Imlifidase-enabled deceased donor kidney transplantation [2304]

NHS England commissioning statement

13 October 2023

Commissioning Position

1. This commissioning statement aims to standardise the criteria for imlifidase-enabled deceased donor kidney transplants to optimise the use of limited resources and ensure equitable access for patients across England.
2. This commissioning statement supports the delivery of the NICE technology appraisal TA809 for imlifidase enabled deceased kidney transplantation and should be used in line with the existing Adult Kidney Transplant Service (16079/S) Specification which sets out standards for commissioned providers.
3. This commissioning statement supersedes the National Imlifidase Multi-disciplinary Team (MDT), which has been disbanded following the publication of this document.

Information Considered

4. A very highly sensitised patient refers to a patient whose blood has human leukocyte antigen (HLA) antibodies to more than 95% of HLA antigens present in deceased donors in the UK. HLA antibodies may develop following pregnancy, transfusion of blood products, and/or prior transplantation. High levels of HLA antibodies can cause antibody-mediated rejection of a new transplanted organ (referred to as a 'graft') leading to graft rejection and failure.
5. Highly sensitised patients are considered higher risk transplant recipients and wait longer to be offered a suitable match with a compatible deceased organ donor than non-sensitised (no HLA antibodies) patients as they must wait for donors that do not have the HLA antigens to which they have antibodies. Highly sensitised patients therefore require dialysis treatment for longer, which has a significant adverse effect on both quality and length of life.
6. For highly sensitised patients, imlifidase removes all antibodies from the patient immediately prior to receiving a deceased donor kidney transplant. Imlifidase is an enzyme that breaks down human immunoglobulin G (IgG) antibodies. This enables imlifidase to create a short period of time with no anti HLA antibodies and therefore no possibility of immediate rejection.
7. In order to facilitate HLA antibody incompatible donor offers, it is necessary to de-list unacceptable antigens listed on the national transplant database. This process is based upon HLA-specific antibody screening results obtained using single antigen bead identification assays. Unacceptable HLA antigens from any locus could be included as potential targets for de-listing. A full risk assessment for individual donor offers must be carried out prospectively at the time of offer. Practice should be according to the British Society for Histocompatibility and Immunogenetics guideline for de-listing HLA unacceptable antigens to support renal transplant provider centres: HLA De- listing guidance.
8. Patients who have received multiple blood transfusions or received previous transplants and women who have been pregnant, have an increased chance of becoming highly sensitised

and so are the main groups likely to benefit from imlifidase treatment (NICE, 2022).

9. The median wait for a deceased donor kidney transplant is approximately five years for highly sensitised patients. This compares with a median waiting time of one and a half to two years for people who are not sensitised (NICE, 2022). Very highly sensitised patients eligible for imlifidase treatment would expect to wait more than 5 years.

Commissioned use

10. In order for a patient to be considered for an imlifidase-enabled transplant, all requirements set out in Annex A must be met. Service providers need to ensure they can fully support highly sensitised patients as defined by NICE, including pre- and post-transplant care and management of transplant rejection or imlifidase related reactions. Service providers need to ensure robust management of imlifidase is in place, including appropriate level pharmacy supervision, correct storage equipment and audit of imlifidase use.

11. Resources to support commissioned providers of Kidney Transplantation services in the delivery of imlifidase treatment have been developed by NHS England and are available on the Renal Services Transformation Programme's Future NHS webpages: Imlifidase - Renal Service Transformation Programme - FutureNHS Collaboration Platform. A good practice example of a provider pharmacy management process for imlifidase can also be found at this link.

Equality statement

12. Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

    - Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
    - Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Links to policies and commissioning statements

13. This policy relates to the following guidance, practices and specification:

    - National Institute for Health and Care Excellence (NICE)
        - NICE TA809 - Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease: NICE/ta809
    - British Society for Histocompatibility and Immunogenetics (BSHI)
        - UK Histocompatibility and Immunogenetics De-Listing HLA specificities for imlifidase-enabled transplantation guidelines: HLA De- listing guidance
    - British Transplant Society (BTS)
        - UK guideline on imlifidase-enabled Deceased Donor Kidney Transplantation - British Transplant Society: BTS UK Guideline

Definitions

De-listing	The national transplant database has a list of unacceptable antigens. These are antigens that are considered too high risk for a transplant to take place. This process is based upon HLA-specific antibody screening results obtained using single antigen identification assays. De-listing does not mean patients are being de-listed from the transplant list. De-listing is the process of removing unacceptable antigens to enable access to transplantation in circumstances where patients may have been previously declined.
Histocompatibility	The compatibility between the tissues of different individuals, so that one accepts a graft from the other without giving an immune reaction.
Immunogenetics	The branch of medical genetics that explores the relationship between the immune system and genetics.
Matchability	A measure of how it difficult it is to match a patient with an organ donor in the UK. This score considers a patient's blood type, HLA type and unacceptable antigens. A patient with a score = 1 is defined as easy to match and a score = 10 as the most difficult to match.

References

Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease: Guidance (no date) NICE. Available at: https://www.nice.org.uk/guidance/ta809/chapter/1-Recommendations (Accessed: May 4, 2023).

NHS Blood and Transplant (2022) Adult Kidney transplants from deceased donors. Available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/29264/dd-kidney-infographic.pdf (Accessed: May 4, 2023).

NHS choices. NHS. Available at: https://www.organdonation.nhs.uk/helping-you-to-decide/about-organ-donation/statistics-about-organ-donation/ (Accessed: May 4, 2023).

