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CLINICAL RESEARCH

Imlifidase in Highly Sensitized Kidney Transplant Recipients With a Positive Crossmatch Against a Deceased Donor

Nassim Kamar[1], Dominique Bertrand[2], Sophie Caillard[3], Danièle Pievani[4], Marie Joelle Apithy[5], Nicolas Congy-Jolivet[6,7], Bertrand Chauveau[8], Fabienne Farce[9], Arnaud François[10], Audrey Delas[11], Jérôme Olagne[12], Cédric Usureau[13], Jean-Luc Taupin[13], Gwenda Line Guidicelli[14] and Lionel Couzi[15]

[1]Department of Nephrology and Organ Transplantation, Toulouse University Hospital, INSERM UMR 1291, Toulouse Institute for Infectious and Inflammatory Diseases (Infinity), Université Paul Sabatier, Toulouse, France; [2]Department of Nephrology, Dialysis and Kidney Transplantation, CHU Rouen, Rouen, France; [3]Department of Nephrology, Dialysis and Transplantation, Strasbourg University Hospital, Strasbourg, France; [4]Department of Nephrology and Renal Transplantation, Saint-Louis Hospital, AP-HP, Université Paris Cité, France CHU Paris-GH Saint-Louis, Paris, France; [5]Laboratoire HLA, Grand Est Blood Center, Strasbourg, France; [6]Laboratoire HLA, Toulouse University Hospital, Toulouse, France; [7]INSERM UMR 1037, DynAct team, CRCT, Université Paul Sabatier, Toulouse, France; [8]Bordeaux University Hospital, Service de Pathologie, UMR-CNRS5164 Immunoconcept, University of Bordeaux, Bordeaux, France; [9]Laboratory of Immunology and Immunogenetics, Etablissement Français du sang, Rouen, France; [10]Department of Pathology, University of Rouen, Rouen, France; [11]Department of Pathology, Toulouse University Hospital, Toulouse, France; [12]Department of Pathology, Strasbourg University Hospital, Strasbourg, France; [13]Laboratory of Immunology and Immunogenetics, Hôpital Saint-Louis, Paris; [14]Laboratory of Immunology and Immunogenetics, CHU de Bordeaux, Bordeaux, France; and [15]Bordeaux University Hospital, Department of Nephrology, Transplantation, Dialysis and Apheresis, UMR-CNRS5164 Immunoconcept, University of Bordeaux, Bordeaux, France

Introduction: Imlifidase is authorized for desensitization of highly sensitized adult kidney transplant candidates with a positive crossmatch (XM) against a deceased donor. Here, we report on the results for the first 9 patients transplanted in this context who had at least 3 months of follow-up.

Methods: The eligibility criteria were as follows: calculated panel reactive antibodies (cPRA) ^{3} 98%, ^{3} 3 years on the waiting list, immunodominant donor-specific antibodies (DSAs) with mean fluorescence intensity (MFI) $>$ 6000 (and $<$ 5000 at 1:10 dilution) and a negative post-imlifidase complement-dependent cytotoxic XM (CDCXM).

Results: All 9 patients had been on dialysis for an average of 123 $\pm$ 41 months, with cPRA at 99% ($n = 2$) or 100% ($n = 7$). At transplantation, the mean number of DSAs was 4.3 $\pm$ 1.4. The median immunodominant DSA MFI was 9153 (6430–16,980). Flow cytometry XM (FCXM) and CDCXM before imlifidase were positive in 9 and 2 patients, respectively. After 1 injection of imlifidase, all were negative. Patients received polyclonal antibodies, i.v. Igs (IVIg), rituximab, tacrolimus, and mycophenolate. Five patients had a DSA rebound within the first 14 days: 2 had concomitant clinical antibody-mediated rejection (ABMR), 2 had subclinical ABMR, and 1 had isolated positive C4d staining. No ABMR was observed in patients without rebound. Chronic Kidney Disease-Epidemiology Collaboration formula estimated glomerular filtration rate (eGFR) was 56 $\pm$ 22 ml/min per 1.73 m^2 at the last follow-up (7 $\pm$ 2.8 months). No graft loss or death were observed. Four patients developed at least 1 infection.

Conclusion: These real-life data demonstrate that the use of imlifidase to desensitize highly sensitized patients can have an acceptable short-term efficacy and safety profile in selected patients.

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Correspondence: Nassim Kamar, Department of Nephrology and Organ Transplantation CHU Toulouse Rangueil, TSA 50032, 31059 Toulouse, Cedex 9 France. E-mail: kamar.n@chu-toulouse.fr; or Lionel Couzi, Department of Nephrology, Transplantation, Dialysis and Apheresis, CHU Bordeaux, Bordeaux, 33000 Bordeaux, France. E-mail: lionel.couzi@chu-bordeaux.fr

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Highly sensitized candidates for kidney transplantation, especially those with cPRA above 98% have very poor access to a compatible donor.[1,2] For these patients, it is essential to consider a living-donor transplantation either directly with a human leukocyte antigen (HLA)-compatible donor or by indirect transplantation through a kidney exchange program, or a

direct HLA-incompatible transplantation. However, living-donor transplantation options are often limited in this context, leading to a reliance on deceased donors.[1] When a compatible deceased donor cannot be found despite national priority programs, transplant teams are encouraged to selectively delist initially unacceptable HLAs. Antigens against which the anti-HLA antibodies had disappeared or are at low MFI levels can actually be delisted[3] for kidney transplantation categorized as EuropeaN Guidelines for th mAnagement of Graft rEcipients (ENGAGE) category 3,[3,4] positive for donor-specific IgG antibodies but with a negative XM. However, these strategies are often not applicable in highly sensitized candidates with persistent high-level HLA antibodies. In these patients, various pretransplant desensitization approaches have been attempted that initially relied on IVIg and rituximab,[5,6] and more recently, bortezomib and apheresis,[7] with controversial efficacy. Finally, several groups have developed sequential or single pretransplant apheresis-based desensitization programs;[8,9] however, challenges, such as high rates of ABMR, persist.

