Imlifidase Desensitization in Crossmatch-positive, Highly Sensitized Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes)

Stanley C. Jordan, MD,[1] Christophe Legendre, MD,[2] Niraj M. Desai, MD,[3] Tomas Lorant, MD,[4,5] Mats Bengtsson, MD,[4] Bonnie E. Lonze, MD,[6] Ashley A. Vo, PharmD,[1] Anna Runström, MSc,[5] Lena Laxmyr, PhD,[5] Kristoffer Sjöholm, PhD,[5] Åsa Schiött, PhD,[5] Elisabeth Sonesson, PhD,[5] Kathryn Wood, MD,[5] Lena Winstedt, PhD,[5] Christian Kjellman, PhD,[5] and Robert A. Montgomery, MD[6]

Background. Highly HLA sensitized patients have limited access to life-saving kidney transplantation because of a paucity of immunologically suitable donors. Imlifidase is a cysteine protease that cleaves IgG leading to a rapid decrease in antibody level and inhibition of IgG-mediated injury. This study investigates the efficacy and safety of imlifidase in converting a positive crossmatch test to negative, allowing highly sensitized patients to be transplanted with a living or deceased donor kidney. **Methods.** This open-label, single-arm, phase 2 trial conducted at 5 transplant centers, evaluated the ability of imlifidase to create a negative crossmatch test within 24 h. Secondary endpoints included postimlifidase donor-specific antibody levels compared with predose levels, renal function, and pharmacokinetic/pharmacodynamic profiles. Safety endpoints included adverse events and immunogenicity profile. **Results.** Of the transplanted patients, 89.5% demonstrated conversion of baseline positive crossmatch to negative within 24 h after imlifidase treatment. Donor-specific antibodies most often rebounded 3–14 d postimlifidase dose, with substantial interpatient variability. Patient survival was 100% with graft survival of 88.9% at 6 mo. With this, 38.9% had early biopsy proven antibody–mediated rejection with onset 2–19 d posttransplantation. Serum IgG levels began to normalize after ~3–7 d posttransplantation. Antidrug antibody levels were consistent with previous studies. Seven adverse events in 6 patients were classified as possibly or probably related to treatment and were mild-moderate in severity. **Conclusions.** Imlifidase was well tolerated, converted positive crossmatches to negative, and enabled patients with a median calculated panel-reactive antibody of 99.83% to undergo kidney transplantation resulting in good kidney function and graft survival at 6 mo.

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INTRODUCTION

End-stage renal disease poses a significant global health burden, affecting nearly 2.5 million patients worldwide.[1] Although kidney transplantation offers a number of benefits over dialysis, including improved survival and quality of life, as well as important long-term healthcare cost savings, many patients remain on transplant waiting lists for years or die while waiting for a suitable organ.[1,2] Beyond issues of supply and demand is the pervasive impact of anti-HLA antibodies among patients on the transplant waitlist. Of 92 685 patients on the US kidney transplant waiting list in 2017, approximately 30% were sensitized to HLA; of these patients, nearly half were considered highly sensitized, with calculated panel-reactive antibody (cPRA) of at least 80%.[3,4] Data from Eurotransplant indicate a similar trend with approximately 19% of 10 320 patients considered sensitized, of which 30% of these fall into the highly sensitized category with a cPRA > 85%.[5] Preformed donor-specific antibodies (DSAs) are significant barriers to finding immunologically suitable donor kidneys, are associated with prolonged waiting times and higher mortality rates, and increase posttransplant risks of antibody-mediated rejection (AMR) and graft failure.[4,6–8] Although paired donation and allocation systems with priority for highly sensitized candidates, including the kidney allocation system (KAS) implemented in the United States in 2014, have improved access for sensitized candidates in general, transplantation rates for the most highly sensitized candidates remain low.[3,9]

There remains a great unmet medical need for sensitized patients awaiting kidney transplantation. Over the past decade, therapeutic desensitization strategies have emerged that decrease sensitized patients' DSA levels and enable transplantation of otherwise incompatible living donor (LD) kidneys. Such protocols are generally based on administration of high-dose intravenous immune globulin (IVIg) or plasma exchange (PLEX) with low-dose IVIg, usually in combination with rituximab or other immunomodulating therapies.[10] Although a number of groups have reported improved survival and quality of life, as well as reduced costs, compared with ongoing dialysis, efficacy is variable, and to date, protocols remain complex, unstandardized, and without regulatory approval.[7,8,11–15] Because it is an inefficient method for lowering total body IgG, PLEX-based treatments require substantial time and planning, effectively precluding use of deceased donor (DD) kidneys.

Imlifidase (previously denoted IdeS) is a cysteine protease that cleaves IgG in a 2-step reaction, with an initial single cleaved IgG, then a fully cleaved IgG resulting in a F(ab')$_2$ fragment and a dimeric Fc fragment. The F(ab')$_2$ fragments retain full binding capacity to epitopes but are unable to participate in Fc-mediated activities. Thus, Fc-dependent effector functions, including antibody-dependent cell-mediated phagocytosis, antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity are efficiently neutralized.[16] Imlifidase specifically cleaves all subclasses of IgG, leading to a rapid decrease in antibody level and inhibition of IgG-mediated immune response. Data from a phase 1 study showed that IgG is rapidly and effectively cleaved and data from recent studies have shown that imlifidase treatment quickly and effectively reduces HLA antibody.[17,18]

A previous imlifidase publication presented safety and dose finding data, as well as initial information about the reduction or elimination of DSAs to facilitate, in some cases, HLA-incompatible transplants performed at a United States and Swedish center. These were heterogenous populations of patients pooled together from 3 separate trials with different treatment protocols. A phase II, single-arm, open-label study assessed the efficacy of imlifidase to convert a positive crossmatch test to negative before transplant with either a LD or DD kidney in 7 patients leading to successful transplantation, in a single center.[19] Here, we report the findings of the pivotal international phase 2 study investigating the efficacy and safety of imlifidase in converting a positive crossmatch test to negative (using a uniform protocol), mitigating the risk of hyperacute rejection, and thus allowing highly sensitized patients to be transplanted with available DD or LD kidneys in a larger cohort with a 6-mo clinical end point. The patients in this study represent a cohort that is more highly sensitized (in comparison to previously published imlifidase studies) with a median cPRA of 99.83%, and enrolled only crossmatch-positive patients, which aligns more closely with the target population of highly sensitized adult kidney transplant patients extremely unlikely to be transplanted under available KASs including prioritization programs for highly sensitized patients.

