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Belgian Consensus Guidelines Within Eurotransplant on Imlifidase-enabled Deceased Donor Kidney Transplantation in Highly Sensitized Patients

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Abstract. Highly sensitized (HS) kidney transplant (KTx) candidates, that is, typically considered internationally as those with panel-reactive antibody levels of >85%, remain a substantial subpopulation of patients with low chance of receiving a compatible organ. Among its many objectives, Eurotransplant—an international transplant organ allocation network serving 8 European countries—aims to improve the management of HS KTx candidates through its prioritized "acceptable mismatch" (AM) program. However, despite this program, some HS patients within the Eurotransplant network who have panel-reactive antibodies >85% still cannot access donor kidneys. For patients who remain in the AM program for ≥3 y without undergoing transplantation, an additional prioritization strategy has been implemented. This involves defining further AMs to allow for desensitization with imlifidase within the AM program. While the AM desensitization program was being developed, the Belgian Imlifidase Scientific Expert Group within the Eurotransplant network independently recognized the need for guidelines on imlifidase desensitization for real-world use in HS KTx candidates (including both AM and Eurotransplant Kidney Allocation System patients). This article describes the consensus guidelines they subsequently developed, which represent a model that any center within the Eurotransplant region could adapt or apply in clinical practice when treating HS KTx candidates who require imlifidase desensitization. The consensus guidelines include patient eligibility criteria for imlifidase treatment that align with Eurotransplant allocation rules and incorporate posttransplant management strategies for HS patients. These guidelines are dynamic and will be reviewed and updated regularly as Eurotransplant rules change and imlifidase experience grows.

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INTRODUCTION

Highly sensitized (HS) patients (still commonly considered internationally to be those with panel-reactive antibody [PRA] levels of >85%)[1] awaiting kidney transplantation (KTx) are at a considerable disadvantage for being offered compatible organs,[2] because their immunization status results in positive crossmatch (XM) with the vast majority of potential donors.[1,3,4] Additionally, the chance of finding a living donor to whom they do not harbor (HLA-specific antibodies is very low.[5]

For many reasons, HS KTx candidates continue to accrue rapidly on transplantation waiting lists.[6] Within the 8 countries served by Eurotransplant (www.eurotransplant.org)—Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia—the proportion of transplant candidates with a PRA level ≥85% awaiting KTx rose from 2.0% in 2011 to 5.6% in 2019.[6] Compared with less-sensitized transplant candidates, across the Eurotransplant region, patients with calculated (c)PRA levels of >85% face longer waiting times and lower chances of receiving an organ offer[7]; such patients are often those who are not transplanted within 2–3 y of joining the acceptable mismatch (AM) program or those who do not fulfill the AM program inclusion criteria. Also, data from Brazil,[8] France,[9] and South Korea[10] clearly indicate that transplant candidates with PRA levels of ≥85% remain unlikely to receive donor kidneys.

Notably, in the United States, the widespread prioritization of HS KTx candidates appears to have had a positive impact, reducing waiting times for organ allocation. US-based patients with PRA 85%–99% now appear to have similar waiting times to those with PRA levels of <80%.[2] Nevertheless, US-based patients with PRA levels of >99.9% remain particularly disadvantaged in terms of access to transplantation.[2] The picture is similar in Europe, among extremely HS transplant candidates. For example, a German subgroup analysis of HS patients on the Eurotransplant Kidney Allocation System (ETKAS) waiting list found that those with a virtual PRA level of >95% were particularly disadvantaged.[11]

Indeed, as of November 12, 2024, the active waiting list for the Eurotransplant region comprised 148 patients with a PRA level of 99.5%, among whom 17 were in Belgium. Of these patients, 93 of 148 (including 9 people from Belgium) were in the AM program; the remainder were registered on the ETKAS waiting list. Over the 3 y before November 2024, only 4 patients with a PRA level of 99.5% on the Eurotransplant list had received KTx, 1 of whom was from Belgium. In 2023, only 5 of such patients were transferred from ETKAS toward the AM program (Frans Claas, personal communication, November 2024).

Several approaches have been developed to improve the chances of achieving KTx in HS candidates, including prioritizing these patients in organ allocation programs,[1,2] offering paired donation schemes,[5] and undertaking desensitization protocols.[12] Organizations such as the European Society for Organ Transplantation[1] and the Eurotransplant Network[13] have also published high-level recommendations to support and extend KTx in HS patients. These recommendations outline what constitutes an AM, and Eurotransplant in particular has incorporated strategies for desensitization into its guidance.

One such desensitization program involves using the IgG-cleaving enzyme imlifidase (Idefirix, imlifidase; Hansa Biopharma, Lund, Sweden).[14,15] Following the European Medicines Agency-Priority Medicine designation, imlifidase was granted a conditional European Commission marketing authorization in August 2020 and is indicated for the desensitization treatment of HS adult KTx patients with positive XM against an available deceased donor. Specifically, imlifidase is reserved for patients unlikely to be transplanted under an available kidney allocation system, including prioritization programs for HS patients.[16-18]

This article describes how, in parallel with regional initiatives, experts within the Belgian Transplant Society (BTS) developed eligibility criteria for desensitization strategies with imlifidase in HS KTx candidates. The Belgian group recognized that although Eurotransplant rapidly adapted its AM transplantation program for HS patients, there was an ongoing need for practical guidance on desensitization with imlifidase. Consequently, this article introduces the Belgian consensus guidelines for the clinical use of imlifidase. Importantly, these guidelines may be suitable for consideration in transplantation centers beyond Belgium, particularly across all countries within the Eurotransplant region: the Belgian guidance was written to align with shared components of the Eurotransplant network. The authors note that modified recommendations may be required for regions where donor pools or kidney-paired donation schemes are different from those applicable within the Eurotransplant network.

