UK GUIDELINE ON IMLIFIDASE ENABLED DECEASED DONOR KIDNEY TRANSPLANTATION

bts.org.uk/uk-guideline-on-imlifidase-enabled-deceased-donor-kidney-transplantation

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BTS British Transplantation Society
The Voice of Transplantation in the UK

BSHI British Society for Histocompatibility and Immunogenetics
Promoting Science and Education in Transplantation

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Introduction and need for the guideline

Sensitisation to Human Leucocyte Antigens (HLA) antigens occurs following blood transfusion, pregnancy or previous solid organ transplantation. Highly sensitised patients wait longer to match with a compatible organ on the UK deceased donor transplant waiting list. The longer wait can be associated with additional disease burden for patients and excess costs to the NHS. Until recently there were no proven interventions to meaningfully reduce sensitisation and improve the chances of matching to an organ.

Imlifidase is a cysteine protease that cleaves the heavy chain of all human IgG sub-classes. Imlifidase administration temporarily reduces donor specific HLA allo-antibodies and creates a window of opportunity to find an acceptable matched organ for highly

sensitised patients. The currently available evidence reporting on imlifidase enabled deceased donor kidney transplantation was reviewed together with guidance published by NICE[1] and SMC[2]. Imlifidase is manufactured by Hansa Biopharma.

In the absence of large scale randomised controlled trial data, there is a lack of high-quality evidence to help derive safe, equitable and effective guidance for the implementation of imlifidase in the deceased donor kidney transplant pathway. There are significant uncertainties extrapolating from currently available small scale uncontrolled study data to real-world UK clinical practice. Specifically, there are uncertainties surrounding

- immunological risk stratification
- logistical practicalities of including imlifidase to the deceased donor kidney transplant pathway in the UK
- the ideal induction anti-rejection treatment that should accompany imlifidase use
- variation in practice across UK transplant units

Given these uncertainties, clinical transplant teams and commissioners for kidney transplantation from all four UK nations agreed to convene an expert group with the mandate to derive guidelines for implementation of imlifidase in the deceased donor kidney transplant pathway. The guidelines were needed to provide advice on clinical, laboratory and logistical domains for transplant multi-disciplinary teams to ensure safe, effective and equitable access to treatment for relevant patients across the UK. Commissioners and the expert group concluded a responsive and ongoing review of relevant outcomes following implementation would be essential to ensure learning from any early signals associated with adverse outcomes and successes.

To enable such learning, accurate, timely and complete data returns from participating centres will be mandated with NHSBT facilitating data collection, analyses and transparent reporting to commissioners, clinicians and patient organisations. On-going reporting and analyses from this ‘Imlifidase registry’ may help identify best practice, monitor centre variation in equity of access and outcomes after imlifidase and facilitate appropriate research to identify practise linked to best outcomes.

Process of writing and methodology

The guideline was developed in accordance with the British Transplantation Society (BTS) Guideline Development Policy 3. An open call for volunteers with a requirement for representation from all four UK nations was made via NHS Blood & Transplant Kidney Advisory Group identified the initial expert group. Iteration within the group identified gaps in expertise and a further targeted call for volunteers to address the gap resulted in the constitution of the final expert group. The expert group initially agreed the scope of guidance, format and timelines. Given the paucity of published literature concerning imlifidase, a formal systematic literature review was deemed unnecessary, and all members of the expert group had access to all imlifidase-relevant publications. The expert group also had discussions with Prof Lionel Couzi, the lead author for imlifidase

implementation guidance in France. Where relevant, the group sign-posted to existing published guidance documents (eg: CytoMegalo Virus {CMV} management). An iterative consensus-driven approach was utilised to derive and sign off on the final wording for the recommendations.

The final draft guideline was circulated for consultation to the membership of the BTS, the executive committee of the British Society of Histocompatibility & Immunogenetics (BSHI), lead commissioners for renal transplantation in all four UK nations and patient and lay representatives. The final version of the guidance incorporates feedback received from the consultation. Patient and lay feedback was received from Mr Richard Smithson, Dr B Ponnle and Prof P Farrand.