MATERIALS AND METHODS

This was an open-label, single-arm, phase 2 (15-HMedIdeS-06, Highdes) trial conducted at 5 transplant centers (Cedars-Sinai Medical Center, Los Angeles, CA; The Johns Hopkins Hospital, Baltimore, MD; New York University Langone Health, New York; Uppsala University Hospital, Uppsala, Sweden; Hôpital Necker, Paris, France) between September 30, 2016, and July 3, 2018 (EudraCT Number: 2016-002064-13). It was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki; all ethical and regulatory approvals were available before any patient was exposed to any study related procedure. The trial was registered at ClinicalTrials.gov (NCT02790437).

Eligibility

Adult (18–70 y) patients on the kidney transplant waiting list who do not have an eligible LD and have failed previous attempts at desensitization with high-dose IVIg/Rituximab or have a breadth and depth of sensitization that would make desensitization improbable either because they did not have an LD (and were not a candidate for plasmapheresis) or had an LD and the DSA was too strong for consideration of plasmapheresis and low-dose IVIg desensitization. At study entry, patients had an available DD or LD kidney with a positive crossmatch test. Additional inclusion criteria in France was a DSA present with mean fluorescence intensity (MFI) ≥3000. Additional inclusion criteria in Sweden required patients to have been on the transplantation waiting list >1 y and have HLA antibody status with PRA ≥80% based on complement-dependent cytotoxicity (CDC) and solid phase assay. Regardless of study site, previous treatment with imlifidase or high-dose IVIg treatment (2 g/kg body weight [BW]) within 28 d before enrollment were exclusions.

Immunological Tests

Crossmatch tests used locally were flow cytometric crossmatch of T and B cells (fluorescence-activated flow cytometric crossmatch [FACS]) with approximately 250 channel shifts or fewer and CDC crossmatch. Donor and recipient HLA typing was performed using next generation sequencing or polymerase chain reaction sequence-specific methods for HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP antigens. Onsite DSAs were measured with solid phase assay systems that were currently in use at the HLA laboratory of each hospital and were EDTA treated and reanalyzed centrally to assess SD between samples at Hansa Biopharma AB, Lund, Sweden using single-antigen beads (SAB, LABScreen, One Lambda, ThermoFisher Scientific, West Hills, CA).

Clinical Evaluation

Renal function was assessed by estimated glomerular filtration rate (eGFR) calculated with the abbreviated modification of diet in renal disease formula. AMR and T cell–mediated rejection was defined according to the current version of Banff criteria during the study period and read by each respective institution's pathologist with biopsy scores (0–3) for the following lesions: interstitial inflammation, tubulitis, intimal arteritis, glomerulitis, peritubular capillaritis, C4d staining, interstitial fibrosis, GBM double contours (cg), mesangial matrix expansion, tubular atrophy, intimal thickening, arteriolar hyalinosis, and inflammation in the area of IFTA.[20] Although biopsy slides were reviewed only by local pathologists, pathology reports were collected centrally and Banff diagnostic categories based on locally generated scores were corroborated centrally in accordance with Banff 2017 guidelines. Delayed graft function (DGF) was defined as the need for dialysis within 7 d posttransplantation. cPRA was determined using the Organ Procurement and Transplantation Network calculator with a 3000 MFI cutoff for unacceptable antigens. DSA rebound was defined as any DSA >1000 MFI.

Imlifidase Treatment

Imlifidase was administered as an intravenous infusion over 15 min subsequent to premedication with glucocorticoids (methylprednisolone) and antihistamines (loratadine or equivalent). All patients received 1 dose of imlifidase 0·25 mg/kg BW on day 0. If it was considered safe by investigators and the desired effect of negative crossmatch test was not achieved after the first dose, an additional 0·25 mg/kg dose of imlifidase could be given within 2 d of the first infusion.[17]

Crossmatch tests were performed predose and postdose. At all sites apart from Cedars-Sinai, only patients with confirmed conversion of the postdose crossmatch test were transplanted. At Cedars-Sinai, the decision to transplant was made based on DSA levels due to long turn-around time for crossmatch tests and confirmatory crossmatch tests were performed within 24 h postimlifidase dosing.

Immunosuppression

All patients received induction therapy with pulse corticosteroids starting intraoperatively and continuing through postoperative day 3 and either equine antithymocyte globulin, 15 mg/kg IV daily for 4 d (equine ATG, ATGAM; Pharmacia & Upjohn Co, Pfizer Inc, New York, NY) initiated intraoperatively or alemtuzumab 30 mg IV (Campath), Sanofi-Genzyme, Cambridge, MA) given postoperative day 4. Maintenance immunosuppression was administered according to standard clinical practice for sensitized patients at each study center, which included corticosteroids, tacrolimus, and mycophenolate mofetil.

To mitigate the potential risk of infections following inactivation of IgG, prophylactic antibiotics were given according to standard clinical practice at each center or until IgG levels returned to acceptable levels as judged by the study investigators.

Postdose, patients received high-dose IVIg 10% solution 2 g/kg BW (max 140 g for patients >70 kg) 7 d after imlifidase infusion and rituximab (anti-CD20) 1 g IV 9 d after imlifidase infusion (Figure 1).[21]

Study Endpoints

The primary efficacy endpoint was the ability of imlifidase to convert a positive to a negative crossmatch test within 24 h after dosing. For an individual patient, the desired effect was achieved if all recorded crossmatch tests (FACS and CDC) were negative within 24 h postdose. Secondary efficacy endpoints included DSA levels at 2, 6, 24, and 48 h and days 3–7, 14, 21, 28, 64, 90, 120, and 180 postimlifidase infusion compared with predose levels, kidney function as estimated by eGFR, the pharmacokinetic profile of imlifidase up to day 14, and the pharmacodynamic profile of imlifidase (cleavage and recovery of IgG) up to day 7 postimlifidase when IVIg was administered. Safety endpoints included adverse events and the immunogenicity profile of imlifidase by measuring antidrug antibodies.

Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics and study endpoints. No formal statistical hypothesis testing was performed. In general, missing data were not imputed or adjusted for in other ways. Median value is presented with minimum and maximum values. All data were tabulated or listed, as applicable.

No sample size calculation was performed for this study. Because of the nature of the primary endpoint of the study, it was expected that data from 15 to 20 patients should suffice to achieve its objectives. The planned sample size was consistent with experiences from previous similar phase II studies to obtain adequate safety, tolerability, and pharmacokinetic data to achieve the objectives of the study. For study purposes, only patients who received a full dose of imlifidase were included in the efficacy analysis whereas all patients who received any proportion of an imlifidase dose were included in the safety analysis.

Role of the Funding Source

The studies were designed, conducted, and evaluated jointly by study investigators and Hansa Biopharma AB. The data were gathered by study investigators, analyzed, and interpreted both at each site and centrally at Hansa Biopharma AB, Lund, Sweden.
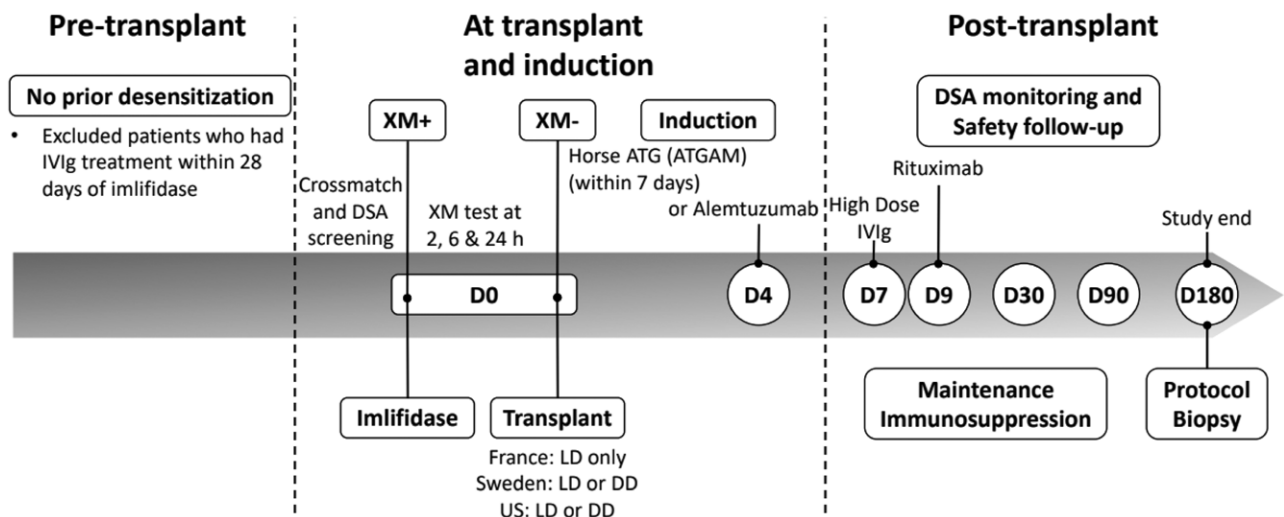
FIGURE 1. Study design. DD, deceased donor; DSA, donor-specific antibody; IVIg, intravenous immune globulin; LD, living donor.

RESULTS

Patient and Donor Characteristics

A total of 21 highly sensitized patients were screened, 19 were enrolled in the study (Figure 2). One patient was excluded because the individual was deemed unable to comply with the protocol, and the other patient had negative T- and B-cell FACS as well as negative CDC-T and -B crossmatches (compatible donor). All patients were confirmed to be incompatible with the available donor (DD or LD), as evidenced by a positive crossmatch test predose. For 1 patient, dosing was interrupted because of an infusion-related reaction and the scheduled LD kidney transplant was not performed as there was no cleavage of IgG resulting in no conversion of crossmatch, resulting in withdrawal from the study. Thirteen patients received kidneys from DDs, and 5 patients received LD kidneys. The median age of recipients was 40 y (range: 20–64). The majority of patients were male (68.4%) and had undergone at least 1 previous kidney transplantation (89.5%, Table 1). Six had received at least 2 prior transplants. At baseline, DSAs were present in all patients, with a median cPRA of 99.83% (range: 77.31–100.0%) with a cutoff of 3000 MFI.

All were ABO compatible. Twelve of 13 DD kidneys originated in standard criteria donors or had Kidney Donor Profile Index <63%; there was 1 extended criteria donor kidney. Five of 13 DD kidneys underwent machine perfusion and 8 kidneys underwent simple cold storage; median CIT for DD kidneys was 27 h (range: 9–46).

Efficacy and Safety

Crossmatch Conversion

Conversion of baseline positive crossmatch to negative within 24 h after imlifidase treatment occurred in 89.5% (n = 17 of 19) of dosed patients (Table 2). One of these failures is attributed to the aforementioned patient with an infusion-related reaction. The residual positive crossmatch (FACS, T cell) in the 1 patient was deemed clinically insignificant and did not correlate with the presence of DSA after imlifidase treatment. This patient along with all 17 patients whose crossmatch converted to negative

proceeded to transplant (n = 18) (Figure 3). The relative strength of the crossmatches and contribution of class I and class II antibodies can be estimated among the 10 patients with the full range of crossmatch testing (both CDC and flow; T and B cell). CDC was not routinely performed at several of the sites. Eight (80%) of the patients were CDC B-cell positive. Four (40%) were flow T-cell positive, of these 2 (20%) were CDC T-cell positive. Three patients received a second dose based on 2-h crossmatch assessments, all within ~13 h after the first dose. Two of these patients had a B-cell positive crossmatch, whereas the third patient had a T-cell positive crossmatch after the first dose of imlifidase. However, 1 of the patients was in fact negative before the second dose, as confirmed by a 6-h postdose sample test.