Very recently, imlifidase, a recombinant cysteine protease capable of cleaving all human IgGs in 4 to 6 hours, has been used to deactivate DSAs as part of a desensitization approach for highly sensitized candidates undergoing kidney transplantation.[10] Phase 1 and 2 trials were conducted and showed promising results with the use of imlifidase as a desensitization agent through which a positive XM is changed to negative.[10-13] Overall, 46 patients were desensitized with imlifidase.[14] Based on these data, imlifidase is now indicated in desensitization treatment for kidney transplantation candidates with preformed anti-HLA DSAs and a positive XM against a deceased donor (i.e., ENGAGE category 1 and 2). After approval of imlifidase in France, French guidelines were established to harmonize its use.[2] Here, we report on the use of imlifidase for the first 9 kidney transplantations with a positive XM against a deceased donor.

METHODS

In France, imlifidase has been approved in an early access authorization program since November 2022. On December 1, 2023, 60 patients were included in this program. We report on the outcome of this multicenter retrospective cohort study of the first 9 transplanted patients (4 in Toulouse, 2 in Bordeaux, 1 in Rouen, 1 in Strasbourg, and 1 in Saint Louis Hospital in Paris) who had a follow-up of at least 3 months, that is, 7 ± 2.8 months. In accordance with the French consensus guidelines,[2] all patients were adults and met the following criteria: (i) aged £ 65 years, (ii) cPRA ³ 98% on the last serum test, (iii) time on the waiting list ³ 3 years, (iv) number of previous kidney transplantations ranging from 0 to 2, and (v) an immunodominant DSA against HLA -A, B, DR, and DQ molecules with an MFI > 6000 and < 5000 at 1:10 dilution on the most recent serum. HLA antibodies with an MFI below 5000 at a 1:10 dilution were delisted when patients were included in the imlifidase program.[2]

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Istanbul. All the data concerning the medical history of these patients were recovered from the digital databases of the different participating Hospitals. All patients gave their written informed consent for the use of their data for medical research. This study was approved by the institutional review board of Bordeaux University Hospital (CER-BDX 2023–116).

Immunosuppressive Treatment

Imlifidase was given in a single dose (0.25 mg/kg, i.v. in 15 minutes) prior to transplantation after premedication with glucocorticoids and antihistamines. In accordance with the French guidelines,[2] patients received decreasing doses of steroids starting on the day of transplantation: 500 mg on day 0, 250 mg from day 1 to day 3, 125 mg on day 4, 20 mg on day 5, then a decrease (according to transplant center practice) to 5 mg/d in 3 months, without corticosteroid discontinuation. It was recommended to give rabbit antithymocyte globulins starting on day 4 at a dose of 1.5 mg/kg/d for a total of 5 days (7.5 mg/kg cumulative dose). When horse antithymocyte globulins were chosen ($n = 1$), the infusion was started on day 1. High-dose IVIg infusions (2 g/kg) were administered on days 4 and 5. Rituximab was given either on day 7 post transplantation (375 mg/m^2 per dose) ($n = 7$), or at least 2 weeks before transplantation ($n = 2$). Standard maintenance therapy was based on tacrolimus (target trough level between 8 and 10 ng/mL) and mycophenolic acid.

In addition to standard cytomegalovirus (CMV) and pneumocystis prophylaxis, a 1-month course of bacterial prophylaxis with penicillin was given. CMV or BK virus infections were managed according to the most recently published recommendations.[15,16]

Immunological Analyses

XMs

The National Institute of Health CDCXM assay was performed on T and B lymphocytes from the lymph node or spleen. The positivity threshold score was above 2 for CDCXM with the National Institute of Health scoring system (scores 1, 2, 4, 6, and 8 defined by 0%–10%, 10%–20%, 20%–50%, 50%–80%, and >80% dead cells). When rituximab was administered

before transplantation, pronase was used during the XM process to avoid false positive results. FCXM was also performed on T and B lymphocytes to identify IgG antibodies. The threshold of positivity for flow cytometry was set at an MFI ratio of 1.5 for T cells and 2 for B cells. The XM negative control was a serum pool from nonallo-sensitized donors in the AB group. Both XMs were performed before and 4 to 6 hours after imlifidase infusion.

Luminex SAFB Technique

Sera of interest were tested in clinical practice for class I and class II antibodies using SAFB assays (luminex platform) that encompassed the A, B, Cw, DR, DQ, and DP antigens (LabScreen single antigen LS1A04 and LS2A01, One Lambda). The positivity threshold for bead MFI was set at 500 after removal of the background according to the "baseline" formula. DSA data were collected retrospectively at the following timepoints: last serum (<3 months) before transplantation, before imlifidase injection (H0), and 4 to 6 hours (H4–H6) postinfusion, as well as on days 3, 7, and 14 in month 1-, and 3-times posttransplantation. There was no missing data. Patients were not tested for non-HLA antibodies such as antiangiotensin type II receptor-1 and antiendothelial antibodies.

Pathological Analyses

In addition to clinically indicated kidney allograft biopsies, routine surveillance biopsies were done between days 7 and 10 as well as 3 months post transplantation. ABMR and T cell-mediated rejection were determined as defined in the 2019 Banff classification.[17]

Statistical Analyses

Mean values were presented with SD, and median value with minimum and maximum values. The GraphPad Prism v10 software was used for figure construction and statistical analyses.

RESULTS

Patients' characteristics are presented in Table 1. According to the guidelines cited above, cPRA for the last serum before transplantation was either 99% ($n = 2$) or 100% ($n = 7$). After delisting based on the results of a dilution to a 1:10 SAFB assay, cPRA dropped to 58% ± 23%. The times on dialysis before transplantation and the time between anti-HLA antibody delisting and transplantation were 123 ± 41 months and 82 ± 53 days, respectively. The mean dose of imlifidase administered was 14.8 ± 1.8 mg. All patients received rituximab, polyclonal antibodies, tacrolimus, mycophenolic acid, and corticosteroids. Eight patients also received IVIg.