Executive Summary of Recommendations

1: Clinical patient selection

1.1: There should be local MDT approval confirming that the patient is medically fit to undergo an imlifidase-enabled kidney transplant and has the physiological reserve to withstand treatment burden including, if necessary, treatments for post-transplant severe Acute Cellular Rejection & Antibody Mediated Rejection. 1C

1.2: Patients should be carefully counselled, using appropriate patient information aids where necessary, regarding risks versus benefits of imlifidase-enabled transplantation and obtain informed consent prior to making changes to unacceptable antigen specificities. 1C

1.3: Inability to satisfy NICE1/SMC2 criteria is considered to be an absolute contraindication for imlifidase-enabled kidney transplantation. 1A

1.4: Breast feeding or pregnancy is considered to be an absolute contraindication for imlifidase-enabled kidney transplantation. 1A

1.5: It is recommended that very careful and individualised consideration of risks versus benefits is undertaken in the following scenarios as they are viewed as relative contraindication/s. 1D

(a) High (>50%) likelihood of early (within 1 year) graft loss due to non-immunological reasons. eg: Recurrent disease

(b) Dependency on humanised monoclonal antibody therapy for organ or life-threatening disease. eg: atypical Haemolytic Uraemic Syndrome needing Eculizumab therapy

(c) Current dependency on IVIg for organ or life-threatening disease.

2: Pre-transplant un-acceptable antigen de-listing

2.1: Before considering the use of imlifidase, an antigen delisting approach should have been considered and were possible already undertaken for at least a six-month period. This approach should be aimed at generating a low (current flow negative, Donor Specific Antibody {DSA} positive) or intermediate (current flow positive within acceptable threshold for the centre, DSA positive) risk deceased donor kidney transplant without the need for imlifidase. 1D

2.2: To perform an imlifidase-enabled transplant, the aim of an antigen delisting strategy should be achieving deceased donor kidney offers that are likely to convert from an HLA incompatible to a compatible transplant, as per local testing policy, following imlifidase treatment. The achieved HLA antibody incompatibility assessment after imlifidase should be a result that equates to a level of risk that is acceptable to the transplant centre and the individual patient under consideration. 1D

2.3: It is strongly recommended that centres adopt a cautious approach in their initial experience with imlifidase and avoid de-listing specificities that might be expected to be associated with a level of risk equivalent to causing a Complement Dependant Cytotoxicity (CDC) positive crossmatch. 1D

To achieve the above aim the following laboratory strategies can be considered:

(a) Utilising established laboratory methods used by the centre, including adjusted Mean Fluorescence Intensity (MFI) thresholds that would be anticipated to cause a positive Flow cytometric Cross Match (FXCM) or Complement Dependant Cytotoxic Cross Match (CDCXM) as the basis for de-listing decisions.

(b) Differential assay cut-offs (eg: HLA-DR vs HLA-DP) predicted to cause a positive cross Match (XM) may be considered based on HLA allele expression and centre expertise.

(c) Test modifications including serial dilution and assessment of C’ binding may be considered on the basis of centre expertise.

(d) Where antibody reactivity to a previous donor or known pregnancy-associated mismatches exist, avoidance of repeat mismatching is initially advised, and greater caution should be applied if delisting is eventually required to gain transplant opportunity.

(e) The delisting strategy should be based on an incremental risk approach with the aim to achieve increased transplant opportunity (as defined by calculated reaction frequency {cRF} or N/10,000) and, where relevant based on the application of available online tools (In silico tools eg: Matchmaker; Sequence alignment; Epitope registry; Allele frequency)4-7.

(f) The delisting strategy should take into account the possibility that HLA antibody levels might be perceived as low in Single Antigen Bead (SAB) tests, due to dilution via the presence of multiple copies of the target epitope (eg: Bw4/6 antibodies). However, such antibodies might provide a stronger than expected result in cell based cross matching

assays. Laboratories need to take this into account when making decisions about delisting antigens, including where necessary utilising surrogate crossmatches for accurate risk assessment.

2.4: It is strongly recommended that centres, at any given time, only have a limited number of patients with Unacceptable Antigen Specificities (UAGs) delisted and ready to receive an imlifidase-enabled transplant. New patients could be added on a 'one in – one out' basis as successful transplants are undertaken. The maximum number of patients active in a centre at any given time should take into account resource requirements for safe and effective post-operative care (eg: concurrent in-patient management of >1 high immunological risk transplant recipients who may require AntiBody Mediated Rejection {ABMR} treatments). 1D

3: Pre-transplant prophylactic vaccination

3.1: Consider offering relevant prophylactic vaccination prior to de-listing of UAGs, including pneumococcal, meningococcal (tetravalent and sero-group B), Influenza and SARS-CoV-2 vaccines for patients eligible to receive imlifidase enabled transplantation. Wherever possible, all relevant vaccinations are to be completed at least two weeks prior to the planned de-listing of UAGs. 2D