DSA Levels

Before imlifidase dosing, all patients had at least 1 DSA resulting in positive crossmatch tests. Pretransplant DSA in some patients were very strong with 3 patients presenting with an immunodominant DSA with an MFI 10 000–20 000 and 7 patients with MFI > 20 000 (Figure 4). Single-antigen bead-HLA bead saturation often occurs in highly sensitized patients, and this was also apparent in this population. When diluting the predose samples 10 times, 11 (61%) patients still had DSA over 2500 MFI and 3 (17%) patients had DSA levels of >20 000. When diluting the predose samples 100 times, 8 (61%) patients had DSA levels >2500 MFI and 1 patient had DSA levels of >20 000 MFI. In 83.3% of patients (n = 15/18), DSA levels decreased to <3000 MFI by 6 h postimlifidase dose (Figure 5). When observed, DSA rebound generally occurred between 3 and 14 d postimlifidase dose, with substantial interpatient variability. Two patients did not have antibody rebound; however, no characteristics were identified to elucidate those who did have rebound versus those who did not. In most cases, DSA rebounded to or below baseline level then decreased. Anamnestic immune responses in HLA-incompatible transplants are accompanied by a significant increase in DSA strength over the pretransplant level. There was no evidence this occurred in any of the patients. At study completion (at
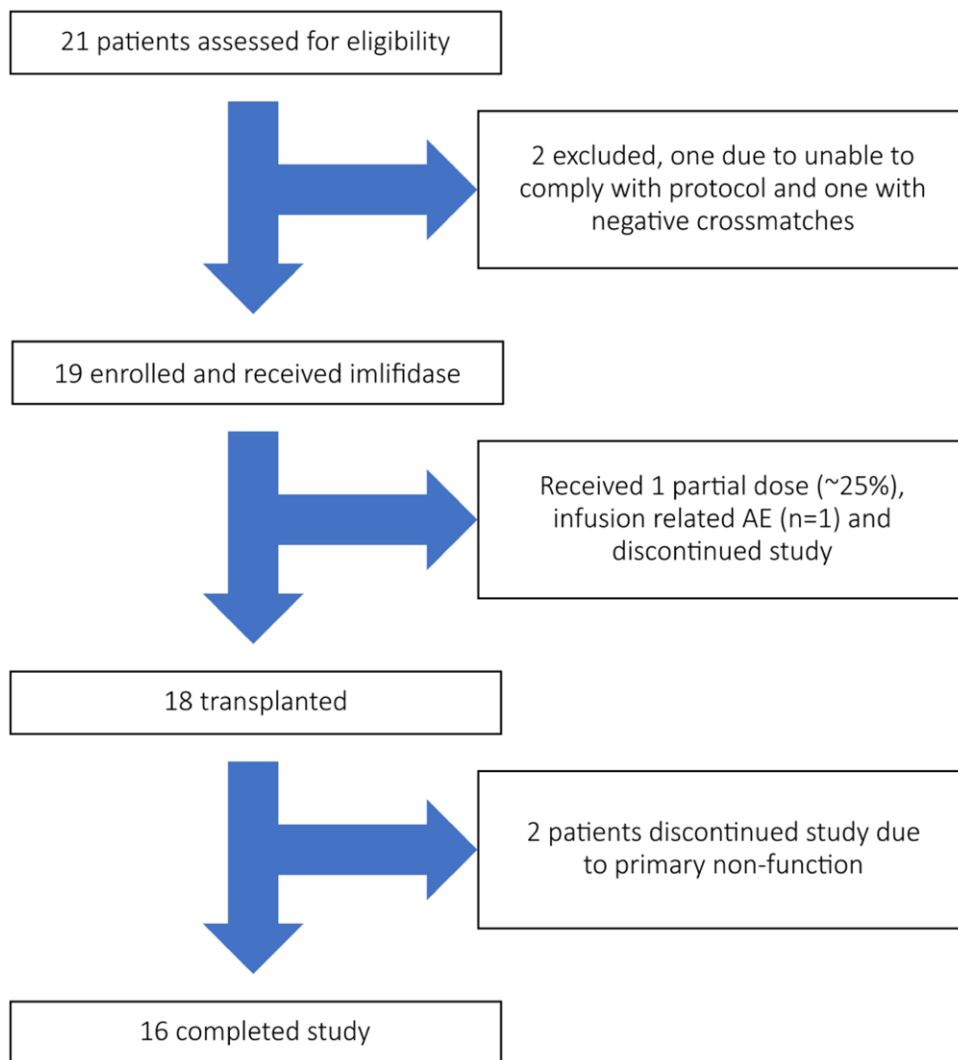
FIGURE 2. Patient disposition.

6 mo), 11 patients had no DSAs >3000 MFI, 6 patients had at least 1 DSA that was >3000 MFI but below baseline value, and 1 patient had a DSA >3000 MFI that was above the baseline value (Figure 6). Class II–specific DSA was present more often (Figure 4) and at greater strength before desensitization but no clear differences in outcome because DSA class specificity was observed in this relatively small number of patients.

Graft Survival, Antibody-mediated Rejection, and eGFR

Overall patient survival was 100% with graft survival of 88.9% at the end of the study. Two patients, both DD recipients, experienced primary allograft nonfunction deemed not secondary to an immune-mediated process (no evidence of AMR), with the adverse event of graft loss recorded at day 77 (after a biopsy demonstrated focal cortical and medullary infarction) and day 128 (although neither graft ever really functioned and 1 recipient was briefly off of dialysis). Both recipients were very medically complex, had preexisting autonomic dysfunction, 1 with profound resting hypotension thought to be the source of the primary allograft nonfunction, and the other was also poorly perfused from the time of transplant.

Seven of 18 patients experienced DGF, including 1 recipient of an LD kidney who had active AMR on day 4 after imlifidase infusion; 5 were able to discontinue dialysis with a duration of DGF lasting a range of 1–40 d (Figure 7). Rejection episodes were reported in 9 of 18 recipients, with onset between days 3 and 167. Seven patients had AMR (n = 6) or presumed (n = 1) active AMR, 38.9%, with an onset between 2 and 19 d posttransplantation. Later cases included borderline cellular rejection (n = 1) and subclinical AMR at protocol biopsy (n = 1). All AMRs were treated with standard therapies, most commonly PLEX, IVIg, optimization of maintenance immunosuppressants, and glucocorticoids. In addition, some patients were treated with rituximab (n = 2) eculizumab (n = 3), bortezomib (n = 2), spleen embolization (n = 1), and splenectomy (n = 1).