Table 1. Patients' characteristics

Variables	*N* = 9
Age (yr, mean ± SD)	47 ± 14
Gender (M/F)	3/6
Body mass index (kg/m^2, mean ± SD)	22 ± 3
Nephropathy	
Genetic	1
Glomerular	3
Tubulointerstitial	3
Indeterminate	2
Dialysis (yes)	9
Time on dialysis (mo, mean ± SD)	123 ± 41
Previous transplantations (0/1/2)	1/7/1
Previous pregnanc(y/ies) (yes)	5
Previous blood transfusion(s) (yes)	9
cPRA on the last serum (99%/100%)	2/7
cPRA after delisting (%, mean ± SD)	58 ± 23
Time between delisting and transplantation (days, mean ± SD)	82 ± 53
Donor Age (yr, mean ± SD)	45 ± 16
Donor gender (M/F)	6/3
Donor serum creatinine (μmol/l, mean ± SD)	74 ± 17
Donor type (Standard/ECD)	7/2
Donor after brain death	9
Use of perfusion machine (*n*)	2
Cardiac arrest	2
Total ischemia time (h, mean ± SD)	13.2 ± 4.3
Cold ischemia time (h, mean ± SD)	14.5 ± 4.3
Delayed graft function	1
Immunosuppression	
Imlifidase dose (mg, mean ± SD)	14.8 ± 1.8
Rituximab	
At delisting	2
At day 7 posttransplantation	7
Polyclonal antibodies	
Rabbit antithymocyte globulins	8
Horse antithymocyte globulins	1
i.v. Ig	8
Tacrolimus/mycophenolic acid/steroids	9

cPRA, calculated panel reactive antibodies; ECD, expanded criteria donor; F, female; M, male.
The last serum sample was obtained less than 3 months before transplantation.

Immunological Parameters at Transplantation

At transplantation, 39 preformed DSAs were identified in the 9 patients based on the analysis of the last serum: 8 were repeated mismatches against previous transplants and 28 were unrepeated mismatches. We were not able to provide this information for the 3 remaining DSAs due to incomplete HLA typing of previous transplants. The median MFIs of these 39 DSAs before and after 1:10 dilution was 4858 (500–16,980) and 897 (0–4627), respectively (Supplementary Table 1).

The mean number of DSAs was 4.3 ± 1.4 (2.6 ± 0.9 for anticlass I DSAs and 1.8 ± 1.6 for anticlass II DSAs). The median immunodominant DSA MFI against HLA -A, B, DR, and DQ (6 class I and 3 class II) was 7300 (6064–16,980). The median immunodominant DSA MFI against HLA -A, B, Cw, DR, DQ and DP (4 class I and 5 class II) was 9153 (6430–16,980) (Figure 1). The predose median sum of DSA MFI was 20,057 (7827–77,779):

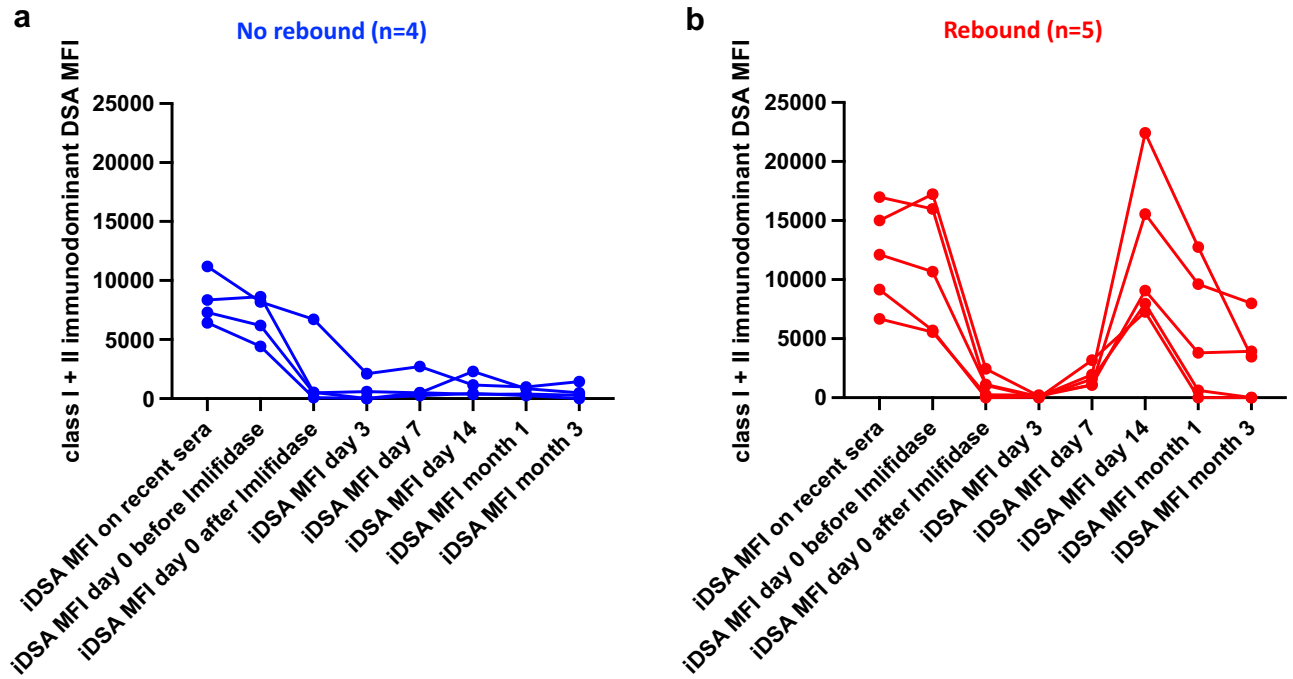

Figure 1. Outcome of immunodominant donor-specific antibodies (DSAs) after transplantation. (a) In blue, class I and class II immunodominant DSAs without posttransplant rebound. (b) In red, class I and class II immunodominant DSAs with posttransplant rebound. iDSA, immunodominant DSA; MFI, mean florescent intensity.

