INTRODUCTION

Allosensitization represents one of the most formidable obstacles in transplantation. Here, an immunologic barrier prohibits access to transplantation for the most highly-HLA sensitized individuals. In 2014, a revised kidney allocation system (KAS) in the United States dramatically improved transplant rates for sensitized patients. However, longer term analysis revealed that transplant rates for the most highly-HLA sensitized (calculated panel reactive antibodies [cPRA] >99.9%) were not impacted by the revised KAS and these patients were more likely to die or be removed from the list than transplanted. Even within the highly sensitized, there are marked differences in transplant rates where the post-KAS transplant rate for candidates with cPRA >99.9% is six times less than that for candidates with a cPRA 99.5%–99.9% despite both groups receiving similar priority under the revised KAS. This information has led to a focus on development of clinical trials for desensitization therapies aimed at this group that has not benefited from the KAS.

Several reports have documented the benefits of desensitization for improving access to transplantation and enhancing long-term patient survival compared to dialysis. However, current therapies are often incomplete, especially for those in the highest cPRA categories. Therapeutic approaches that can rapidly and durably remove anti-HLA antibodies are needed to improve access to transplantation for highly sensitized patients.

The IgG-degrading enzyme derived from Streptococcus pyogenes (Imlifidase, Hansa Biopharma) is a novel agent that cleaves all four human subclasses of IgG and has therapeutic potential for HLA desensitization in kidney transplantation and antibody-mediated rejection. Data from clinical trials in kidney transplantation demonstrated rapid degradation of anti-HLA donor-specific antibodies facilitating HLA-incompatible transplantation, which led to conditional approval of imlifidase by the European Medicines Agency for desensitization in kidney transplant recipients of a deceased donor with a positive cross match. Important considerations arising from the early experiences with imlifidase on kinetics of donor-specific antibodies after administration, timing of complementary therapeutic monoclonal or polyclonal IgG antibodies, and interference with cross match assays should be recognized as imlifidase emerges as a therapeutic agent for clinical transplantation.

KEYWORDS
alloantibody, clinical research, desensitization, immune modulation, immunosuppressant – other, immunosuppression, kidney transplantation, nephrology, practice, rejection: antibody-mediated (ABMR), sensitization
circulating donor-specific antibodies (DSA), removing their capacity to induce complement-dependent cytotoxicity (CDC) and antibody-mediated cellular cytotoxicity (ADCC), would help improve access to transplantation for highly sensitized patients.

The IgG-degrading enzyme derived from Streptococcus pyogenes (IdeS, Imlifidase, GenBank accession number, ADF13949.1) is a recombinant cysteine protease derived from S. pyogenes produced recombinantly in Escherichia coli which has the capacity to cleave all four human subclasses of IgG with precise specificity (Figure 1A). IgG-degrading pathways are a common evolutionary strategy used by pathogenic bacteria to defeat host humoral immune responses. Imlifidase hydrolyzes IgG at Gly236 in the lower hinge region of human and rabbit IgG heavy chains.6,7 Cleavage at this site is critical, since the Fc region of IgG interacts with Fcγ receptors on immune cells and binds complement components that initiate immune injury. Thus, the hydrolyzation of IgG molecules with removal of Fc fragments completely inhibits IgG-mediated ADCC and CDC, two processes that are critical for initiation and perpetuation of AMR (Figures 1B and 2A,B). The ability to degrade pathogenic antibodies has important implications for a number of human diseases.8

Imlifidase was first studied for desensitization of highly-HLA sensitized patients for kidney transplantation9 and has received conditional approval for desensitization in deceased donor kidney transplant recipients with a positive cross match from the European Medicines Agency (EMA).10 Additionally, imlifidase is being investigated for treatment of AMR (NCT03897205).

The purpose of this review is to discuss important clinical and therapeutic considerations that have emerged from the early

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**FIGURE 1**

(A) Mechanisms of action of IdeS (IgG endopeptidase). (B) Implications of IdeS on IgG-mediated effector functions

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pre-clinical and clinical experiences that should be recognized as imlifidase matures from investigational to commercial use.

