the absence of a control group and the variation in the number of tocilizumab administrations. However, based on our observation, we think that tocilizumab monotherapy was not efficient at reducing the magnitude of HLA sensitization in kidney transplant candidates. It is possible that the addition of immunosuppressants, for example tacrolimus plus mycophenolic acid or rituximab plus IVIg may be a more effective regimen to reduce anti-HLA alloantibodies.

We conclude that tocilizumab monotherapy in naïve highly sensitized kidney transplant candidates had an insufficient effect on anti-HLA sensitization, particularly on its broadness and amplitude in terms of MFIs.

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