

# Final report of the workshop ‘Management of transplant patients with HLA antibodies’

11 October 2022, Cardiff, United Kingdom

## Programme

11:00 am – 11:20 am	Welcome coffee break (20 minutes)	
11:20 am – 11:50 am	Current landscape – definition of HLA sensitisation – consensus between units	Siân Griffin   Cardiff, United Kingdom Amy De-Ath   Cardiff, United Kingdom
11:50 am – 12:10 pm	Impact of the 2019 Kidney Offering Scheme	Matthew Robb   Bristol, United Kingdom
12:10 pm – 12:30 pm	Improving risk stratification	Sunil Daga   Leeds, United Kingdom
12:30 pm – 1:15pm	Defining the patient population who would benefit from imlifidase	Nicholas Torpey   Cambridge, United Kingdom Discussion
<b>1:15 pm – 2 pm</b>	<b>Lunch break</b>	
2 pm – 2:20 pm	Safe, effective and equitable implementation of an Imlifidase enabled kidney transplant pathway – a 4 nation view	Rommel Ravanan   Bristol, United Kingdom
2:20 pm – 2:50 pm	Pathway to implementation: Protocol standardisation and data collection	Discussion
2:50 pm – 3:20 pm	Future potential of T regulatory cells and cytotoxic therapies	Anthony Dorling   London, United Kingdom
3:20 pm – 3:50 pm	Management options for treating ABMR post-Imlifidase	Michelle Willicombe   London, United Kingdom
3:50 pm – 4:30 pm	Discussion and final wrap up (40 mins)	All

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## Attendees

David Briggs | Birmingham, United Kingdom  
Aisling Courtney | Belfast, United Kingdom  
Sunil Daga | Leeds, United Kingdom  
Amy De-Ath | Cardiff, United Kingdom  
Anthony Dorling | London, United Kingdom  
Siân Griffin | Cardiff, United Kingdom  
Matthew Howse | Liverpool, United Kingdom  
Katrin Jones | Newcastle, United Kingdom  
Durga Kanigicherla | Manchester, United Kingdom  
Muhammad Khurram | London, United Kingdom  
Nithya Krishnan | Coventry, United Kingdom  
Phil Mason | Oxford, United Kingdom  
William McKane | Sheffield, United Kingdom  
Fotini Partheniou | Liverpool, United Kingdom  
Sarah Peacock | Cambridge, United Kingdom  
Deborah Pritchard | Cardiff, United Kingdom  
Rommel Ravanan | Bristol, United Kingdom  
Tracey Rees | Cardiff, United Kingdom  
Matthew Robb | Bristol, United Kingdom  
Adnan Sharif | Birmingham, United Kingdom  
Nicholas Torpey | Cambridge, United Kingdom  
Michelle Willicombe | London, United Kingdom

## Workshop rationale

Discussion of the management of highly sensitised kidney transplant patients, based on the framework of recent European guidelines authored by an ESOT working group and [published](#) in *Transplant International*, and assessment of how these apply to kidney transplant programmes in the UK.

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## Current landscape – definition of human leukocyte antigen (HLA) sensitisation, consensus between units

**Amy De'Ath**

### Presentation

- The National External Quality Assessment Service (NEQAS) provides external quality assessment for histocompatibility and immunogenetics (H&I) labs globally, providing blind samples for clinical testing, the results of which are then tested against the consensus from other labs
  - A threshold of 75% of surveyed labs is used to define 'consensus'
- Very few labs are graded as 'poor performers' in the UK and Northern Ireland, and overall, standards improved between 2017 and 2021
- Across labs there is a consistent 'grey zone' of ~10–15% of antibodies with no consensus on whether or not they are detectable
  - Analysis of differences between testing kits does not seem to account for the inconsistency
  - These antibodies seem to be identified at mid-range mean fluorescence intensity (MFI)
- Labs can submit optional data on the MFI of antibodies and what they would class as an unacceptable antigen (UA)
  - In 10 samples provided to labs in the UK and Ireland in 1 year (2019–2020), the highest variability seen in calculated reaction frequency (cRF) was 36%, based on each lab's UA classification
    - There appears to be less inter-lab difference when the cRF is higher
    - More complex antibody profiles may result in less concordance between labs
  - Antibodies with lower MFI ranges were more inconsistently listed as UAs
    - The decision to list relatively low MFI antibodies as UAs can result in quite dramatic increases in cRF
  - Antibodies identified at high MFI were more likely to be listed as UAs
    - However, a minority of high MFI antibodies were not listed as UAs
    - In the 5,001–9,999 MFI range, these tended to be Class II specificities defined at HLA-DR51/52/53 and (DPB) antibodies
    - In the >10,000 MFI range, the majority of these were DPB antibodies
    - At this time (2019–2020), labs were not defining DPB antibodies as unacceptable antigens for transplants, which may account for some of these findings
- Educational scenarios are paper-based cases which present patient details and laboratory information and ask for clinical interpretation
- Cases can highlight variability in standard practice between labs
  - One case involved a 26-year-old male patient who had not started dialysis, had a history of transfusions 4 years earlier, and was Class I single antigen bead (SAB) negative but positive for DR4 and DR7 antibodies with an MFI <1,500
    - 47% of labs in the UK and Ireland reported that they would not list any UAs