2 | EVOLUTION OF IMLIFIDASE IN CLINICAL TRIALS

The primary mechanism of action of imlifidase involves cleavage of IgG. This was demonstrated in a phase I trial where imlifidase 0.12–0.24 mg/kg body weight was administered to healthy volunteers. Within minutes, single cleavage of one of the two heavy chains of IgG was observed and by 4–6 hours, the entire IgG pool was degraded into F(ab’)2 and Fc fragments. De novo IgG production was detected as early as 2–3 days after treatment and by three weeks, intact IgG constituted the main IgG fraction in serum. However, total intact IgG levels remained below baseline for 2 months or more.

After treatment with imlifidase, the resultant F(ab’)2 fragment can still bind antigen; however, both CDC and ADCC are disarmed in the absence of an intact Fc. In a study of eight sensitized patients awaiting kidney transplantation given one to two doses of imlifidase 0.12–0.25 mg/kg, there was a significant reduction in CDC panel reactive antibody (PRA) reactivity seen as early as one hour post-infusion with maximal effect seen by 24 hours. Additionally, single antigen bead assays revealed that C1q-binding antibodies were completely eliminated within one hour of treatment and remained undetectable beyond one week in most patients.

In vitro studies indicate that natural killer (NK) cell activity and ADCC are also inhibited following treatment with imlifidase. NK cell activation measured with an intracellular cytokine flow cytometry assay of intracellular IFN-γ production was significantly reduced in a dose-dependent manner when peripheral blood mononuclear cells (PBMCs) coated with sera from highly-sensitized patients were treated in vitro with escalating doses of imlifidase. A similar observation was found on ADCC using sera from highly-sensitized patients pre-treated in vitro with imlifidase and were corroborated using banked sera from imlifidase-treated patients, where significant reductions in NK cell activity were seen comparing sera obtained before and after treatment. These experiments validate that ADCC requires intact IgG Fc binding to PBMC Fcγ receptors and cannot be initiated in the presence of a cleaved Fc. Another important observation from this study was the ability of imlifidase to cleave pathogenic IgG bound to cellular targets. This suggests that imlifidase would likely have utility in treatment of AMR not only by cleaving circulating IgG but by disarming pathogenic IgG bound to allogenic targets, thus limiting ADCC- and CDC-mediated injury.

Imlifidase not only cleaves free IgG but also B cell receptors (BCR) on CD19+/CD27+, IgG-memory B cells, temporarily rendering them unable to bind and respond to their specific antigen. Thus, a temporary reduction in BCR-dependent differentiation of antigen-specific memory B cells into plasma cells or long-lived plasma cells might be expected following imlifidase treatment.
3 | CLINICAL EXPERIENCE WITH IMLIFIDASE IN KIDNEY TRANSPLANTATION

The published clinical experience with imlifidase to date has involved its use for desensitization in kidney transplantation. The initial experience was published in 2017 as a report of two independent phase 1–2 studies involving 25 patients from Sweden (n = 11) and the United States (n = 14) undergoing kidney transplantation, 22 of whom had DSA, 18 of whom had a positive flow cytometry cross match, and two of whom were CDC crossmatch-positive. Patients were given imlifidase 4–6 hours before transplant followed by horse anti-thymocyte globulin (ATG) in the Swedish cohort and alemtuzumab in the United States cohort. For the Swedish study, horse ATG was used instead of the more commonly used rabbit ATG because rabbit, but not horse, IgG is susceptible to cleavage by imlifidase. Additionally, patients in the United States study were treated with IVIG 2 g/kg on days 7–14 and rituximab 375 mg/m² on days 14–21 after transplant.

Within six hours of treatment, there was near-complete elimination of DSA in all patients. However, rebound DSA developed by day 7–14 among patients in the Swedish study with 3/11 patients developing C4d+ AMR. In comparison, rebound DSA was less common and developed later among patients in the United States study. Two of 14 patients in the United States study developed AMR at 2 and 5 months posttransplant. DSA remained absent up to 12 months after transplant in most patients which was attributed to the use of IVIG and rituximab to prevent antibody rebound in the United States study.