AM PROGRAM

For >30 y, the Eurotransplant network has run a pioneering AM program for HS patients. This program identifies HLA mismatches that most likely will not result in a positive XM and defines HLA antigens to which the patient has not yet reacted to alloantibodies, which might be acceptable for the patient. The AM program has increased access to KTx by prioritizing HS patients over those on the regular ETKAS waiting list; it also aims to improve the longevity of transplanted kidneys[6] (Figure 1). Notably, the Eurotransplant AM program accepts HS patients who have been on the regular ETKAS waiting list for >2 y (defined by date of first dialysis), with ≥85% PRA tested by complement-dependent cytotoxicity (CDC, in 2 different sera excluding irrelevant antibodies). Antibodies

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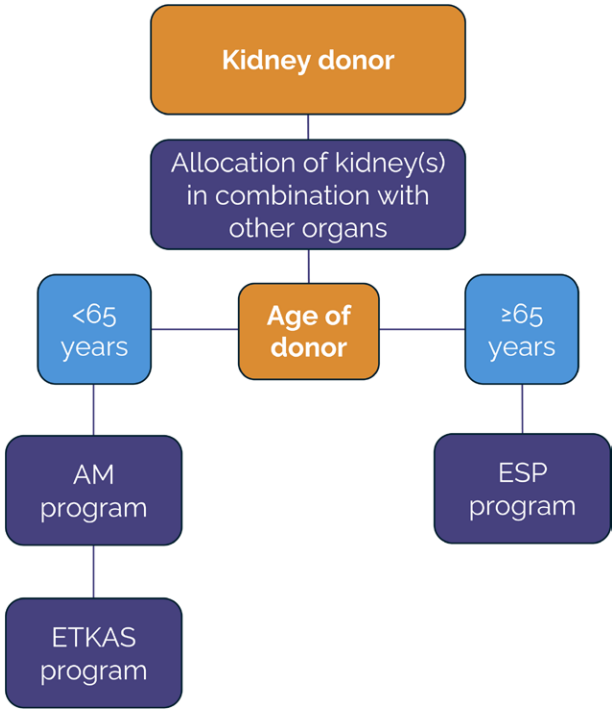

FIGURE 1. Eurotransplant, the general scheme of kidney allocation.[13] The AM Desensitization program is managed by Eurotransplant. From the ETKAS list, the imlifidase option is managed by centers without additional support from Eurotransplant to get an organ. Adapted from Eurotransplant Manual version 2023.5 (https://www.eurotransplant.org/allocation/eurotransplant-manual/)[13] AM, acceptable mismatch; ESP, Eurotransplant Senior Program (age 65 y or older); ETKAS, Eurotransplant Kidney Allocation System.

detectable only by assays are considered if they can be explained by immunizing events.[13]

However, the AM program alone does not stop the accumulation of HS KTx candidates: ~20% of patients remain wait-listed on the AM program for 3 y without receiving a new kidney.[19] There are also patients who are HS against HLA antigens but who do not meet the stringent inclusion criteria for the AM program and who remain wait-listed on dialysis for many years[11] because of a very low matching probability in ETKAS. Such patients are those with a broad sensitization status coupled with uncommon HLA phenotypes. For these people, other options are required if they ever want to achieve KTx.

Importantly, further investigation within subgroups of patients with ongoing unmet needs is required to identify strategies that may improve their chances of achieving transplantation. These investigations should start with the perspective that considerations for transplant suitability are multifactorial, going beyond the individual's immunological risk.

IMLIFIDASE DESENSITIZATION AND DELISTING STRATEGIES

To help address some of the key ongoing unmet needs for donor organs in HS patients, Eurotransplant rapidly adapted its AM program to include a desensitization strategy that uses imlifidase.[15] Imlifidase is a cysteine proteinase derived from the IgG-degrading enzyme of *Streptococcus pyogenes* that effectively cleaves preformed IgG anti-HLA antibodies, inhibiting CDC and antibody-dependent cellular cytotoxicity within hours of administration and without additional preconditioning.[14,20] Information on the Eurotransplant AM Desensitization program can be found by contacting Eurotransplant directly via https://www.eurotransplant.org/. Organizations that are members of Eurotransplant can access the desensitization program at https://my.eurotransplant.org/desensitization/program.

Imlifidase desensitization and delisting strategies should increase the potential for successful KTx among HS patients who have spent several years on either the ETKAS list or the AM program and who have very high PRA levels with a low chance of an organ offer. Delisting strategies that reduce the patient's cPRA score may consequently increase their possibility of receiving a KTx offer.[13]

In the AM Desensitization program, following Eurotransplant Kidney Advisory Committee working-group guidance and due to concerns of high antibody-mediated rejection (AMR) rates and early graft losses, possible antigens to be delisted under imlifidase were restricted to CDC-negative, solid-phase assay, and/or flow XM-positive antigens.[21]

Belgian Imlifidase Consensus Guidelines: Rationale

Within the Eurotransplant network, while the AM Desensitization program was in development, the first consensus guidelines for imlifidase use in real-world practice were drafted by the Belgian Imlifidase Scientific Expert Group. This multidisciplinary team (MDT) initiative is led by the 7 transplant centers in Belgium and endorsed by the BTS. Figure 2 presents the thinking journey and objectives of the guideline development process, and the present article provides the first ratified version of the full guidelines (version 12.0; September 2024).