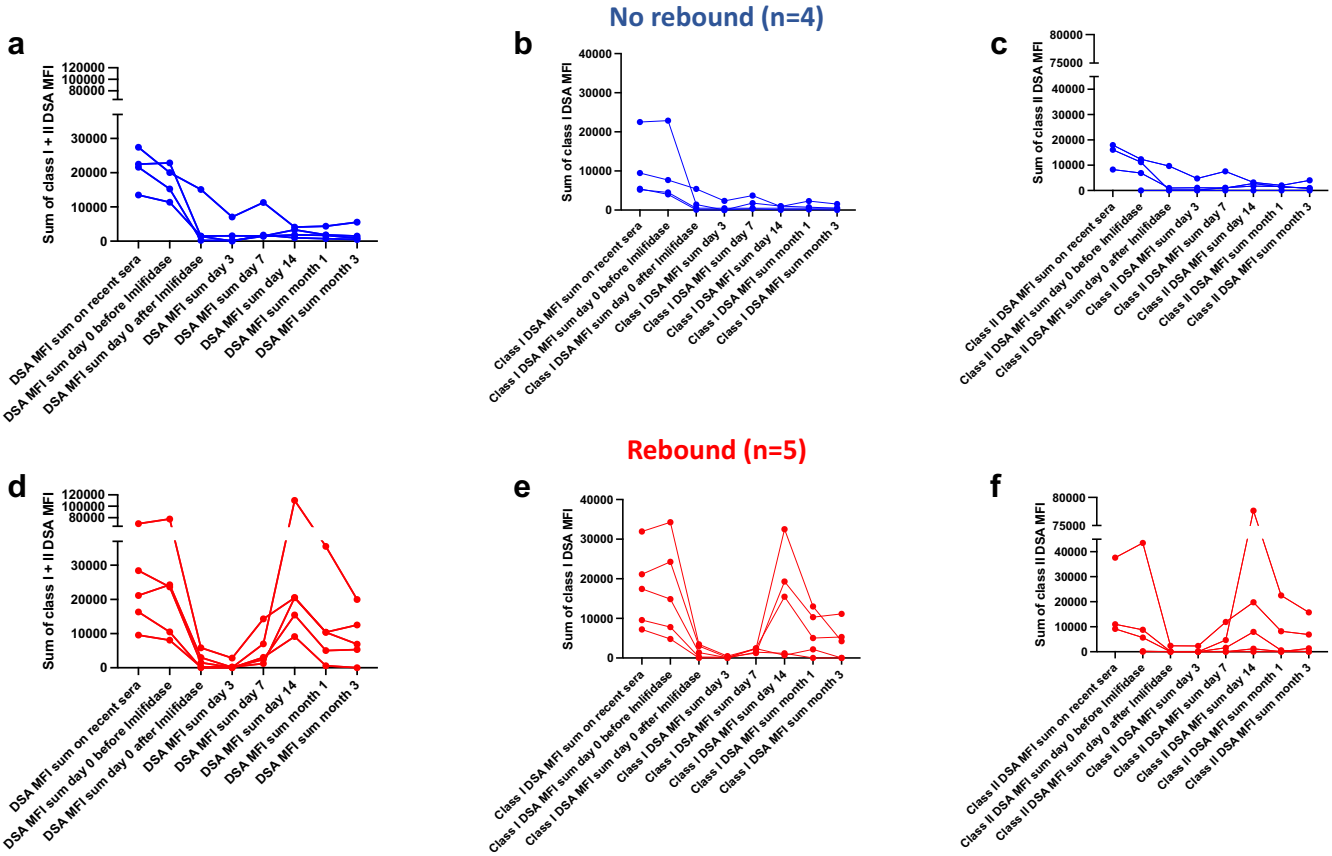

Figure 2. Outcome of donor-specific antibodies (DSAs) after transplantation. (a) In blue, sum of class I and class II DSAs, (b) class I DSAs, and (c) class II DSAs in patients without posttransplant rebound. (d) In red, sum of class I and class II DSAs, (e) class I DSAs, and (f) class II DSAs in patients with posttransplantation rebound.