4: Day of transplant – laboratory assessment

4.1: At the time of the organ offer, an initial Virtual Crossmatch (VXM) guided by local crossmatch policy must be undertaken on a recent (<1 month) sample tested by SAB. Based on donor HLA type, the local transplant and laboratory multi-disciplinary team will conclude as to whether: 1D

(a) The transplant can proceed without imlifidase

(b) The transplant can proceed with the use of imlifidase (within recommendations)

(c) The transplant cannot proceed as the immunological risk is excessive

4.2: Greater caution is recommended when considering organ offers with multi-specificity donor specific reactivity. Consideration should be given to the cumulative MFI values, the loci to which the antibody is directed, the sensitising event(s) and the longevity of the antibodies. Inferior long term graft outcomes are associated with transplants with =/>3 pre-existing donor reactive specificities 8. 1B

4.3: If an organ offer is accepted, the decision to administer imlifidase should only be undertaken after: 1D

(a) confirmation of surgical suitability of organ for transplantation (see below)

(b) SAB or laboratory crossmatch using day of transplant serum sample confirms an allo-IgG dependant incompatibility as per local crossmatch policy. If local policy requires a cellular (FXCM or CDCXM) crossmatch to be performed using the day zero recipient

sample, then every effort should be made to obtain and test using donor peripheral blood leucocytes prior to organ arrival at the centre

(c) confirmation there are no clinical contraindications and obtaining informed patient consent

4.4: A post-imlifidase recipient sample should be used to perform a prospective cellular (FXCM or CDCXM) crossmatch and/or SAB testing to confirm conversion to a negative allo-IgG crossmatch as per local testing policy. It is recommended that the post-imlifidase samples are tested at a minimum of four hours and ideally at six hours after drug administration is complete. If the four-hour sample continues to demonstrate allo-IgG reactivity, the crossmatch test should be repeated with the six-hour sample. In all cases, samples that continue to be crossmatch positive (at a level above the acceptable threshold for the centre) at six hours post imlifidase should be considered an absolute contraindication to proceed with transplantation. 1D

4.5: Imlifidase cleaves Rabbit IgG in addition to human IgG. Therefore, caution should be applied when selecting primary and secondary detection antibodies for use in laboratory testing for imlifidase treated patients. 2D
4.6: The final crossmatch report must include the patient's immunological risk pre and post imlifidase administration. 1D

4.7: If the crossmatch remains positive with the six-hours post imlifidase sample and transplantation with that specific organ offer can no longer proceed and/or if the transplant could not proceed for non-immunological reasons after imlifidase administration, centres should have an agreed protocol on accepting organ offers for the recipient when the antibody profile will have been modified in the brief window (up to 4-5 days) post-imlifidase. It is recommended the protocol specifies: 1D

(a) timing and nature of repeat immunological assessment post-imlifidase

(b) process for urgently revising unacceptable antigens listed with NHSBT as per repeat immunological assessment and the duration (number of days) during which this revised un-acceptable antigen profile is appropriate

(c) process for re-listing all baseline unacceptable antigens after the imlifidase effect has abated and patient's antibody profile has returned to baseline.

5: Day of transplant – donor & organ offer clinical assessment

5.1: The local transplant team receiving the organ offer should carefully consider organ offer variables that could be predicted to adversely impact outcomes if combined with prolonged Cold Ischaemia Time (CIT) associated with the imlifidase pathway. The organ offers that are more likely to be associated with reduced risk of non-immunological injury (eg: D1 or D2 kidneys) may be preferable and decisions must be individualized to the recipient's need. 1D

5.2: Imlifidase administration should commence only after confirmation that the implanting surgical team are satisfied that the organ is transplantable. In most cases, this assessment will take place in the implanting centre. If an on-site assessment is not possible due to logistical or clinical reasons, a decision following discussion between the retrieval and recipient surgical teams, supported by review of digital images (if necessary) is recommended. 1D

5.3: Transplanting Centres should aim to minimise CIT including availability and where possible utilising time-efficient organ transport options to enable assessment of the organ prior to imlifidase. 1D

5.4: Prior to administration of the drug, patient review by a senior decision maker to confirm clinical suitability to receive imlifidase and obtaining informed consent regarding risks-vs-benefits of proceeding with imlifidase-enabled transplant for the specific organ offer, is recommended. This consent process should specifically include consideration that imlifidase can only be administered once and, hence, the risk of not proceeding to a transplant due to immunological or non-immunological reasons. 1D

5.5: Transplant centres must identify a clinically and immunologically suitable backup recipient who can receive the organ if the transplant cannot proceed with the 'imlifidase recipient'. A consideration in selecting a backup recipient could include someone who is suitable for a VXM and would not prolong CIT by requiring additional testing to be performed pre-transplant. 1D