Briefly, the Belgian imlifidase consensus guidelines include patient eligibility criteria for imlifidase-enabled deceased donor KTx that align with the Eurotransplant organ allocation rules. They also incorporate ratified guidance for the posttransplant management of HS KTx recipients. Notably, although some points may require further clarification outside the Belgian region, these consensus guidelines may be relevant in any country where imlifidase is indicated for HS candidates, certainly within transplantation centers across the entire Eurotransplant network.

Importantly, the Belgian imlifidase consensus guidelines represent a dynamic, common-practice framework that facilitates the generation and analysis of further data on this orphan-drug product. Consequently, all aspects of the guidelines are subject to change as experience evolves and the Eurotransplant network refines its criteria: the Belgian guidelines will always remain aligned with Eurotransplant policies. These guidelines are endorsed by the BTS and are expected to be reappraised and updated regularly in alignment with clinical experience and emerging data.

BELGIAN IMLIFIDASE CONSENSUS GUIDELINES

Introduction

This article presents the first iteration of the BTS imlifidase consensus guidelines. These guidelines will be updated as clinical experience and data evolve, and will always align with Eurotransplant guidance.

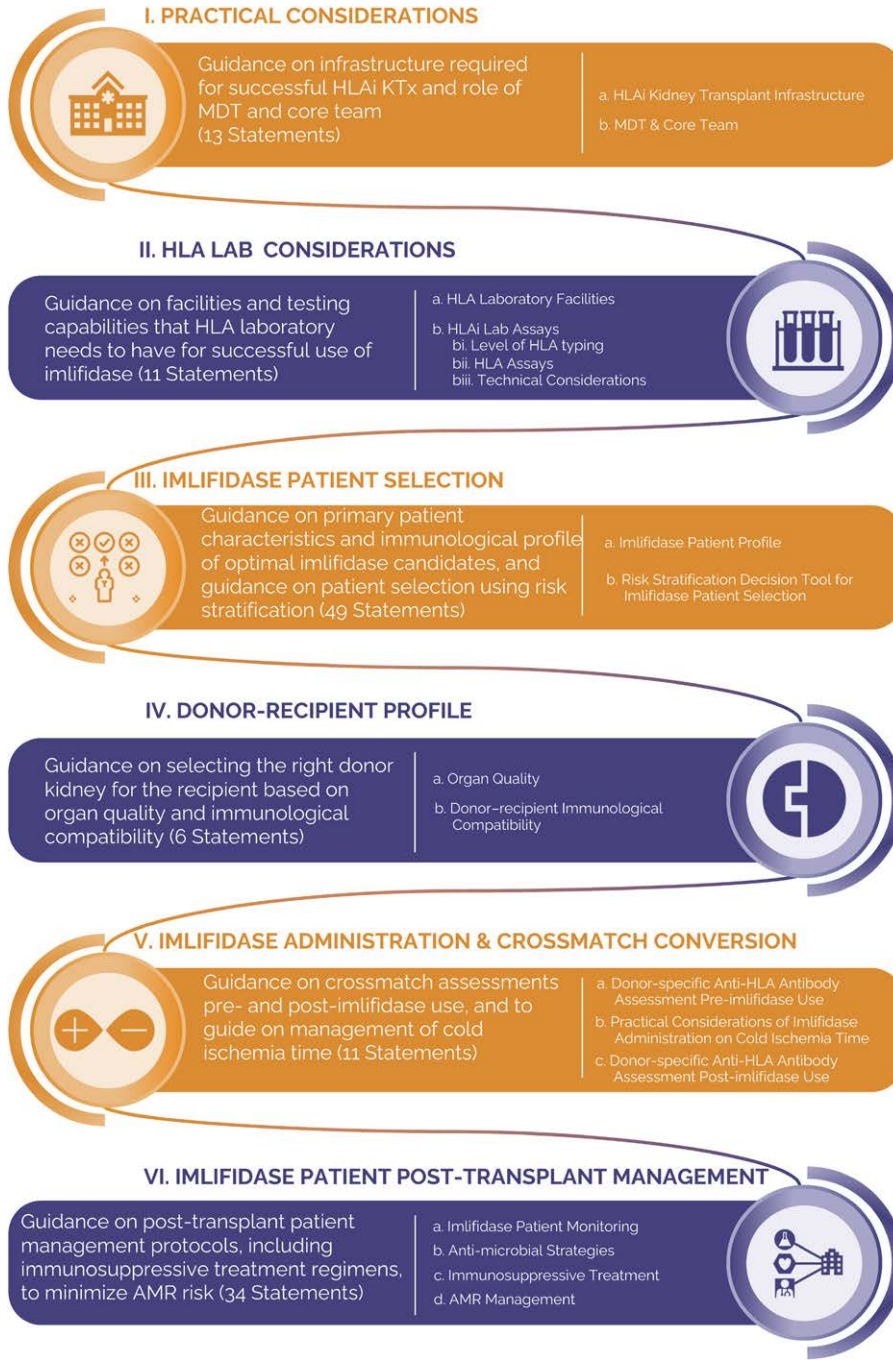

FIGURE 2. Thinking journey and objectives used by the Belgian Transplant Society in the development of consensus guidelines for real-world imlifidase use in kidney transplantation. AMR, antibody-mediated rejection.