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- 6% of labs would list DR7 as unacceptable, resulting in a cRF of 25%
  - 12% of labs would list DR4 as unacceptable (cRF 33%)
  - 35% of labs would list both DR4 and DR7 as unacceptable (cRF 53%)
- Another, more complex, case involving a patient with Class I and II antibodies, reactivity to self and previous transplants resulted in 18 different UA profiles from labs in the UK and Ireland
  - The number of antibodies listed as UAs varied from 0 to 21, resulting in a cRF range of 0–97%, illustrating how subjective cRF values can be
- As a result, a survey was sent to labs in the UK and Ireland on UA definitions, which showed:
  - 81% use a defined cut-off for UAs (usually aligned to clinical outcome or positive flow cytometry crossmatch [FC XM])
  - 69% detect an antibody twice in separate samples before listing as a UA, 19% only once, 12% other (sensitising events)
  - 44% perform additional testing to assist definition of UAs (modified SAB, 3rd party FC XM, epitope analysis)
  - 25% would list a mismatch from a previous graft even if no antibodies are defined (44% would list if an antibody is present but below standard cut-off)
  - 56% would adjust the positive threshold if auto-reactivity is present
  - 50% review UAs after every sample tested
  - 88% will delist UAs
- Consensus is difficult for many reasons, including differences between assays, interpretation of what is a clinically significant result and what is an acceptable risk for each individual patient

## Discussion

- Imlifidase is a new drug with a defined patient population in its labelling, but there are clear differences in approaches to reaching this definition
  - The indication in the labelling is quite broad and open to interpretation
- At cRF >95% there tends to be good consistency seen between labs, even more so at >99%
- Delisting UAs in patients with cRF >99.5% may increase the chance of an organ offer, but in the NEQAS survey, only 88% of labs said they actively delist UAs
  - The perceived 'strictness' on delisting may reflect the profile of cases sent to labs by NEQAS – delisting UAs is unlikely to be the difference between receiving an offer or not for patients with lower cRF values
  - It is important to define the level of sensitisation at which delisting becomes an important factor in potential organ allocation
  - A personalised approach to delisting is becoming more prominent
    - This is more difficult in larger centres with higher numbers of patients on the waiting list; however, the availability (and cost) of imlifidase highlights the need for this type of management for all patients
- In the absence of defined protocols/thresholds for interpretation of antigen testing, it may be helpful for different labs to take different approaches, as comparison of outcomes can lead to clinical insights

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- Quality assurance data such as those provided by NEQAS should be interpreted with caution, as they may not necessarily reflect the interpretation employed for real patients
- Sensitisation resulting from blood transfusion is considered by many clinicians to be less clinically significant and more transient in nature than other sensitising events, and the variability seen in UA listing for case study 1 was surprising