Of 16 patients with functioning grafts at the end of the study, 12 underwent surveillance biopsies at day 180. For 4 patients who had maintained prolonged stable graft function up to day 180, the end of study biopsy was declined. Two patients' biopsy samples were nondiagnostic, and biopsies were not reattempted in those cases as the risk of repeat biopsy was deemed to outweigh the benefit. Thus, 10 surveillance biopsy samples were

TABLE 1.
Patient demographics and baseline characteristics

Characteristic	Patients (n = 19)
Age, median (range), y	40 (20, 64)
Male, n (%)	13 (68.4)
Race, n (%)	
• Asian	1 (5.3)
• Black or African-American	4 (21.0)
• White	12 (63.2)
• Other	2 (10.5)
≥1 previous kidney transplant, n (%)	17 (89.5)
Cause of end-stage renal disease, n (%)	
• Diabetes	1 (5)
• Glomerulonephritis	3 (16)
• Inherited disease	2 (11)
• Structural	4 (21)
• Autoimmune	6 (32)
• Unknown	3 (16)
Duration of dialysis, mean (range), y	
After previous transplant (n = 15)[a]	5.1 (0–13.5)
Not previously transplanted (n = 2)	11.6 (0.8–22.4)
Previous desensitization attempts, n/N (%)	5/19 (26·3)
Median recipient cPRA[b] (%), range	99.83 (77.31–100.0)
Number of HLA antibodies[c] at baseline, median (range)	71·5 (20, 112)
Deceased donor, n/N (%)[d]	13/18 (72.2)
Median DD cold ischemia time (range), h	27 (9–46)
Standard criteria donor, n/N (%)	12/13 (92.3)
KDPI <63% n/N (%)	12/13 (92.3)
Extended criteria donor, n/N (%)	1/13 (7)
Machine perfusion, n/N (%)	3/13 (38)
Cold storage, n/N (%)	8/13 (62)
Induction therapy	
• Equine ATG, n/N (%)	4/18 (22)
• Alemtuzumab, n/N (%)	14/18 (78)

[a]15 of 17 patients with previous kidney transplantation had received dialysis since the procedure. The remaining 2 patients had not been on dialysis since transplantation.
[b]MFI cutoff level of 3000; 1 patient did not have any HLA data for cPRA calculations because of exclusion from study.
[c]Number of positive SAB-HLA at baseline, median (range).
[d]18 patients received transplants.
cPRA, calculated panel-reactive antibody; DD, deceased donor; KDPI, kidney donor profile index; MFI, mean fluorescence intensity.

TABLE 2.
Summary of predose crossmatch results by type of test

Response	FACS-T n (%)	FACS-B n (%)	CDC-T n (%)	CDC-B n (%)	Virtual n (%)
Positive	7 (36.8)	18 (94.7)	2 (10.5)	8 (42.1)	5 (26.3)
Negative	12 (63.2)	0	11 (57.9)	2 (10.5)	0
Not done	0	1 (5.3)	6 (31.6)	9 (47.4)	14 (73.7)

%, percentage of patients out of a total of 19 patients; CDC, complement-dependent cytotoxicity; FACS, fluorescence-activated flow cytometric crossmatch; n, number of patients.

Adverse Events

All exposed patients reported at least 1 treatment-emergent adverse event (TEAE) within 30 d of imlifidase dosing but only 7 events in 6 patients were classified as possibly or probably related to treatment (Table 4). Most TEAEs, regardless of relationship to imlifidase, were mild to moderate in severity. There were 18 serious TEAEs reported, of which 2 were classified as related. One was a grade 2 infusion-related reaction, and the other a grade 3 mixed cellular and humoral acute transplant rejection in a patient with 2 previous kidney transplantations. There were no grade 4 TEAEs reported, and no deaths occurred during the study. Imlifidase infusion was temporarily halted in 2 patients because of grade 2 infusion-related reactions, 1 of which was considered related to treatment. There were no infections considered serious and related to imlifidase. Infections considered probably related to imlifidase but not serious include 1 urinary tract infection. Thirty-one other infections were reported in 14 patients over the course of the 6-mo study as not serious and not related to imlifidase. All infectious pathogens were unspecified, and there were no signals to delineate differences between viral, fungal, or bacterial infections.

DISCUSSION

Highly sensitized patients face a significant barrier in finding a compatible donor, resulting in prolonged time on the kidney transplant waitlist, putting them at high risk of getting delisted or dying.[9,22] This international, phase 2 study enrolled highly sensitized patients with a median cPRA of 99.83%; administration of imlifidase enabled a transplant to occur among all 18 patients who received a full dose. Crossmatch conversion was achieved within 24 h in 17 of 18 patients who received a full dose of imlifidase, with 1 additional patient displaying a borderline positive crossmatch not correlated to the presence of DSAs and considered not clinically relevant by the responsible physician. At study completion, 6 mo posttransplantation, patient survival was 100% and graft survival was 88.9%. Many of the patients have persistent DSA and some at relatively high strength, however, only 2 out of 10 with available biopsies at 6 mo have cg > 0 (both are cg 1). These 2 patients have chronic active AMR and will likely progress. The patient with the strongest DSA (MFI 18 087) has C4d 3+ but no microcirculation inflammation.

The patients who experienced early AMR had a slightly lower eGFR at 6 mo compared with those without rejection, with improvement at each subsequent study visit (Figure 1, SDC, http://links.lww.com/TP/C34). Qualitative proteinuria was measured starting day 14 in most centers and at last measurement, the majority of patients

available for evaluation at the end of the study. Seven of these 10 patients had DSA at end of study with MFI ranging from 8000 to 18 000. The Banff lesion scores did not differ significantly between patients with and without DSA (Table 3). Two patients had a cg > 0, 1 with chronic active AMR with positive C4d and DSA MFI ~9000, the other with C4d negative chronic active AMR without DSA. At study completion, median eGFR among those with a functioning graft was 47 mL/min/1.73 m^2 (range: 21–92; Figure 7).