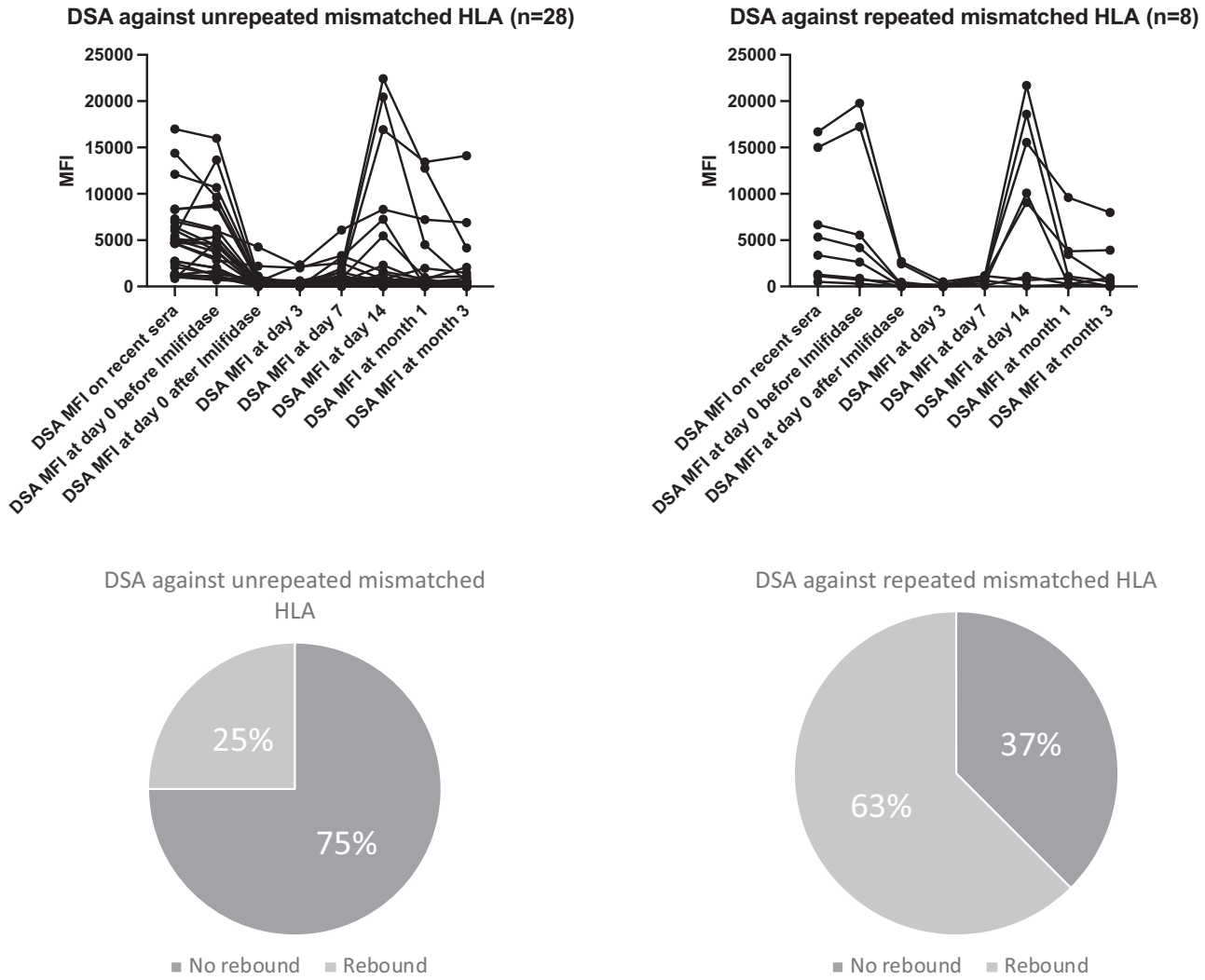

Figure 3. Posttransplant evolution of repeated and unrepeated anti-HLA DSA mismatches. DSA, donor-specific antibody; HLA, human leukocyte antigen.

7827 (4004–34,271) for anti-Class I DSAs and 10,011 (5704–43,508) for anticlass II DSAs. The postdose median sum of DSA MFI was 1497 (17–15,108): 1388 (0–5413) for anticlass I DSAs and 134 (0–9695) for anticlass II DSAs (Figure 2).

All 9 patients had both a CDCXM and an FCXM. FCXMs was positive in all patients before imlifidase and converted to negative after imlifidase. CDCXMs were positive in only 2 patients before imlifidase and converted to negative after imlifidase in these 2 patients.

DSA Rebound and Acute Rejection

After transplantation, 5 out of 9 patients (patients 5–9) presented a DSA rebound, which occurred between days 7 and 14 (Figure 1). In these patients, a rebound in non-DSA HLA antibodies was also observed. Among the 5 patients who had a rebound, all but 1 (patient 7) had repeated anti-HLA DSA mismatches (80%). Conversely, among the 4 patients who did not experience a rebound, only 1 of them (patient 2) (20%) had a repeated anti-HLA DSA mismatch.

Seven out of the 28 unrepeated anti-HLA DSA mismatches (25%) and 5 out the 8 repeated anti-HLA DSA mismatches (62.5%) had a rebound after transplantation (Figure 3).

Among the 5 patients who had a rebound, 2 experienced a clinical ABMR (22.2%) before day 14. Of the surveillance biopsies performed between days 7 and 10, 1 had a subclinical ABMR, another had a subclinical ABMR and T cell-mediated rejection, and the last one had isolated positive C4d staining. No early acute rejection was observed among the patients with no DSA rebound (patients 1–4). The complete results of kidney biopsies performed between days 7 and 10 posttransplantation is presented in Table 2.

Patients who had a Clinical ABMR

Patient 5. On day 9 posttransplantation, serum creatinine dramatically increased from 90 to 600 μmol/l. A

Table 2. Histological features at day 7 to 10 and in 3 months

	Rebound	Kidney biopsy	Sum DSA MFI	t	i	ptc	g	v	ti	t-IFTA	i-IFTA	ct	ci	cv	cg	ah	mm	C4d	TMA	Banff diagnosis
P1	No	d 7–10	1453	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	N	No rejection
		mo 3	859	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	N	No rejection
P2	No	d 7–10	11,310	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	N	Acute tubular necrosis
		mo 3	5571	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	N	No rejection
P3	No	d 7–10	1796	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	N	Acute tubular necrosis
		mo 3	498	1	1	2	1	0	1	0	1	1	1	1	0	0	1	0	N	Subclinical borderline[a]
P4	No	d 7–10	1497	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	N	Acute tubular necrosis[b]
		mo 3	1497	0	0	0	0	0	0	0	0	1	2	1	0	0	0	0	N	No rejection
P5	Yes	d 7–10	97,773	0	0	2	2	0	0	0	0	0	0	1	0	0	1	3	Y	Clinical ABMR
		mo 3	19,982	0	1	1	0	0	1	0	0	0	0	0	0	0	0	3	N	Subclinical ABMR
P6	Yes	d 7–10	20,567	0	0	1	2	0	0	0	0	0	0	0	0	0	0	3	N	Clinical ABMR
		mo 3	12,534	0	0	3	1	0	0	0	0	0	0	0	0	0	0	3	N	Subclinical ABMR
P7	Yes	d 7–10	9147	0	0	1	1	0	0	0	0	1	1	1	0	1	0	2	N	Subclinical ABMR
		mo 3	0	1	0	1	1	0	1	0	1	1	1	2	1	0	1	1	Y	Subclinical ABMR
P8	Yes	d 7–10	20,480	2	2	2	1	0	0	0	0	0	0	0	0	0	0	3	N	Subclinical ABMR + TCMR
		mo 3	6900	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	N	Subclinical borderline
P9	Yes	d 7–10	15,470	0	1	0	0	0	1	0	1	1	1	0	0	0	0	3	N	Isolated C4d
		mo 3	5331	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	N	Isolated C4d