## Impact of the 2019 Kidney Offering Scheme

**Matthew Robb**

### Presentation

- Objectives of the 2019 Kidney Offering Scheme included:
  - Unifying the donation offering after brain death and donation after circulatory death
  - More effective 'quality' matching between donor and recipient
  - Better tailored HLA matching depending on age
  - Geographical equity of access
  - Avoid prolonged waiting times that are predictable
  - Waiting time from earliest of start of dialysis or activation on the list
  - Age should be a continuous factor (not binary allocation according to <18 or ≥18 years)
- The scheme prioritises patients with a matchability score of 10, a cRF of 100% or ≥7 years waiting time
- Thirty-six potential scheme algorithms were simulated for 4 years of activity using standard pools of real kidney donors and listed patients
- Compared with the 2006 scheme, the simulation of the chosen 2019 scheme showed more equitable waiting times for patients with higher matchability and cRF score
  - Reductions in predicted waiting times for patients with a cRF of 100% were more modest, but these patients would get priority in Tier A under new allocation rules
- Compared with the previous 3 years, data from the first 3 years of the new scheme (to July 2022) showed:
  - A 6% increase in transplants to highly sensitised recipients (cRF ≥85%), including a shift from 2% to 4% among cRF 100% patients (211 transplants)
  - A 3% increase in transplants to black, Asian and minority ethnic recipients
  - The proportion of Tier A patients on the waiting list decreased from 16% to 9%
  - The proportion of highly sensitised patients on the waiting list decreased from 26% to 19%
- During the first 3 years of the new scheme:
  - The number of highly sensitised recipients on the waiting list decreased by 8%
  - The number of patients waiting ≥5 years decreased by 3%
  - More than half of kidneys in each donor risk group were transplanted into recipients in the equivalent risk group
  - The proportion of transplants with ≥20 years age difference between donor and recipient decreased from 17% to 13%

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- The proportion of organs that were declined due to donor age decreased from 17% to 7%
- Both patient and graft survival at 12 months show no evidence of difference to the previous scheme

## Discussion

- Median waiting times are measured over long periods. Although waiting times have come down over the past 10 years, it is expected that a rise due to the COVID-19 pandemic will become apparent
  - More data are needed before the median waiting time of the new scheme can be compared with the 2006 scheme
- There was an increase in Tier A transplants soon after the introduction of the new scheme, which has since levelled off, but the positive effects of the new allocation system also benefit all new patients joining the waiting list
- Future revisions of how cRF is derived might consider more granular definitions of cRF 100% patients (currently 100% refers to all patients with cRF  $\geq 99.5\%$ )
  - Inclusion of DBP antibodies is also important, as some patients are highly sensitised only to DBP and there is currently no way to define these patients
  - All donor kidneys are now HLA-DBP typed to prevent positive crossmatch (XM) due to high levels of DBP antibodies
    - Work done in Cardiff has shown that MFI  $>10,000$  results in a positive XM across DBP expressions, but MFI  $<10,000$  is a 'grey zone' for XM
- In the context of imlifidase and donor-specific antibody (DSA)-positive or XM-positive transplants, it becomes much more important for clinicians to understand how labs are defining risk associated with DSAs

## Improving risk stratification

### *Sunil Daga*

## Presentation

- Risk stratification must encompass immunological, patient and technical factors
- Even among patients with cRF 100%, when other risk stratification factors are considered, only a small number may be appropriate for imlifidase treatment (the imlifidase Post Approval Efficacy and Safety [PAES] study has identified two of 45 patients with cRF 100%)
- Most current literature on risk stratification for HLA incompatible (HLAi) transplant is based on living donors, and it remains to be seen how this applies to deceased donors
- There is debate around how long historical DSAs should remain listed; 5 years may be too long – in Leeds, this has been changed to 1 year with success
- Antibody-mediated rejection (AMR) within the first month may not be a significant factor in long-term graft outcomes
  - Antibody profile and persistence of AMR are more important predictors of graft outcomes
  - Predicting which patients are likely to experience persistent or recurrent AMR is likely to lead to better long-term graft survival