Practical Considerations

Infrastructure

MDT and imlifidase core reference team

- Before planning transplantation using imlifidase for desensitization, an MDT with previous experience in KTx and management of AMR (including prompt histological diagnostics) should be in place in each transplant center.
- From this MDT, a dedicated core reference team for imlifidase use should be identified, with the minimum inclusion requirements of a nephrologist, a transplant surgeon, an HLA specialist, and a transplant coordinator.
- All patients eligible for imlifidase therapy must be discussed with the MDT, and the whole MDT should be familiar with the imlifidase clinical protocol before initiating the imlifidase treatment process. Refinements to the imlifidase national clinical protocol (with regard to microbial prophylaxis as AMR treatment) must be discussed by the MDT on a case-by-case basis and adapted to follow each center's local practice.
- The imlifidase core reference team will need to be available at all times (24/7 coverage) to treat/advise as soon as an organ offer is made.

HLA/Pathology Laboratory Considerations

HLA Laboratory Availability

- All-hours availability is required (24/7).

XM Conversion Capabilities

- To confirm conversion to a negative XM after imlifidase administration, a CDC-XM must be performed. For other prospective or retrospective XM tests, acceptable and available platforms are either CDC-XM or flow cytometry crossmatch (FC-XM) on T and/or B cells or single antigen bead (SAB) assays for virtual XM (V-XM).
- CDC-XM on B and T cells post–imlifidase administration must be performed prospectively and must be negative before proceeding with transplantation.
- The turnaround time should be ~4–6 h for CDC-XM.
- Routine CDC-XM assays should not be amplified with anti-human globulin, so this should not be an issue when using imlifidase in Belgium, where CDC-XM without anti-human globulin is already a common practice.

Donor-Specific Antibody Analysis

- Timing of sample collection is the responsibility of the treating physician. Samples should be taken according to clinical need and stored if deemed appropriate; they must also conform to European Federation for Immunogenetics standards[22] and Eurotransplant Chapter 10 requirements.[23]

Renal Biopsies

- The turnaround time for results should ideally be <2 working days; it is recognized that processing biopsies at weekends is unlikely to be feasible in most centers. (In urgent situations, a prompt review of a frozen section of the renal tissue should be obtained, awaiting the results of the processed and stained histology samples).
- It is advised that if there is any suspicion of rejection, treatment should proceed without a requirement to wait for biopsy results.

Imlifidase Patient Selection

General Patient Characteristics

- Patients should be adults aged 65 y or younger and in a medically and physically sufficient state of health to support surgery and intensive immunosuppressive therapy.
- Patients should currently be on dialysis.
- Patients may have pressing clinical needs requiring an expedited KTx (Eurotransplant high urgency list).
- Identify any exclusion criteria:
  - It is advised that patients with atypical hemolytic uremic syndrome be considered as being at high risk of disease recurrence, and thus, the concept of desensitization in these patients should be approached with caution.
  - Please consult the imlifidase Summary of Product Characteristics (SmPC)[14] for the full exclusion criteria.

Eligibility Criteria

- Inclusion on Eurotransplant kidney waiting list; either:
  - Inclusion in the Eurotransplant AM program for at least 36 mo (or adapted according to the most recent criteria of Eurotransplant).
  - Inclusion in the Eurotransplant AM "Desensitization program" (imlifidase subgroup) as a possible candidate for treatment with imlifidase.

  or
  - Inclusion in the ETKAS list for at least 48 mo (or adapted according to the most recent criteria of Eurotransplant).
- Assessment and approval by the Belgian Imlifidase Scientific Expert Group on imlifidase in collaboration with the Orphan Drug College.
- cPRA level ≥85%.
- An "AM" donor according to the most recent Eurotransplant criteria for the AM "Desensitization program" (imlifidase subgroup).[13]
- No positive T-cell CDC-XM with the potential donor (based and estimated on V-XM – at the time of organ offer) before imlifidase administration.
- Patients remaining in ETKAS but not eligible for the current AM program still have options within the system:
  - Regular consideration of the list to avoid outdated quarterly screening.
- Careful delisting of unacceptable antigens to increase matching probability.
- Imlifidase treatment outside the Eurotransplant AM program after careful delisting of unacceptable HLA antigens and through ETKAS allocation.