6: Immunosuppression and anti-microbial prophylaxis

6.1: Patients should be given corticosteroids (eg: Hydrocortisone 100mg) and antihistamines (eg: Chlorpheniramine 10mg) to reduce the risk of imlifidase associated infusion reactions. 1C

6.2: Patients should receive methylprednisolone 500mg IV or equivalent alternative corticosteroid immediately prior to surgery or intraoperatively and 125mg IV daily or equivalent alternative corticosteroid up to and including day +4. 1C

6.3: Patients should receive lymphocyte depleting therapy with either: 1C
– alemtuzumab 30mg IV or subcutaneously on day 4 (or dosing as per local protocol)
OR
– equine Anti Thymocyte Globulin (ATG) (3mg/Kg daily on days 1-3) or rabbit ATG 1.5mg/kg daily on days 4-7 (or dosing as per local protocol). It is noted that imlifidase SPC9 recommends delaying rabbit-ATG use until day +7 but an ongoing trial protocol requires rabbit ATG use from day +4. This recommendation to use rabbit-ATG from day +4 is an off-label use and needs to be recognised as such by clinical teams.

6.4: Maintenance immunosuppression with "triple therapy" including best tolerated calcineurin inhibitor, anti-proliferative and corticosteroids is recommended. For most patients this will be tacrolimus, mycophenolate or mycophenolic acid and prednisolone.

Local centre policy for high immunological risk transplants and tolerability will guide mycophenolate/mycophenolic acid dose and target trough level adjusted tacrolimus dose in the early and long-term management of patients. 1C

6.5: Patients should receive antibiotic prophylaxis for four weeks to reduce the risk of bacterial respiratory infection, with antibiotic choice guided by advice from local antimicrobial stewardship leadership. 1C

6.6: Patients should receive Pneumocystis Jirovecci Pneumonia (PJP) prophylaxis for 3 months or longer as per centre policy for the care of high immunological risk kidney transplant recipients. 1C

6.7: Patients should receive, in the absence of intolerance, CMV prophylaxis for at least 100 days in all scenarios except D-R- CMV status. Further guidance is available from the BTS https://bts.org.uk/guidelines-standards/ (Prevention and management of CMV disease after solid organ transplantation) 10. 1D

6.8: Patients should receive anti-fungal and Tuberculosis prophylaxis as per centre policy for the care of high immunological risk kidney transplantation. 1C

The expert group carefully reviewed the immunosuppressive protocols used alongside imlifidase in published literature 11-15. Specifically, routine prophylactic use of rituximab and IVIg was extensively discussed. Based on current evidence, and in the context of the above recommendations that UK centres adopt a cautious start before building experience with using imlifidase plus the use of powerful depleting antibody induction therapy, the group concluded that rituximab and IVIg would continue to remain treatment options for ABMR but, did not require to be routinely used prophylactically. The expert group also concluded that routine adoption of other prophylactic treatments (eg: eculizumab, splenectomy) was not warranted.

Imlifidase has a molecular weight of 35 kDa. It is likely imlifidase will not be removed by haemodialysis or haemodiafiltration but confirmative data is not currently available.

7: Post-transplant monitoring and rejection treatment

7.1: Monitoring for DSA rebound is recommended on days +4, +7, +10, +14 and weekly thereafter for 6 weeks or as clinically indicated in response to graft dysfunction. Medium to longer term routine serological sampling for DSA can be performed at time intervals as per centre protocol, to enable an urgent analysis of DSA status if clinically required. 1D

7.2: Rebound of DSA is expected, and in the context of stable allograft function, does not require intervention. 2D

7.3: The diagnosis of acute active rejection should be made on allograft biopsy with concurrent serological sampling for DSA, as defined by the current Banff criteria for allograft pathology. 1B

7.4: Clinical or biopsy proven cellular or antibody mediated rejection should be treated as per local practice. Further detailed guidance on diagnosis and management of antibody mediated rejection is also available from the BTS – Antibody incompatible transplantation guideline16 and Expert consensus from the Transplantation society working group 17. Based on the above guidance, we recommend

(a) Patients with a diagnosis of acute active ABMR receive extracorporeal antibody removal with a minimum of five treatments. 1C

(b) Patients with a diagnosis of acute active ABMR receive IVIG 100mg/kg after each extracorporeal treatment or 2g/kg at the end of treatment. 1C

(c) Patients with a diagnosis of acute active ABMR have baseline immunosuppression optimised and are treated with high dose steroids. 1C