Additional data on imlifidase for desensitization in kidney transplantation was recently published. The Highdes trial was a single-arm open label phase 2 study that enrolled 19 patients with an incompatible living or deceased donor from the United States, Sweden, and France, where the median cPRA was 99.83% (range 77.31%–100.0%). Imlifidase 0.25 mg/kg was given before transplant with an additional 0.25 mg/kg dose allowed if a negative cross match was not achieved after the first dose. Patients were induced with horse ATG or alemtuzumab, IVIG 2 g/kg on post-transplant day 7, and rituximab 1 gram on day 9. Of 19 patients enrolled, 18 underwent transplantation. One patient experienced an infusion-related reaction and did not complete the treatment; this transplant was not performed because of a persistently positive cross match. Seventeen patients had a negative cross match after treatment and only one patient underwent transplant with a positive cross match. This patient had a positive T-flow cross match that did not correlate with the DSA profile and was transplanted successfully. At six months, patient survival was 100% and graft survival was 89%.

In a pooled study of four open label single-arm, phase 2 clinical trials, long-term outcomes of 39 highly-HLA sensitized (median cPRA 99.62%) and crossmatch-positive patients transplanted after desensitization with imlifidase therapy was reported. The incidence of AMR was 38%. Among patients who experienced AMR, the MFI of the immunodominant DSA pre-imlifidase treatment was significantly higher (median MFI ~13 000, IQR 6500–22 000) compared to those who did not develop AMR (median MFI ~6000, IQR 3000–9000; p < .05). At three years, patient survival was 90%, allograft survival was 84%, and the mean eGFR was 55 ml/min/1.73 m². A sub-group analysis of deceased donor recipients with cPRA ≥99.9% considered unlikely to be transplanted without imlifidase desensitization exhibited similar graft survival and eGFR to the overall population but a higher AMR rate. These data suggest that imlifidase desensitization could be useful for the most highly-HLA sensitized patients unlikely to receive a transplant under the current KAS.

Given the initial experience with imlifidase for desensitization in kidney transplantation, a study is now being performed investigating its use for treatment of AMR (NCT03897205). This is a randomized study enrolling patients from the United States, France, Australia, Germany, and Austria that compares imlifidase 0.25 mg/kg versus 5–10 sessions of plasmapheresis among kidney transplant patients with acute or chronic active AMR. The primary endpoint is the maximum reduction in DSA MFI within 5 days following the start of treatment. Additional secondary endpoints will also be assessed, including DSA and HLA antibody levels up to 180 days after treatment, change in eGFR from baseline to 180 days, and changes in histology and mRNA transcriptional profile were assessed by MMDx from baseline to 29 and 180 days. Thirty patients are anticipated to be enrolled and the study is now underway.

4 | KINETICS OF ANTIBODY REBOUND FOLLOWING TREATMENT WITH IMLIFIDASE

There is a signal from the early desensitization experience in kidney transplantation that DSA can rebound following treatment with imlifidase. Although treatment with IVIG and rituximab effectively suppressed antibody rebound in the initial phase 1–2 United States trial, DSA rebound was observed in 16/18 patients through six months in the Highdes trial, generally occurring between 3 and 14 days after transplant. Additionally, 8/18 participants (44%) experienced AMR. Of these, six patients had definite, one patient had presumed, and one patient had subclinical AMR. Most cases of DSA rebound were to or below baseline levels and then decreased thereafter. At 6 months, seven patients had DSA with MFI ≥3000, although only one had DSA above baseline levels.

Rebound patterns after imlifidase treatment for desensitization was recently examined in 10 patients for total IgG, anti-imlifidase IgG, DSA, and vaccine specific IgG titers. Results from this analysis showed that total IgG rebound was generally detected between 3 and 6 days with substantial variability. DSA IgG rebounded faster than total but leveled at a steady state at or below the time 0 determinations. Anti-imlifidase antibodies rebounded at similar rates, but to a higher titer compared to DSA IgG. Anti-vaccine antibodies rebound was similar to that seen with total IgG. Thus, antibody rebound seen with imlifidase is consistent with other desensitization strategies and remains a major
obstacle in HLA-incompatible transplantation. These observations underscore the need for better anti-rebound therapies to help prevent DSA rebound and AMR.