ABMR, antibody mediated rejection; ah, arteriolar hyalinosis; mm, mesangial matrix expansion; cg, glomerular basement membrane double contours; ci, interstitial fibrosis; ct, tubular atrophy; cv, vascular fibrous intimal thickening; DSA, donor-specific antibodies; g, glomerulitis; i, interstitial inflammation; i-IFTA, inflammation in the area of IFTA; MFI, mean fluorescence intensity; ptc, peritubular capillaritis; t, tubulitis; TCMR, T cell-mediated rejection; ti, total inflammation; t-IFTA, tubulitis in areas of interstitial fibrosis and tubular atrophy; TMA, thrombotic microangiopathy; v, intimal arteritis.
[a]The presence of a borderline infiltrate led us to consider that the peritubular capillaritis lesions were not in favor of an ABMR.
[b]C4d staining in peritubular capillaries was graded as C4d1 by immunofluorescence on frozen sections and was considered non-significant to retain an ABMR diagnosis in association with the acute tubular necrosis lesions.

concomitant rebound of class I and class II antibodies was observed. A kidney biopsy revealed features of ABMR (Table 2). One dialysis session was required. The patient was treated with immunoadsorption (13 sessions), corticosteroid pulses, 1 additional dose of rituximab (375 mg/m^2), IVIg, and eculizumab (900 mg/wk for 3 weeks and then every 15 days) which will continue until the last follow-up (8 months). At 3 months posttransplantation, histological features of subclinical ABMR were observed. At the last follow-up, eGFR was at 74 ml/min per 1.73 m^2.

Patient 6. On day 14 posttransplantation, serum creatinine increased from 110 to 174 μmol/l. A concomitant rebound of class I and class II antibodies was observed. A kidney biopsy revealed signs of ABMR (Table 2). The patient was treated with immunoadsorption (13 sessions), IVIg, and daratumumab (1800 mg/wk for 4 weeks). At 3 months posttransplantation, histological signs of subclinical ABMR were observed. Unfortunately, 1 month after rejection therapy, the patient contracted a BK polyomavirus-associated nephropathy that is still active. At the last follow-up (6 months), the eGFR was 37 ml/min per 1.73 m^2.

Patients who had a Subclinical ABMR

Patient 7. Although kidney function was preserved, due to the histological signs of ABMR observed on the routine kidney biopsy performed on day 10, the patient was treated with plasma exchanges (8 sessions), corticosteroid pulses, IVIg, and 1 dose of rituximab (375 mg/m^2). Three months posttransplantation, he had histological signs of subclinical ABMR and at the last follow-up (5 months), the eGFR was 39 ml/min per 1.73 m^2.

Patient 8. A kidney biopsy performed on day 7 revealed signs of ABMR and T cell-mediated rejection. The patient was treated with polyclonal antibodies, corticosteroid pulses, IVIg, and eculizumab (1200 mg every 15 days), which continues. Three months posttransplantation, she had histological signs of subclinical borderline rejection and at the last follow-up (10 months), the eGFR was 99 ml/min per 1.73 m^2.

Other Patients

Patient 9 had a transient rebound and isolated positive C4d staining but received no additional treatment. No ABMR was observed in patients without a rebound. Because of subclinical borderline histological features on the routine kidney biopsy at month 3, patient 3

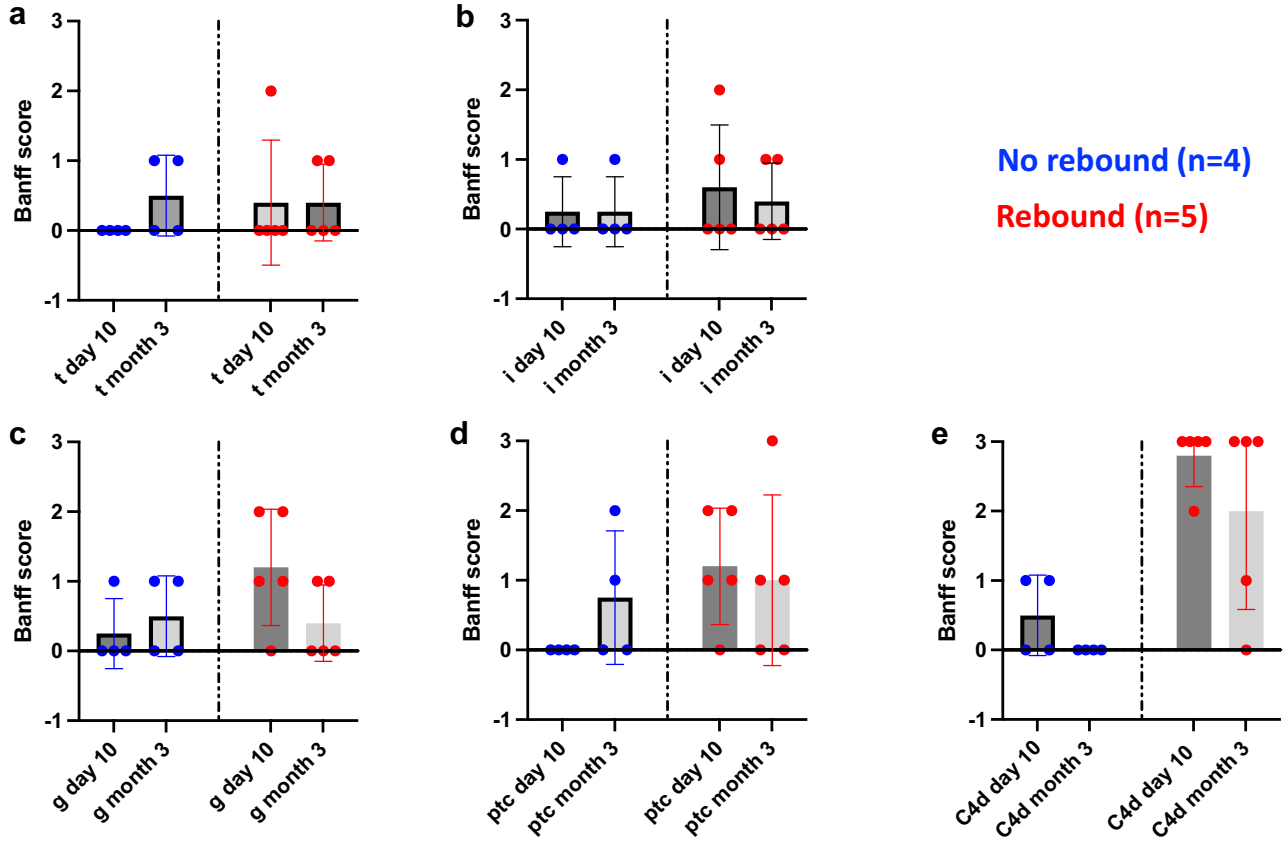

Figure 4. Histological features at days 7 to 10 and month 3 in patients with and without posttransplant rebound. Panel a, tubulitis (t). Panel b, inflammation (i). Panel c, glomerulitis (g). Panel d, peritubular capillaritis (ptc). Panel e, C4d staining.

received corticosteroid pulses and IVIg (2 g/kg). Patients' outcome and treatments are summarized in Figure 4 and Table 3.