Donor-Specific Antibody Characteristics and XM

Delisting strategy (removal of unacceptable HLA antigens)

- There is no advised limitation on the number of delisted unacceptable HLA antigens. This should be decided on an individual basis by the MDT depending on the patient's history, comorbidities, and specific immunological profile.
  - A practical approach is advised whereby sufficient unacceptable HLA antigens are delisted to enable offers. However, delisting many unacceptable antigens may lead to offers with many mismatches; such organs should be refused where possible. It is not mandatory to accept the first organ offer.
  - Delisting unacceptable HLAs should aim for a reasonable and clinically relevant increase in "matching probability" to increase the patient's chances of receiving a kidney offer.
  - It is advised to aim for a balance between delisting too many unacceptable HLA antigens and the avoidance of refusing multiple organ offers, as each organ offer refusal leads to increased cold ischemia time (CIT) of organs that may subsequently be offered to another patient.
  - Adaptation of the patient's specific profile within the Eurotransplant Network Information System (ENISnext) database must be performed when delisting unacceptable HLAs/allowing more mismatches (eg, more than a minimal 1 B 1 DR match).
- A stepwise delisting approach is advised; consider delisting as many unacceptable antigens as deemed appropriate according to the following parameters:
  - Delisting of unacceptable antigens for which the corresponding anti-HLA antibodies can be detected in a current CDC antibody screening and/or identification test "is not allowed," as they will cause a positive T-cell CDC-XM if the donor bears the corresponding antigens (see Eligibility criteria section).
  - Start delisting unacceptable antigens for which corresponding anti-HLA antibodies have a median fluorescence intensity (MFI) threshold of <2000 on the most recent (≤3 mo) and every relevant historical serum sample available after 1/16 serum dilution.

- Then, delist unacceptable antigens for which corresponding anti-HLA antibodies have an MFI threshold <6000 after 1/16 serum dilution for both the most recent (≤3 mo) and every relevant historical serum sample available.
- Avoid delisting unacceptable HLA antigens for which the corresponding antibody has shared eplets with cytotoxic antibodies or any antibodies from previous sensitizing events.
- Consider the additional contributing risk factors when assessing HLA antibody strength and the potential post-transplant rebound risk.
- Anti-HLA A, B, DR, and DQ (including DQA) antibodies should be considered; however, there is insufficient evidence in the literature for the consideration of anti-HLA DPA1/DPB1 and HLA-C antibodies to be essential.

At the time of the organ offer, the patient should have the following:

- Donor-specific antibody (DSA): (neat on current serum) MFI of cumulative delisted DSA A, B, DRB1, DQA1, DQB1 (with the exception of DP, Cw) ≥6000 MFI with at least 1 DSA ≥2000 MFI; considering the SAB-HLA assay (Immucor, Werfen, Peachtree Corners, GA) currently used in all Belgian HLA laboratories.
- Positive V-XM pre–imlifidase administration on a recent serum sample with an estimated positive B and/or T-cell FC-XM and negative T-cell CDC-XM. (NB: the following supplementary information is not part of the BTS guidelines but should be considered: and/or positive B-cell CDC-XM but negative T-cell CDC-XM [for HS ETKAS patients].)

Donor–Recipient Profile

Allocation Programs

- All organs in Belgium will be allocated under the ETKAS/AM programs (for AM: via the "AM Desensitization program").

Allocation Strategy

- It is acceptable to use V-XM for organ allocation.
- Each organ should be quality checked before administration of imlifidase for parameters such as organ anatomy, texture, and so on; however, as Belgium is a small territory with an established trust in colleagues' assessments, the decision may be made collaboratively.

CIT Strategy

- It is acceptable to use V-XM for the organ allocation decision.
- Organ damage from extended CIT ought not to be an issue in Belgium in cases using national harvesting. In all other cases, an organ quality check is deemed appropriate before imlifidase administration.

Imlifidase Administration and XM Conversion

- Appropriate donor samples (donor cells [spleen] and ethylenediaminetetraacetic acid samples) must be obtained as soon as possible and shipped to the HLA laboratory to speed up the XM pre– and post–imlifidase administration to minimize CIT.

XM pre–imlifidase administration

- Positive V-XM pre–imlifidase administration on a recent serum sample with an estimated positive B- and/or T-cell FC-XM and negative T-cell CDC-XM. (NB: The following supplementary information is not part of the BTS guidelines but should be considered: and/or positive B-cell CDC-XM but negative T-cell CDC-XM.)
- A CDC-XM (on T and B cells pre–imlifidase administration) must be performed, at least retrospectively, using donor cells and serum samples pre–imlifidase administration (Figure 3).

XM post–imlifidase administration

- A physical negative T- and B-cell CDC-XM post–imlifidase administration is deemed mandatory by the expert group to proceed with transplantation.
- Samples for confirmation of XM conversion must be taken 4–6 h post–imlifidase administration.
- If the CDC-XM after the first dose of imlifidase is positive, administration of a second dose of imlifidase can be considered. In this case, a sample for confirmation of XM conversion will be taken 2 h after administration of the second dose of imlifidase, and a physical negative CDC-XM is deemed mandatory to proceed with transplantation (Figure 3).

Imlifidase reconstitution and administration

- Imlifidase dosage: 0.25 mg/kg in a 15-min intravenous infusion.
- Care should be taken to follow the imlifidase SmPC instructions fully.[14]
- Of special note: a sterile, inline, nonpyrogenic, low-protein binding filter (pore size of 0.2 μm) must be used.