Organ donation and Transplantation Activity Data: England (no date). Available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/28509/nhsbt-england-summary-report-dec-22.pdf (Accessed: May 4, 2023).

UK guideline on IMLIFIDASE enabled deceased donor kidney transplantation (2023) British Transplantation Society. Available at: https://bts.org.uk/uk-guideline-on-imlifidase-enabled-deceased-donor-kidney-transplantation/#ExecutiveSummaryofRecommendations (Accessed: May 4, 2023).

Starting arrangements for all patients

1. The guidance for treatment with imlifidase is covered by the NICE technology appraisal (TA809) on imlifidase-enabled deceased donor kidney transplantation.

Starting criteria

2. The patient must be discussed at a local MDT confirming they are medically fit to undergo an imlifidase-enabled kidney transplant and have the physiological reserve to withstand treatment burden including, if necessary, treatments for post-transplant severe Acute Cellular & Antibody Mediated Rejection.
3. The patient must be carefully counselled, using appropriate patient information aids where necessary, regarding risks versus benefits of imlifidase-enabled transplantation and informed consent obtained prior to making changes to unacceptable antigen specificities.
4. Consider offering relevant prophylactic vaccination prior to de-listing, 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 unacceptable antigen specificities (UAGs).

First Level Workup (Low / Intermediate Risk Transplant)

5. In order for a patient to be considered for an imlifidase-enabled transplant, the following requirements need to be met:
    - Historic positive specificities and previous repeat mismatched HLA antigens (organ transplant) should be de-listed if currently negative on single antigen beads assay. Include any specificities that have tested negative in three consecutive samples within the last 6 months or longer. For some patients, this step may not be achievable. If this is the case, move directly to second level workup.
    - Try to achieve a minimum target of n/10,000 = 100 to attract donor offers.
    - Review after 3-6 months and if no donor offers have been received, and no further specificities can be de-listed, proceed to imlifidase-enabled Transplant.

Second Level Workup - (High Risk Transplant)

6. In order for a patient to be considered for an imlifidase-enabled transplant, the following requirements need to be met:
    - Unacceptable antigens should only be considered for de-listing after the corresponding HLA antibody profile has stabilised or is falling.
    - Prioritise specificities for de-listing starting with weaker and progressing to stronger antibodies. Titration could be used for specificities at or close to the single antigen bead assay saturation point. If possible, delisting repeat mismatches with previous transplants should be avoided (see BTS guidelines).
    - Where titration is used, prioritise the de-listing of specificities for which the MFI of the related antibody shows clear reduction upon dilution at 1:16 or lower. Aim to achieve n/10,000 *if possible* ≥100, but it is accepted that this may be difficult to achieve (a cautious lower number is acceptable but will clearly reduce the chance of an offer).

If this first stage does not generate donor offers, review the case and extend the de-listing process to include higher level antibodies.

- If possible, avoid multiple de-listed unacceptable antigens giving an unacceptably high cumulative MFI. If de-listing specificities that are in linkage disequilibrium, only de-list the specificity that is most frequently seen in the UK population. If this does not generate donor offers, add in additional specificities until n/10,000 is increased.
- All de-listings must be agreed by the local MDT before implementation.
- Review de-listed unacceptable antigens every 3 months (minimum) and continue to release additional specificities with increasing risk as outlined.

Inclusion Criteria

7. Patients must meet **all** of the following inclusion criteria to be eligible for imlifidase-enabled transplantation. The patient:
   - is an adult (18 and above) who is waiting for a kidney transplant from a deceased donor[1]
   - has had the appropriate level of workup as detailed above
   - satisfies all NICE criteria:
     - has a calculated reaction frequency (CRF) of at least 99%
     - has a matchability score of 10 (or 9 if Blood Group AB)
     - has been on the waiting list for a transplant for at least 2 years
   - has a positive crossmatch (actual or predicted) with the donor and are unlikely to have a transplant under the available kidney allocation system (including prioritisation programmes for highly sensitised people).

Exclusion Criteria

8. Patients who meet **any** of the following exclusion criteria are contraindicated from treatment with imlifidase:
   - Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC)
   - Ongoing serious infection
   - Thrombotic thrombocytopenic purpura (TTP). Patients with this blood disorder may be at risk of developing serum sickness
   - Inability to satisfy NICE criteria
   - Breast feeding or pregnancy
9. 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 contraindications:
   - High (>50%) likelihood of early (within 1 year) graft loss due to non-immunological reasons. e.g., recurrent disease
   - Dependency on humanised monoclonal antibody therapy for organ or life-threatening disease. E.g., atypical Haemolytic Uraemic Syndrome needing eculizumab therapy

[1] Imlifidase is not licensed for use in children. Access for post pubescent children may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services Policy (NHS England 170001/P, 2017).

- Current dependency on intravenous immunoglobulin (IVIg) for organ or life-threatening disease

Effective from

10. The commissioning statement is effective from the date of publication.
11. This commissioning statement will be reviewed in line with any updates to the NICE technology appraisal for imlifidase, next due in 2025.

Recommendations for governance and data collection

12. All centres will return data on all patients undergoing imlifidase-enabled kidney transplantation to the NHS Blood and Transplant clinical audit registry to inform clinical practice about improvements in the assessment, selection, and quality of care of transplant patients in line with the NHS Standard Contract and as outlined in the adult kidney transplant (16079/S) service specification.
13. The use of the Imlifidase will be subject to the NHS England prior approval (Blueteq) system.