Pharmacokinetics/Pharmacodynamics

IgG started to recover after 3–7 d posttransplantation for most patients. DSA reappearance was seen along with the IgG synthesis in most patients posttransplantation. The levels of antidrug antibodies measured in this study were consistent with previous studies.[17,18]

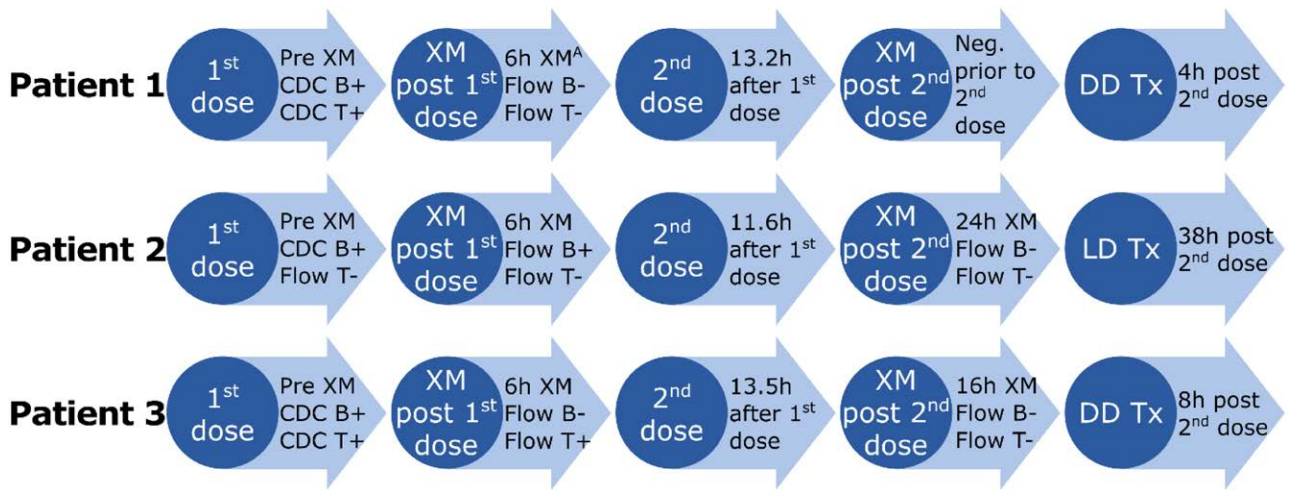**FIGURE 3.** Dosing and crossmatch of patients receiving >1 dose of imlifidase. CDC, complement-dependent cytotoxicity; DD, deceased donor; LD, living donor.
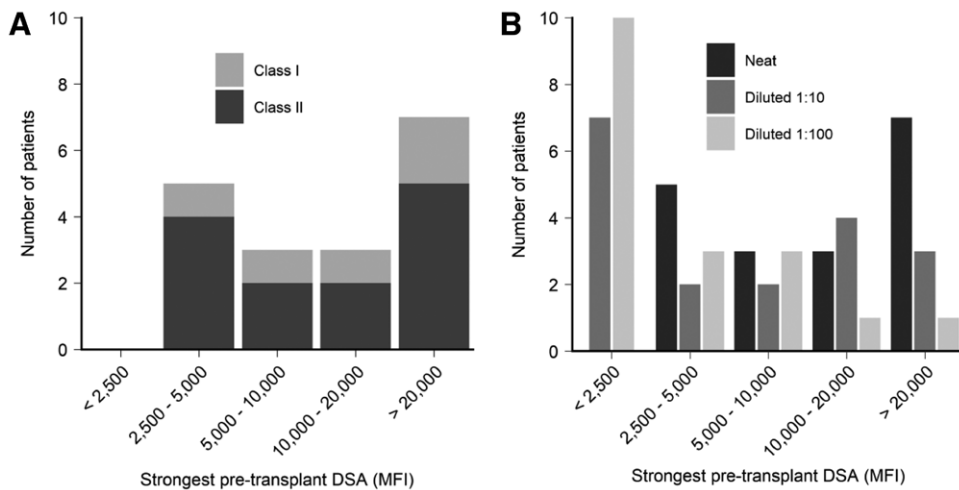

FIGURE 4. Pretransplant DSAs. DSA, donor-specific antibody; MFI, mean fluorescence intensity.
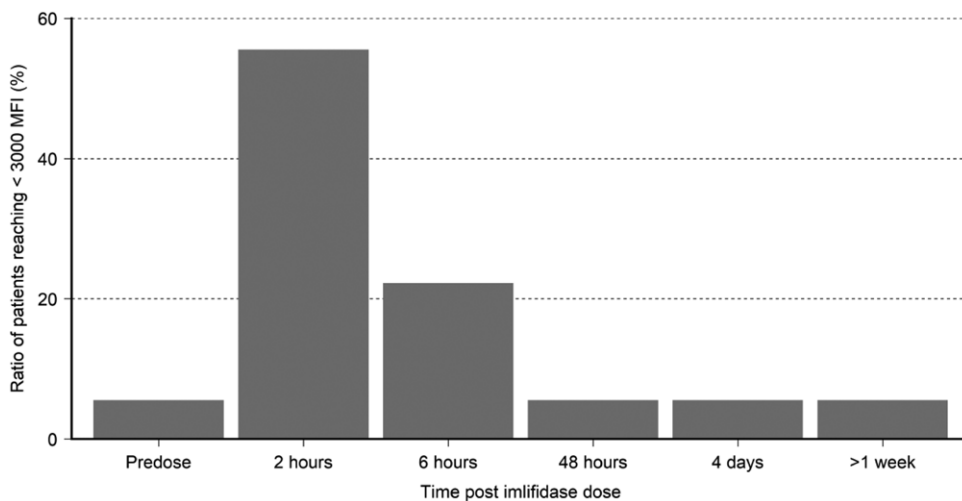