The observation of antibody rebound is consistent with an earlier study of imlifidase in healthy volunteers. Rebound antibodies were also seen in a study using imlifidase for treatment of anti-glomerular basement membrane disease. Re-population of anti-HLA antibodies can begin as early as 2–3 days after treatment but the duration of suppression can be variable, with levels remaining below baseline for 2 weeks in some and more than two months in others. Most cases of rebound DSA responded favorably to antibody reduction therapies in the Highdes trial, including plasmapheresis, IVIG, rituximab, and bortezomib.

Given the existing experience in kidney transplantation, current and future clinical trials of imlifidase for transplantation will administer it in combination with other therapies to inhibit repopulation of antibodies. Moving forward, the strategy will be to time these therapies in a sequence that optimizes the efficacy of each agent and avoids interactions. In the ongoing AMR trial, IVIG 2 g/kg will be given three days after imlifidase administration and anti-CD20 five days after IVIG. Although this strategy was effective in the phase 1–2 United States desensitization trial, it was less successful at preventing antibody rebound in the phase 2 Highdes trial. Close monitoring for DSA rebound with prompt intervention with plasmapheresis and/or IVIG or other agents will likely be necessary if treating with imlifidase.

5 | SAFETY

Data from the early imlifidase trials have not reported significant safety concerns. In the initial phase 1–2 trials, there were 13 infection events, nine of which were classified as either unrelated or unlikely to be related to imlifidase treatment. There was only one viral infection that was due to parvovirus and was considered possibly related to treatment. Similarly, in the Highdes trial, there were no serious infections reported by the investigators as related to imlifidase and only one non-serious infection that was considered probably related (urinary tract infection). There were seven treatment-emergent adverse events considered possibly or probably related to treatment in the Highdes trial. These included two infusion-related reactions, one of which was considered related to the treatment where the infusion was discontinued. Imlifidase infusion was temporarily halted in the other patient. No infusion-related reactions were reported in the initial phase 1-2 trials.

6 | CLINICAL SIGNIFICANCE OF ANTI-IMLIFIDASE ANTIBODIES

Given that imlifidase is derived from Streptococcus pyogenes, endogenous anti-imlifidase antibodies are prevalent even among patients naïve to imlifidase if previously exposed to Streptococcus pyogenes. Anti-imlifidase IgG antibodies are cleaved after treatment with imlifidase but can return approximately one week later and peaks around 2 weeks. There is concern that re-development of anti-imlifidase antibodies after initial treatment may limit its efficacy if re-treatment is required. If clinically necessary, a second dose of imlifidase is allowable but only within 24 hours of the first dose due to the pharmacokinetics of imlifidase and the pharmacodynamics of the anti-imlifidase IgG antibodies.

7 | IMPLICATIONS FOR CONCOMITANT ADMINISTRATION OF IMLIFIDASE WITH THERAPEUTIC IgG ANTIBODIES

Therapeutic human monoclonals (i.e., alemtuzumab and anti-CD20 antibodies) and polyclonal rabbit IgG antibodies (Thymoglobulin) are commonly used as desensitization or induction agents in HLA-incompatible transplantation and may be inactivated by imlifidase. In the original trials of imlifidase in highly-HLA sensitized patients, there was significant consideration given to how to avoid imlifidase inactivation of therapeutic antibodies. Initial studies with alemtuzumab showed that imlifidase effectively inactivated the antibody, but in serum obtained 4 days after imlifidase administration, this effect was minimal. Based on these early unpublished observations, we waited 4 days post-imlifidase infusion to administer alemtuzumab and were able to effectively achieve T cell depletion. More recently, similar experiments were performed evaluating the impact of imlifidase on cleavage patterns of rabbit ATG (Thymoglobulin). Here, serum samples obtained pre-imlifidase through 14 days post-imlifidase from 11 healthy volunteers were incubated with clinically relevant fixed concentrations of rabbit ATG (50 mg/ml).