Imlifidase redosing

- Redosing with imlifidase can be considered where negative CDC-XM conversion is not confirmed 4–6 h post–imlifidase administration.
- Imlifidase redosing must be performed within 24 h after the first dose as indicated in the imlifidase SmPC.[14]

Associated Therapies

Premedication Imlifidase Administration

- Premedication with corticosteroids (CS) and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant center practices:
  - CS: the CS imlifidase premedication will be part of the classical steroid induction scheme administered pre-transplant consisting of 500 mg methylprednisolone (or equivalent, depending on center practice) on day 0 (D0) pretransplantation. (NB: The following supplementary information is not part of the BTS guidelines but should be considered: consult the imlifidase SmPC[14] for details on CS administration.)
- Antihistamine: loratadine 10 mg orally or an equipotent antihistamine depending on local practice.

Prophylactic Anti-Infectives

- Prophylactic oral antibiotics covering respiratory tract pathogens should be added to the standard of care for 4 wk post–imlifidase administration.

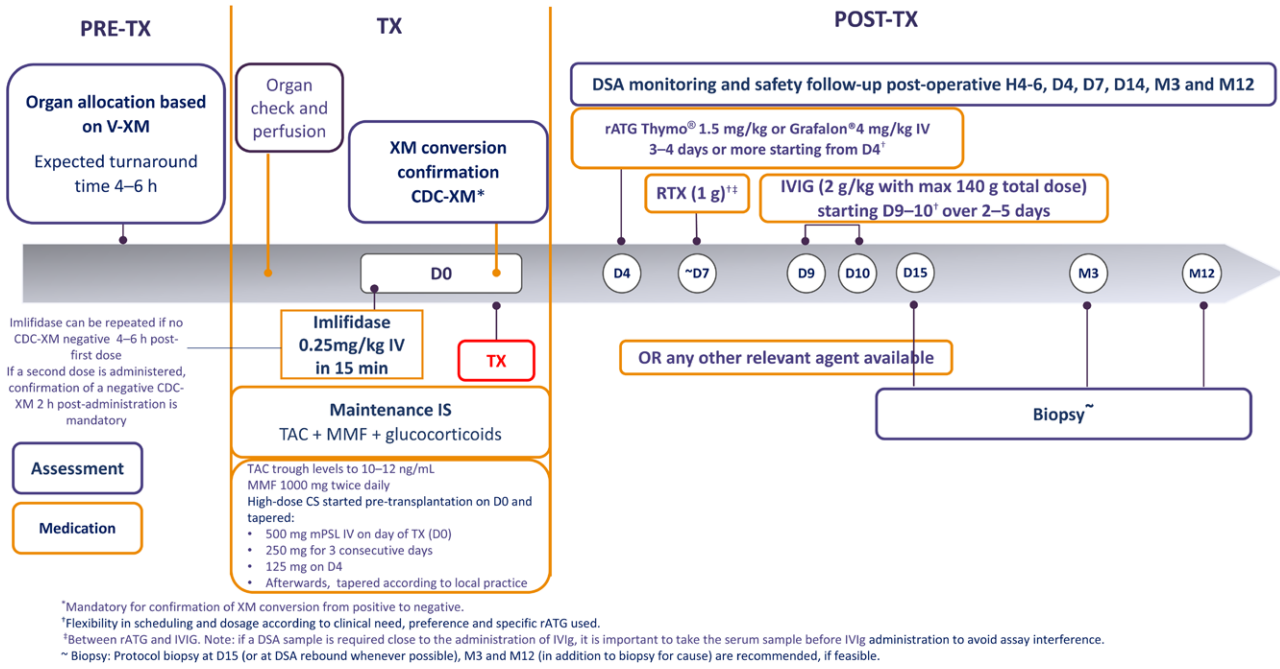

FIGURE 3. Pre- and posttransplantation considerations when using imlifidase for highly sensitized kidney transplant candidates. CDC, complement-dependent cytotoxicity; CS, corticosteroids; D, day; DSA, donor-specific antibody; FC-XM, flow cytometry crossmatch; IS, immunosuppression; M, month; MMF, mycophenolate mofetil; mPSL, methylprednisolone; rATG, rabbit antithymocyte globulin; RTX, rituximab; TAC, tacrolimus; TX, transplantation; V-XM, virtual crossmatch.

- Patients should receive standard prophylaxis in accordance with local clinical routines for Pneumocystis pneumonia, cytomegalovirus, and *Candida* infections.
- In addition to local clinical practice, it is strongly recommended to encourage patient vaccination against *Pneumococcus pneumoniae*, *Neisseria meningitidis*, influenza virus, and SARS-COV-2 when considered eligible for desensitization with imlifidase.

Immunosuppressive Therapies

Immunosuppression scheme induction and maintenance

- The immunosuppression scheme for induction and maintenance is shown in Table 1. Patients were monitored and followed up posttransplant.

DSA Monitoring

- As a minimum, it is recommended to test for DSA with the SAB technique at the following time points: before imlifidase administration and post–imlifidase administration (4–6 h), D4, D7, D14, month 3 (M3), and M12, then ad hoc if deemed appropriate (flexibility in scheduling according to clinical need and preference).
- Increased creatinine levels may be an indication for additional DSA monitoring (ie, additional time points).
- It is suggested not to perform DSA monitoring within 5 d of giving IVIG or rituximab due to interference with assays.
- Serum samples can be taken more frequently and stored for later testing if deemed appropriate.

AMR Diagnosis and Treatment

- Serum/plasma creatinine surveillance; kidney graft biopsies for cause should be taken if AMR is suspected.
  - Treat AMR according to local practice.