Kidney Function

Serum creatinine levels and eGFR are presented in Figure 5. After a mean follow-up of 7 ± 2.8 months, serum creatinine level was 122 ± 38 μmol/l and Chronic Kidney Disease Epidemiology Collaboration formula eGFR was 56 ± 22 ml/min per 1.73 m^2. Proteinuria at 3 months was 0.12 ± 0.12 g/g of creatininuria. No graft loss or death was observed during follow-up.

Safety

Four out of 9 patients developed an infection. Patient 1 presented with SARS-CoV2 and a pulmonary infection. Patient 4 presented with asymptomatic CMV reactivation and 2 acute episodes of pyelonephritis. Patient 6 developed BK polyomavirus nephropathy as well as an asymptomatic CMV infection and repeated episodes of acute pyelonephritis. Patient 7 was hospitalized for an infected lymphocele and presented with transient positive BK virus DNAemia that did not require immunosuppressants' dose modification. No malignancy occurred during this short follow-up.

DISCUSSION

In phase 1 and 2 trials, 46 highly sensitized patients received imlifidase at transplantation as a desensitization agent. Thirty-nine of these patients had a positive XM against a deceased or living donor. In the Highdes phase 2 trial, 89.5% of the patients converted from a positive baseline XM to a negative XM within 24 hours after imlifidase treatment.[13] In this retrospective study, we report on the use of imlifidase in 9 highly sensitized patients. Patients were selected according to previously published French guidelines.[2] All patients had a positive FCXM that converted to negative after imlifidase. However, before imlifidase, only 2 patients had a positive CDCXM despite high sums of DSAs MFI. Both converted to negative. All 9 patients required only 1 dose of imlifidase. At transplantation, the mean number of DSA was 4.3 ± 1.4. The predose median immunodominant DSA MFI against HLA -A, B, DR, and DQ was like that observed in previous trials,[14] that is, 7300 (6064–16,980) and 7791 (4108–16,320), respectively. The predose and postdose median sum of DSA MFI was 20,057 (8078–77,779) and 1497 (17–15,108), respectively.

In the study by Kjellamn *et al.*[14] which pooled the data of all phase 1 and 2 trials, after transplantation, a

Table 3. Outcome for transplanted patients treated with imlifidase

Patients	Number of DSAs at transplantation (class I/ class II)	Sum of DSAs before imlifidase	iDSA before imlifidase	CDC-XM	FC-XM MFI ratio on T cells before imlifidase	FC-XM MFI ratio on B cells before imlifidase	Rebound	Sum of DSAs at d 7 or 10 (Highest value)	iDSA at d 7 or 10 (Highest value)	Kidney biopsy at d 7 to 10	ABMR treatment	Sum of DSAs at mo 3	iDSA at mo 3	Kidney biopsy at mo 3	Last follow-up (mo)	eGFR at last follow-up (ml/min per 1.73 m^2)
P1	5 (2/3)	15,249	6430	negative	6.02	5.81	No	1453	455	no rejection	No	859	0	no rejection	6	42
P2	6 (3/3)	20,057	11,208	negative	-	3.5	No	11,310	2709	ATN	No	5571	1447	no rejection	4	57
P3	4 (4/0)	22,872	8369	negative	1.8	3	No	1796	517	ATN	No	498	282	Subclinical borderline	9	75
P4	3 (1/2)	11,400	7300	negative	1.17	2.03	No	1497	499	ATN	No	1497	499	no rejection	12	32
P5	6 (2/4)	23,658	12,111	negative	2.6	4.9	Yes	97,773	22,428	Clinical ABMR	IA, pulse corticosteroid, rituximab, IVIg, eculizumab	19,982	3470	Subclinical ABMR	8	74
P6	3 (3/0)	8078	6676	negative	6.4	22	Yes	20,567	15,548	Clinical ABMR	IA, IVIg, daratumumab	12,534	7986	Subclinical ABMR	6	37
P7	3 (2/1)	10,511	9153	negative	2.21	3.52	Yes	9147	7964	Subclinical ABMR	PE, pulse corticosteroid, IVIg, rituximab	0	0	Subclinical ABMR	5	39
P8	6 (3/3)	77,779	16,980	positive	39.4	38.4	Yes	20,480	7270	Subclinical ABMR + TCMR	Polyclonal antibodies, pulse corticosteroid, IVIg Eculizumab	6900	0	Subclinical borderline	10	99
P9	3 (3/0)	24,282	15,008	positive	5.7	6	Yes	15,470	9081	Isolated C4d	No	5331	3920	Isolated C4d	5	50

ABMR, antibody mediated rejection; ATN, acute tubular necrosis; CDC-XM, complement-dependent cytotoxicity crossmatch; DSA, donor-specific antibodies; eGFR, estimated glomerular filtration rate; IA, immunoadsorption; iDSA, immunodominant DSA before imlifidase; IVIg, i.v. Ig; PE, plasma exchange; TCMR, T cell-mediated rejection.