| Medicinal product | Recommended time interval after imlifidase administration |
|-------------------|-------------------------------------------------------------|
| Equine anti-thymocyte globulin (Atgam®) | No time interval needed (can be administered concomitantly with imlifidase) |
| Eculizumab (Soliris®) | 12 hours |
| Intravenous immunoglobulin (IVIG) | 4 days |
| Alemtuzumab (Campath®) | 1 week |
| Adalimumab (Entyvio®) | 3 days |
| Basiliximab (Simulect®) | 5 days |
| Denosumab (Xgeva®) | 7 days |
| Etanercept (Enbrel®) | 7 days |
| Rituximab (Rituxan®) | 7 days |
| Rabbit antithymocyte globulin (rATG, Thymoglobulin®) | 7 days |
| Belatacept (Nulojix®) | 7 days |

Although not tested, the recommend time interval is recommended for anti-CD20 biosimilars.
Serum imlifidase concentrations rapidly declined to near baseline at 96 hours. In addition, the impact of imlifidase on cleavage of rabbit ATG analyzed by SDS PAGE and Western blot was rapid and complete at 1 hour post-infusion but was minimal at 96 hours. The authors conclude that rabbit ATG may be started as early as 4 days post-imlifidase treatment taking into consideration that a proportion of the first dose may be cleaved in some patients but with a reasonable expectation of efficacy. Thus, for human monoclonals and rabbit ATG, administration 4 days after imlifidase should avoid antibody cleavage and ensure efficacy.

The interaction of imlifidase with IVIG is more complex and bidirectional. IVIG likely contains neutralizing antibodies against imlifidase, which may inactivate imlifidase, especially if IVIG is given before imlifidase treatment. Since the half-life of IVIG is 24–28 days, this should be considered before imlifidase administration in patients recently treated with IVIG. In clinical studies, IVIG was not administered within 4 weeks before imlifidase infusion and was not given until 1 week post-imlifidase administration. We recently reported on the impact of IVIG on circulating IgG concentrations when patients were given a single 2 gm/kg infusion on dialysis (maximum dose 140 g). IgG levels increased approximately 3-fold following IVIg administration and slowly returned to baseline by day 28. It is not known if supra-physiologic levels of IgG in the circulation would impede the efficacy of imlifidase aimed at pathogenic antibodies and needs to be studied.

Table 1 describes the recommended time intervals for administration of antibody-based therapeutics with imlifidase.

8 | CONSIDERATIONS OF IMLIFIDASE USE WITH ASSAY INTERFERENCE

Imlifidase generates an intermediate single cleaved IgG (sclG) that may be indistinguishable from intact IgG when evaluated with assays using anti-Fc detection methods. To avoid false positive results with the complement-dependent cytotoxicity crossmatch (CDCXM), the use of anti-human globulin (AHG) should be avoided. If used, it should be confirmed that the AHG is directed against the Fc-porton and not against the Fab-porton of the IgG, which will not allow correct readout of a CDCXM in an imlifidase-treated patient. sclG may also produce a similar false-positive when evaluated with the LABScreen™ single antigen bead assay as HLA-binding sclG is recognized by the Fc-specific detection antibody used in LABScreen™. In contrast, comparative assessment with the C1qScreen™ indicated that only intact IgG were able to fix C1q and no signal was generated from either sclG or fully cleaved IgG.

9 | CONCLUSIONS

Imlifidase is a promising agent that has conditional approval from the European Medicines Agency for desensitization in kidney transplant recipients of a deceased donor with a positive cross match. The rapid and pronounced effect of imlifidase on DSA makes it a promising treatment for desensitization and AMR in combination with additional agents that suppress antibody production. Because imlifidase non-specifically degrades IgG, therapeutic monoclonal antibodies or rabbit ATG (Thymoglobulin) should be administered at least four days after treatment. Clinical trials are currently being developed and conducted to further establish its efficacy as a desensitization agent and treatment for AMR and are expected to change the paradigm for how anti-HLA antibodies are treated in transplantation.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data sharing not applicable as no datasets were generated or analyzed for this manuscript.

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