Renal Biopsies

- In addition to the kidney graft biopsies for cause, it is recommended to perform systemic surveillance (per protocol biopsies) of the kidney graft at the following time points: D15 (or at DSA rebound whenever possible), M3, and M12.

DISCUSSION

The Belgian imlifidase consensus guidelines (Figure 4) present imlifidase desensitization therapy and delisting as potential strategies to help reduce the ongoing accumulation of HS KTx candidates on waiting lists. Without further innovative approaches, a considerable proportion of HS patients will remain inadequately served by organ allocation strategies globally. It is a clinical priority to optimize the feasibility and success of KTx for all patients.

The authors acknowledge that clinically effective management of extremely HS candidates, such as those with PRA ≥98%, is an ongoing worldwide challenge. The accrual of research evidence and practical experience with imlifidase in these patients will be important for guiding future clinical strategies: such data will be closely considered in forthcoming iterations of the Belgian guidelines. For example, whether extremely HS patients should be moved to the imlifidase program immediately (or after a short number of months) rather than being wait-listed for 3–4 y is a key topic for discussion, as knowledge and experience with imlifidase increase. To balance the importance of transplantation following desensitization against the morbidity/mortality risks associated with ongoing dialysis remains a complex matter.

TABLE 1.

Induction and maintenance immunosuppression scheme[24-30]

	Tacrolimus/MMF/steroids			Other immunosuppressive (proposed sequence)[a]		
	Tacrolimus	MMF	Steroids	rATG	Rituximab	IVIG
Drug	Prograf Advagraf	CellCept	mPSL or equivalent Solu-Medrol(IV) Medrol (OS)	rATG (or horse ATG–ATGAM or alemtuzumab if available) Thymoglobulin Grafalon	Rituximab	IVIG
Dosage	Tacrolimus trough levels should be maintained in the range of 10–12 ng/mL (depending on local practice)	1000 mg twice daily	500 mg IV on day of transplantation (D0) 250 mg IV D1–3 125 mg IV D4 Then tapered according to local clinical practice	Thymoglobulin 1.5 mg/kg IV Grafalon 4 mg/kg IV	Rituximab 1 g IV administered after rATG and before IVIG administration (flexibility in scheduling according to clinical need and preference) ~D7	IVIG 10% 2 g/kg (maximum dose 140 g) with flexibility in size of fractions
Timing administration	Start D0 (day of transplantation) until D4 onward			Start D4 owing to imlifidase IgG-cleaving activity until this time If ATGAM: start D0 If alemtuzumab start D4	~D7 (after rATG and before IVIG)	Start ~D9–10, according to clinical need and over 2–5 d
Duration	D0–D4 onward (local practice)	D0–D4 onward (local practice)	D4 onward no CS withdrawal	From D4 for 3–4 d or more (rATG)	~D7 (once)	D9–D10 (can be extended to 5 d)

[a]Or any other relevant agents available to the prescriber. (NB: excluding imlifidase, no other drugs listed are registered within this indication).
Prograf (Astellas Pharma, Addlestone, United Kingdom[24]); Advagraf (Astellas Pharma, Addlestone, United Kingdom[25]); CellCept: (Roche, Basel, Switzerland[26]); Solu-Medrol/Solu-Medrone (Pfizer Inc, New York, NY[27]); Medrol/Medrone (Pfizer Inc, New York, NY[28]); Grafalon (rATG; Neovii Pharmaceuticals, Rapperswil-Jona, Switzerland[29]); Thymoglobulin (rATG; Sanofi-Aventis LLC, Bridgewater, NJ[30]).
ATGAM, lymphocyte immune globulin, antithymocyte globulin (equine); CS, corticosteroid; D, day; IV, intravenous; MMF, mycophenolate mofetil; mPSL, methylprednisolone; rATG, rabbit antithymocyte globulin.

The Eurotransplant network—of which Belgium is a member—is unique in that it was the first independent, official, multinational allocation organization to rapidly adopt a pioneering approach to imlifidase desensitization. This strategy is now a key component of its priority kidney allocation program, which will be evaluated after an appropriate small cohort of patients is transplanted. Such prompt action by Eurotransplant aims to facilitate transplantation in a higher proportion of HS KTx candidates than was previously possible. The parallel development of the consensus guidelines by the Belgian Imlifidase Scientific Expert Group complements the Eurotransplant initiatives with real-world, comprehensive guidance, including patient selection criteria. Furthermore, the Belgian imlifidase consensus guidelines also include HS patients who are not part of the Eurotransplant AM Desensitization program who are accumulating on the ETKAS list, thus complementing the Eurotransplant approach.

Notably, the availability of imlifidase has provided the transplant community with fresh opportunities to adapt working practices, especially with regard to delisting strategies. These opportunities should help increase organ offers for HS KTx candidates. In some cases, the revised delisting strategies alone may facilitate compatible offers that do not require imlifidase treatment.

The authors are confident that the Belgian imlifidase consensus guidelines have potential value beyond their national border, certainly across the Eurotransplant network. The ratified guidance is relevant to all transplantation centers, including those that already use imlifidase in their allocation systems (eg, centers within Germany and the Netherlands).