rebound to approximatively 80% of pretransplantation levels was observed, with a peak on day 14.[14] However, the proportion of patients who had a rebound was not mentioned. Thirty-eight percent of the patients (15 out of 39 patients) had an ABMR. ABMR occurred within the first month posttransplantation in 11 patients. In the 4 remaining patients, ABMR occurred between months 2 and 6.[14] In the present study, 5 of the 9 patients (55.5%) presented with a rebound between days 7 and 14:2 (22.2%) had an early clinical ABMR, 1 had a subclinical ABMR, another had both a subclinical ABMR and a T cell-mediated rejection, and the last patient had a transient rebound with isolated positive C4d staining. On the 3-month surveillance biopsy, 3 of the 4 patients who had ABMR still had histological signs of subclinical ABMR, 1 had subclinical borderline rejection, whereas the last patient still had isolated positive C4d staining (Table 3). This last patient received no additional therapy at rebound. Interestingly, patients who did not experience a rebound remained ABMR-free. Kjellamn *et al.*[14] found that predose immunodominant DSA MFI was significantly lower in patients who did not present with an ABMR compared to those who did.[14] Due to the small number of patients, we were not able to document an association between rebound or ABMR and the baseline immunological parameters before imlifidase (Table 3). We can only stress that the 2 patients with a positive CDCXM had a rebound. Interestingly, we observed that DSA rebounds after transplantation occur in patients with or without repeated HLA mismatches. However, the rebound occurs more frequently in patients transplanted with a repeated HLA mismatch. This rebound probably reflects the reactivation of a memory cellular humoral response. It would probably be useful to analyze the different cellular strata involved in the memory response to test additional treatments targeting the involved cells.

Patients with ABMR were treated mainly with apheresis, corticosteroids, and IVIg. Two patients received rituximab, 2 patients eculizumab, and another was treated with daratumumab. Similar strategies were used in the development phase trials. Of note, contrary to treatments for 2 patients in the phase 1 and 2 trials, none of our patients underwent spleen embolization or splenectomy. ABMR treatment provided an improvement in histological signs and kidney function in all patients except 1, who received daratumumab and who subsequently developed BK polyomavirus nephropathy.

At the last follow-up, kidney function tests showed eGFR at 56 $\pm$ 22 ml/min per 1.73 m^2. eGFR was $>$ 30 ml/min per 1.73 m^2 in all patients. Patient and graft

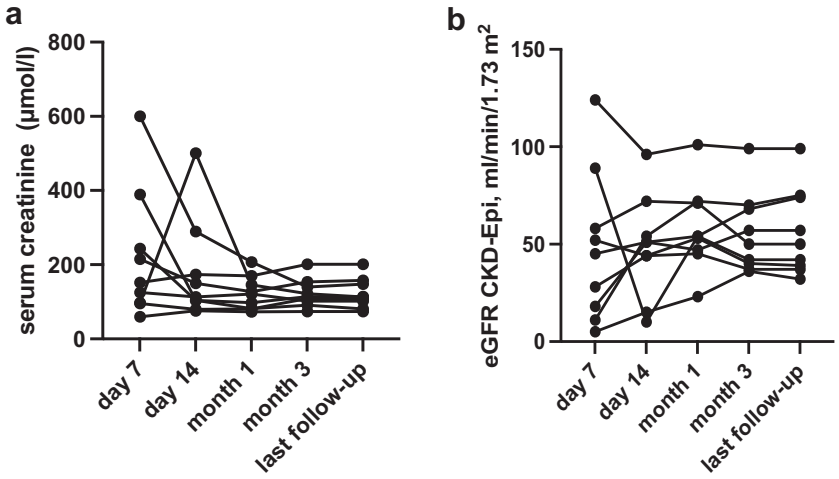

Figure 5. Outcome of (a) serum creatinine level and (b) CKD EPI estimated glomerular filtration rate, after transplantation. CKD EPI, chronic kidney disease epidemiology collaboration formula.

survivals were 100%. Four patients presented with quite common infectious complications such as acute pyelonephritis, pulmonary infection, and asymptomatic CMV infection. Only 1 patient developed BK polyomavirus nephropathy.

Therefore, overall, our real-life short-term results are in line with previously published reports. Imlifidase can be used in selected highly sensitized patients who have been waiting for transplantation for a long period. Seven of the 9 patients had a cPRA of 100%, and all had been waiting for a transplantation for 123 ± 41 months. They were transplanted 82 ± 53 days after anti-HLA antibodies had been delisted according to the 1:10 dilution criteria.

The study has several obvious limitations, mainly the small number of patients and the short follow-up period. However, its strength is that it included a homogenous population selected and transplanted according to national guidelines.

In conclusion, the use of imlifidase to desensitize highly sensitized patients in the context of French recommendations was associated with 22.2% early clinical ABMR and 22.2% early subclinical AMBR. Additional immunosuppression was required in these patients; however, the short-term efficacy and safety profile appears to be acceptable. These results cannot be generalized to patients selected outside the French guidelines. Further studies and a longer follow-up are necessary to confirm these data and identify patients at risk of rebound and ABMR.

DISCLOSURE

NK has received speakers' fees, consultancy fees, and was a member of advisory boards for Astellas, AstraZeneca, Biotest, BMS, CSL Behring, Chiesi, ExeViR, Gilead, Hansa, MSD, Glasgow Smith Kline, Neovii, Novartis Pharma, Roche, Sanofi, Sandoz, and Takeda. DB has received speakers' fees, consultancy fees, and was a member of advisory boards for AstraZeneca, Biotest, BMS, Chiesi, Hansa, and Takeda. SC has received consultancy fees and was a member of advisory boards for Astra Zeneca, Alexion, Chiesi, Pierre Fabre and Pfizer. J-LT has received consultancy fees as a member of advisory board for Hansa, and research grants from Hansa and ThermoFisher Scientific. GLG was a member of advisory boards for Hansa. LC has received speakers' fees, consultancy fees and was a member of advisory boards for Astellas, Biotest, Chiesi, Glasgow Smith Kline, Hansa, Neovii, Novartis, Ostuka Sandoz, Takeda, and Vifor. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are openly available in the repository at Bordeaux University Hospital (accession number: CER-BDX 2023–116).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Donors' specific antibodies before and after 1:10 dilution as well as before and after imlifidase in the 9 patients.

STROBE Checklist.

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