(d) Patients with a diagnosis of acute active ABMR are considered for other agents, eg: anti-CD20 therapy in combination with recommended treatments. 2C

Executive Summary of Research and Audit Recommendations

The United Kingdom is well placed to address major knowledge gaps in the safe and effective use of imlifidase by leveraging UK-wide data collection and reporting by NHSBT. Centres will be required to submit standard 30-day and one-year data returns required for deceased donor transplantation plus mandatory additional data items specific for imlifidase-enabled transplantation at the same time points and an additional data return at 90 days. Regular and complete data returns from centres is critical to timely and accurate tracking of activity and outcomes at a UK level. Such registry analyses will facilitate identification at pace and scale of demographic, clinical or immunological signals associated with favourable or poor outcomes. These real-world results will help to further update these guidelines in addition to results from ongoing or future clinical trials.

In adult patients who have received imlifidase:

1. What are the baseline demographic, clinical and immunological variables associated with post-imlifidase (single dose) successful or un-successful conversion from incompatible to compatible crossmatch

2. What are the early and long-term graft and patient survival outcomes for imlifidase-enabled transplantation versus compatible deceased donor and HLAi (from living donor) transplantation

3. What are the adverse events (rejection – including type and timing, DSA rebound, infection, length of stay and hospitalisation) outcomes for imlifidase-enabled transplantation versus compatible deceased donor and HLAi (from living donor) transplantation?

4. Analysis of organs requiring local re-allocation or redirection to a backup recipient due to persistent positive crossmatch six hours post imlifidase and impact assessment on other wait-listed patients, including Tier A recipients, as a result of such local/regional re-offering

5. What induction and maintenance immunosuppressive therapy is associated with the best graft outcomes and minimal adverse events?

6. What are the Patient Reported Outcome Measures (PROMs)/Patient Reported Experience Measures (PREMs) in recipients of imlifidase-enabled transplant patients and, where possible, when compared withequivalent patients on the transplant list and HLAi (from living donor) transplant recipients?

7. NHSBT to facilitate interim review of outcomes after 10 imlifidase-enabled transplants in the UK and ongoing further review at appropriate time points. The primary purpose of the review would be to identify any signals which may be associated with adverse outcomes including organ utilisation and requirement for reoffering.

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Conflicts of Interest

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The other authors do not have any relevant conflicts of interest.

Grading of Recommendations

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice.

In these guidelines the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been used to rate the strength of evidence and the strength of recommendations[18]. Explicit recommendations are made on the basis of the trade-offs between the benefits on one hand, and the risks, burden, and costs on the other.

For each recommendation the quality of evidence has been graded as:

A (high)

B (moderate)

C (low)

D (very low)

Grade A evidence means high quality evidence that comes from consistent results from well performed randomised controlled trials, or overwhelming evidence of another sort (such as well-executed observational studies with very strong effects).

Grade B evidence means moderate quality evidence from randomised trials that suffer from serious flaws in conduct, consistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.

Grade C evidence means low quality evidence from observational evidence, or from controlled trials with several very serious limitations.

Grade D evidence is based only on case studies or expert opinion.

A **Level 1** recommendation is a strong recommendation to do (or not to do) something where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients.

A **Level 2** recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain.

Abbreviations

ABMR AntiBody Mediated Rejection

aHUS atypical Hemolytic Uremic Syndrome

ATG Anti-Thymocyte Globulin

CDC Complement Dependent Cytotoxicity

CIT Cold Ischaemia Time

CMV CytoMegalo Virus

cRF calculated Reaction Frequency

DSA Donor Specific Antibody

FXM Flow cytometric cross Match

HLA Human Leucocyte Antigen

HLAi Human Leucocyte Antigen incompatible

IV Intra Venous

IVIg Intra Venous Immuno globulin

MCF Mean Channel Shift

MFI Mean Fluorescence Intensity

NHSBT NHS Blood & Transplant

NICE National Institute of Clinical Excellence

PJP Pneumocystis Jirovecci Pneumonia

PROM Patient Reported Outcome Measure

PREM Patient Reported Experience Measure

SAB Single Antigen Bead

SMC Scottish Medicines Consortium

SPC Summary of Product Characteristics

VXM Virtual cross Match

XM cross Match

Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in these aspects of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine.

These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool. It follows that the guidelines should be interpreted in the spirit rather than the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient.

The guidelines are not designed to be prescriptive, nor to define a standard of care. The British Transplantation Society or British Society of Histocompatibility & Immunogenetics cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

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