The Belgian Imlifidase Scientific Expert Group has switched its focus toward updating the guidelines based on shared clinical experiences with imlifidase. Early case reports demonstrate the successful use of imlifidase-based desensitization protocols.[31-33] Real-world and clinical-research publications will help to refine both patient selection criteria and updates to the consensus guidelines themselves as immunosuppressive strategies evolve to prevent rejection and graft loss. Primarily, the consensus guidelines for imlifidase use in clinical settings are living documents for local use, and the authors recognize that regular reappraisal is necessary if the content is to maintain its clinical value.

Other national European guidelines for imlifidase use exist.[34-36] The importance and high quality of these guidelines are acknowledged by the authors, but the Belgian consensus guidelines potentially fulfill a wider need because they have a degree of uniformity that suits all countries across the Eurotransplant network.

In summary, the imlifidase desensitization clinical guidelines, developed by the Belgian Imlifidase Scientific Expert group, represent an important step in the ongoing

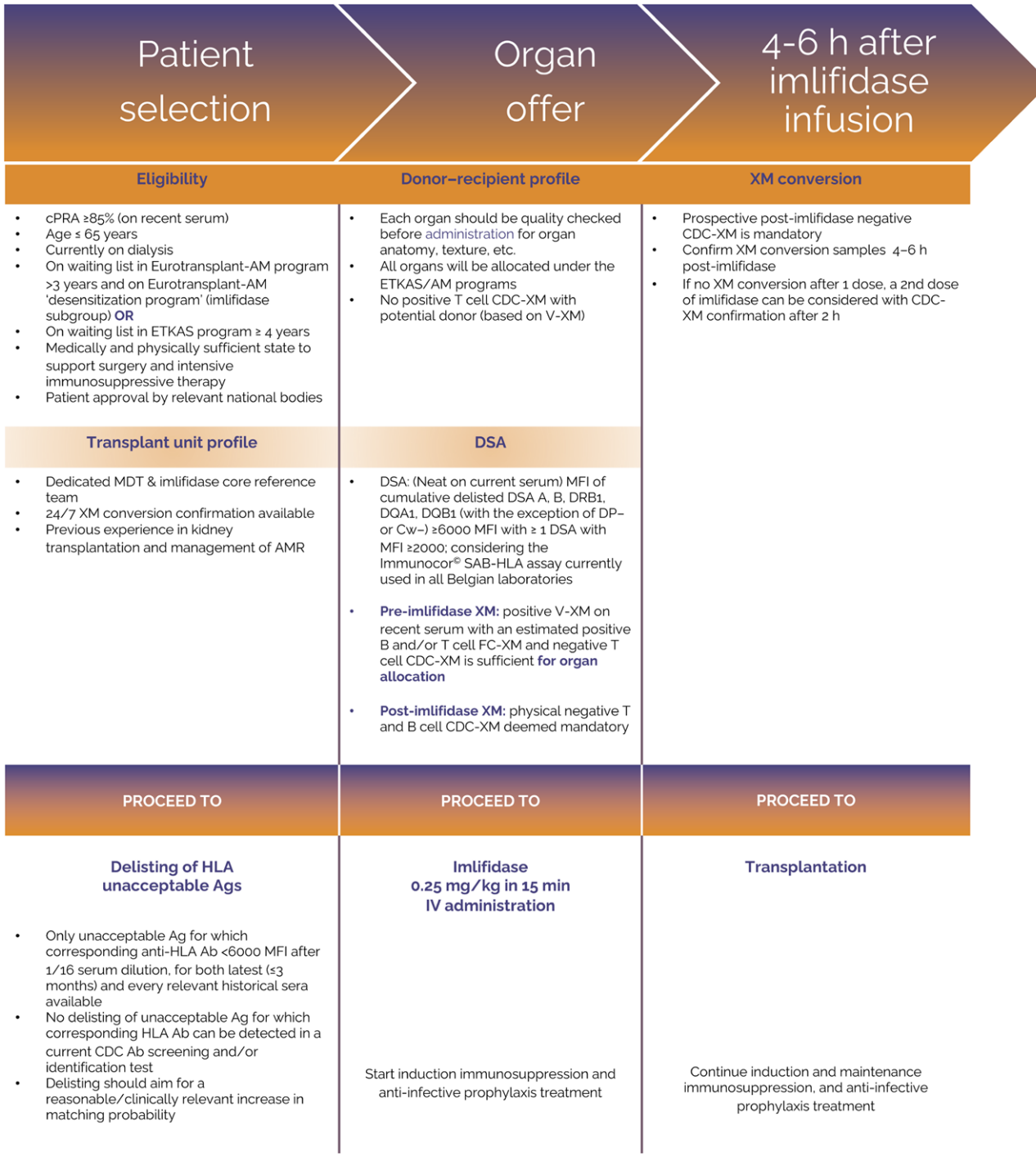

FIGURE 4. Visual summary of Belgian criteria for selecting highly sensitized patients for imlifidase treatment. Ab, antibody; Ag, antigen; AM, acceptable mismatch; AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; cPRA, calculated panel-reactive antibody; DSA, donor-specific antibody; ETKAS, Eurotransplant Kidney Allocation System; FC-XM, flow cytometry crossmatch; IV, intravenous; MDT, multidisciplinary team; MFI, median fluorescence intensity; SAB, single antigen bead; V-XM, virtual XM. Immunocor, Werfen, Peachtree Corners, GA.

improvement of real-world access to KTx across Europe, especially for HS patients.

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