FIGURE 5. Time postimlifidase dose to reach MFI <3000 for all individual DSAs of a patient. DSA, donor-specific antibody; MFI, mean fluorescence intensity.
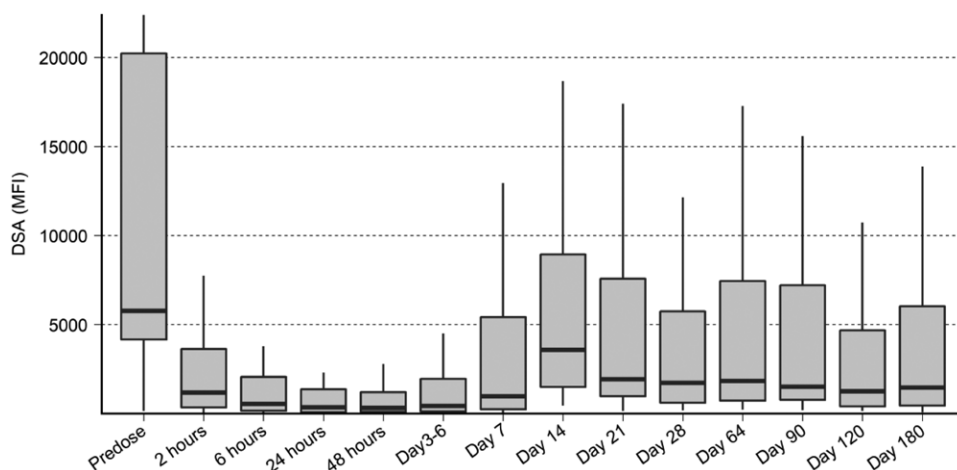
FIGURE 6. DSA levels over 6 mo. DSA, donor-specific antibody; MFI, mean fluorescence intensity.
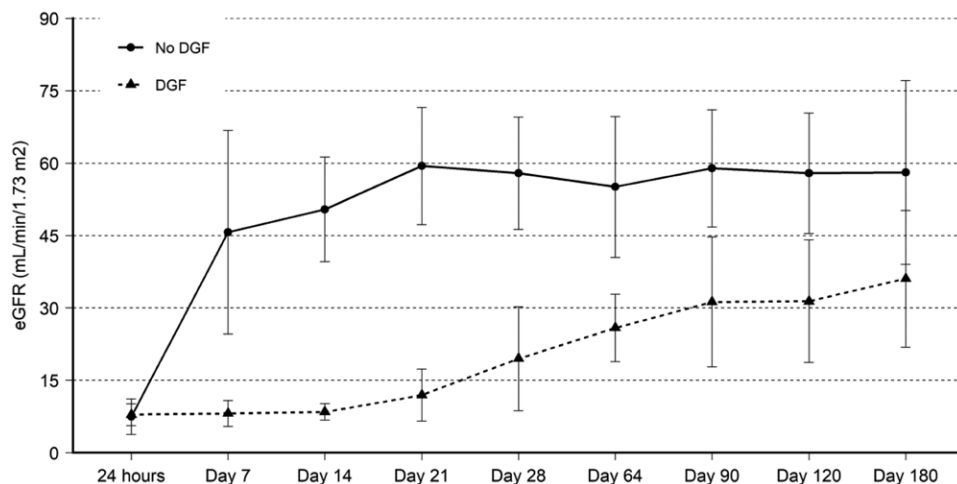

FIGURE 7. Median eGFR for patient with and without DGF. DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

TABLE 3.

Surveillance biopsies at d 180

Case	eGFR (mL/min/ 1.73 m2)	DSA MFI at time of biopsy	g	mm	cg	i	Ci	t	ct	v	cv	ptc	ah	C4d	Diagnosis[a]
Detectable DSAs at time of biopsy															
1	56.1	8988	3	1–2	1	0–1	1	0–1	1	1	2	3	0	2	Active cAMR[b]
2	>60	8949	2	0	0	0	0	0	0	0	0	1–2	0	0	Active AMR[b]
3	20.5	14987	0–1	0	0	0	1–2	0	1–2	0	1	0	0	0	No AMR
4	30.6	12201	0	0	0	1	1	1	0	0	2	1	0	0	No AMR
5	>60	11297	1	0	0	1	1	1	1	0	0	1–2	0	0	No AMR, borderline CMR[b]
6	>60	18087	0	1	0	0	0	0	0	0	0	0	0	3	No AMR
7	39.1	13875	0	1	0	0	0	0	0	0	0	1	0	0	No AMR
Negative DSAs at time of biopsy															
8	35.6	None	0–1	2	0	0	0	0	0	0	0	1–2	1	0	No AMR
9	42.1	None	1	1	0	1	0–1	0	0–1	0	2–3	1–2	1	0	No AMR
10	>60	None	2	1	1	0–1	1	0–1	1	0	1	2	0–1	0	cAMR

[a]Diagnosis in accordance with Banff 2017 criteria.
[b]Subclinical.

ah, arteriolar hyalinosis; AMR, antibody-mediated rejection; C4d, c4d staining; cAMR, chronic antibody–mediated rejection; cg, GBM double contours; Ci, interstitial fibrosis; CMR, cellular mediated rejection; ct, tubular atrophy; cv, vascular fibrous intimal thickening; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; g, glomerulitis; i, interstitial inflammation; MFI, mean fluorescence intensity; mm, mesangial matrix expansion; ptc, peritubular capillaritis; t, tubulitis; v, intimal arteritis.

TABLE 4.

TEAE considered to be related to imlifidase

	0.25 mg/kg dose (n = 16) n (%) E	2 x 0.25 mg/kg dose (n = 3) n (%) E	Total (N = 19) n (%) E
Any related TEAE	5 (31·3) 6	1 (33·3) 1	6 (31·6) 7
Anemia	1 (6·3) 1		1 (5·3) 1
Transplant rejection	1 (6·3) 1		1 (5·3) 1
Urinary tract infection	1 (6·3) 1		1 (5·3) 1
Infusion-related reaction	2 (12·5) 2		2 (10·5) 2
Rash		1 (33·3) 1	1 (5·3) 1
Hypotension	1 (6·3) 1		1 (5·3) 1

%, proportion of patients with event; E, number of events; n, number of patients with event; TEAE, treatment-emergent adverse event.

were positive regardless of whether they experienced AMR, although no quantitative measurements were available. Some patients who experienced significant antibody rebound did not develop AMR, whereas all patients with AMR had DSA rebound (Figure 2, SDC, http://links.lww.com/TP/C34). The findings of proteinuria, lower than expected eGFR, and the ongoing presence of DSA among a majority of patients in the cohort is of concern in terms of the known predictive value of the presence of these characteristics on reduced graft half-life.

Imlifidase demonstrated good tolerability, with 7 adverse events considered to be related to study drug. As the treatment of AMR was not the focus of this study, rather it was recorded as an adverse event of the treatment protocol, management of all adverse events (including rejection) was left to the standard of care at each center. The heterogeneity of AMR treatment reflects the real world heterogeneity of treatment between centers, due to the lack of consensus in the field.

As DGF is a contributor to decreased longevity of allografts after transplantation, its influence on the rejection rates and eGFR outcomes in this study must be considered. The DGF rate was within the range of what has been reported for immunologic high-risk kidney transplant recipients and was expected because of the timing required for multiple crossmatches and the wide range of CIT related to multiple factors including the travel distances and logistics for organ transportation for KAS kidneys in the United States.[23] The revised KAS in the United States was intended to give highly sensitized patients priority access to local, regional, and national organs, but this has also led to increased CIT, most profoundly for the most highly sensitized patients on the national allocation list.[9]

Despite favorable treatment of highly sensitized patients in Europe (eg, acceptable mismatch programs) and the United States (KAS and paired donor exchange programs), there remain a significant number of candidates who have very low probability of receiving a transplant. Despite the new KAS, recent reports indicate that <10% of the most highly sensitized candidates (cPRA > 99.9%) like the patients enrolled in this study, were transplanted in 2016–2017, and patients were more likely to die or be delisted than receive a transplant.[9] DD organs make up the majority of transplants for the 100% cPRA (99.5%–100.0%) patients with only 1.4% of patients receiving organs from

LDs.[9] Previous studies have shown that the cumulative waitlist mortality rate in this group of patients is about 50% from waiting 5 y.[15] For patients with cPRAs ≥ 98%, utilization of LD kidneys has fallen sharply and high-waitlist mortality rates have failed to improve post-KAS, although access to DD organs has improved in some cPRA categories.[9,22] Transplanting these patients earlier with safe and effective desensitization therapy can be achieved with imlifidase and would be predicted both to save lives and increase utilization of LD. The ability to effectively desensitize patients to DDs may justify expanding desensitization beyond >2700 patients on the US waitlist with cPRAs ≥ 99.9% to patients with cPRAs > 99.7% (the inflection point where transplant rates drop dramatically) and to highly sensitized patients who have LDs to prevent excess waitlist mortality.

There are no authority approved methods for desensitization and current center-specific protocols are only available at a very limited number of transplant centers. These methods all require rigorous planning, high-resource utilization and have variable efficacy, particularly for the most highly sensitized patients.[7,10,24] They are usually not feasible for the DD setting since they require weeks or months of desensitization with the uncertainly of receiving a kidney. The number of LD paired exchange transplants for highly sensitized patients is now actually decreasing.[25]

Imlifidase presents a potential paradigm-shifting addition to the desensitization armamentarium, as it not only successfully converts a positive crossmatch test to a negative test but does so with rapidity and completeness regardless of initial DSA strength or number. By using imlifidase to inactivate IgG, an antibody-free window can be created resulting in an opportunity for highly sensitized patients to receive a transplant, which is a fundamental change in how the current system is designed to approach these patients.[26] The data generated by this study highlight more clearly the varied timing, strength, and contributions to clinical outcomes of DSA rebound after imlifidase use. Currently, it is not feasible to predict which patients will experience graft dysfunction solely based on the rebound of DSA, donor, or recipient characteristics and more studies and long-term data are needed to elucidate the possible contributors.

There are limitations to this study that warrant discussion. A randomized placebo-controlled trial or comparison to standard of care therapy in this patient population was not feasible since the potential control treatments would already have been tried unsuccessfully or the likelihood of success in decreasing the HLA antibodies to a level that would result in a negative crossmatch using standard of care desensitization is low due to the breadth and strength of sensitization. The regulatory requirement for entry into this trial was the failure of a previous desensitization attempt or an HLA antibody profile that would have made transplantation or desensitization with standard therapies highly unlikely. Therefore, this study was a single-arm study with limited prestudy statistical analyses. Every effort was made to standardize the study protocol and procedures within all study sites; however, with regard to such things as surveillance biopsies and AMR treatment protocols, for which consensus is lacking, it was left up to the discretion of participating centers.[27]

A continuing concern has been the graft and patient survival outcomes of highly sensitized patients undergoing desensitization regimens compared with outcomes of patients undergoing HLA-compatible transplants. However, outcomes of patients undergoing desensitization should be compared with other options that are actually available to them, which in the case of ultrasensitized patients consists of remaining on dialysis with a mortality rate of 70% at 8 y.[15] Interestingly, posttransplant survival rates for patients with cPRAs > 98% have not changed despite patients receiving more compatible kidneys through KAS.[22] In this study, active AMR occurred in 38.9% of the patients, all responded to treatment but we know AMR affects long-term outcomes. This is similar to the rate of AMR associated with desensitization using plasmapheresis and low-dose IVIg.[28] Another important consideration is the comorbidities that accumulate in the highly HLA sensitized patients that often manifest as extended years on dialysis associated with increasing risk of death or medical instability prohibiting or degrading results of an eventual transplant.

In conclusion, imlifidase treatment was well tolerated, converted positive crossmatches to negative, and enabled patients with a median cPRA of 99.83% to undergo kidney transplantation resulting in good kidney function and graft survival at 6 mo. Patients included in this pivotal study were the most highly sensitized patients who are the most difficult to desensitize and successfully transplant, especially from DDs. The results from this study demonstrate that desensitization with imlifidase represents a therapeutic strategy that can operationalize desensitization, allowing life-saving transplants from DD and LD to proceed in highly sensitized kidney transplant candidates with minimal risk of hyperacute rejection.

ACKNOWLEDGMENTS

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