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- Younger male patients with a complement-dependent cytotoxicity (CDC) titre of >1:2 and pre-treatment total DSA >6,600 MFI (median 9,800) are those most at risk
- Data from the Antibody Incompatible Transplant (AiT) registry in 2017, showed that the lowest 5-year graft survival was among patients who were FC XM positive and did not have a CDC XM performed (63%)
  - As centres are moving away from CDC XM, there may be more qualitative work to be done in this area. It has been suggested that CDC titre may be predictive of graft survival
  - Some other assays may be useful in predicting CDC XM when it is not conducted; presence of C3d DSAs has shown predictive value
- Post-transplant monitoring can give clues to how to stratify risk pre-transplant
  - In a study of dynamic behaviour of DSAs soon after HLAi transplant, a machine learning tool categorised DSA into clusters; one such cluster was common among women with pregnancy as a sensitising event, and was typified by rapid increase then decrease of DSA levels
    - Although most of these patients had AMR, their long-term graft survival was very good
- MFI is not able to assess the quantity vs quality of antibody binding, which impacts *in vivo* antibody-dependent cell signalling and pro-inflammatory responses
  - Clinically, this is apparent when patients with similarly high MFI levels have different responses to plasma exchange (PLEX) therapy
  - Using diluted patient serum on testing assays may provide additional qualitative information on antibody binding quality, and therefore identify potential difficulties in desensitising using PLEX or intravenous immunoglobulin (IVIg), and identify potential patients for imlifidase
- Imlifidase works in a two-step process, first creating single-cleaved immunoglobulin G (IgG), followed by fully cleaved IgG
  - Hansa advice is to wait 6 hours after administration of imlifidase before assay assessment for transplant eligibility (cross match conversion), as single-cleaved IgG can lead to positive assay results before this time
  - These timings must be considered in the overall procedure, including the impact on cold ischaemia time
  - One unknown is the residual effect of circulating imlifidase on assay results after the transplant procedure

## Discussion

- Responses to PLEX may also depend on the rate of antibody production – very high rates of production will lead to lack of PLEX response
  - Plasmon resonance studies into antibody binding affinities are currently in their infancy, but may shed further light on the impact of binding quantity vs quality
- Imlifidase does cleave other antibody treatments in the IgG class, and it is recommended that these are not administered within certain antibody-specific time periods (detailed in the label)

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- Barriers to risk stratification for imlifidase suitability include the high likelihood of AMR and the need for patients to be able to cope with AMR treatment; patients with significant comorbidities may not be suitable for this reason

## Defining the patient population who would benefit from imlifidase

*Nicholas Torpey*

### Presentation

- Imlifidase should be considered in difficult-to-transplant patients for whom efforts to secure a compatible or low-risk incompatible kidney are unsuccessful, provided imlifidase therapy does not pose undue risk
- The US allocation scheme was changed to favour sensitised patients in 2014
  - One year later, the number of patients with a cRF of 99–100% receiving a transplant increased from 2.4% to 12.3%
  - Three years after the new scheme was introduced, the chance of patients with cRF  $\geq 99.9\%$  receiving a transplant was  $\sim 20\%$ , compared with  $\sim 4\%$  in the 3 years before the scheme was introduced
    - In addition to this, the chance of an offer for patients with cRF 99.5–99.9% increased to the degree that it exceeded the chances of the general waiting list population
    - This showed that only a very small change in cRF could drastically change the probability of a kidney offer, bringing it more in line with that of the general waiting list
    - However, among patients with cRF  $\geq 99.5\%$ , the vast majority have cRF  $\geq 99.9\%$  and so still accumulate on the waiting list
- Similarly, in the UK, the waiting list is dominated by patients with either cRF 0% or  $\geq 99\%$ 
  - In February 2020, 13.5% of patients on the waiting list had cRF  $\geq 99\%$  and 10.9% had cRF 100%
  - Patients with cRF 100% are least likely to be transplanted, so efforts should be made to establish whether these patients really do have cRF 100%
    - This is influenced by the use of inconsistent MFI thresholds and listing of historical antibodies as unacceptable
    - In the context of imlifidase, it is crucial that antigens to which patients do not have antibodies, or have low levels of antibodies are not listed as unacceptable
    - These patients should undergo regular review of delisted antibodies to remove barriers to transplantation that are not clinically important
- The cRF of patients in the imlifidase clinical development programme was very variable, and included patients with cRF  $< 85\%$ 
  - In the UK, these patients could be transplanted through allocation with a reasonable waiting time, and therefore would not be considered for imlifidase
  - Additionally in the US, where many patients were enlisted in these studies, a rigorous protocol is missing for updating serum analysis for patients on the waiting list

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- Seven patients in the imlifidase trials did not have DSA or a positive XM
- At one US study site (Cedars Sinai), the turnaround for a XM test is 24 hours, meaning imlifidase was administered before positive XM was confirmed, including to some patients who subsequently had a negative XM
- The rate of AMR was high in US patients in the Phase 2 study of imlifidase, and the therapies used to treat it in the trial are not readily available in the UK
- Among clinical trial patients with cRF  $\geq 99.9\%$  who received a deceased donor kidney, 58% had AMR, illustrating the risk of imlifidase therapy with very high-risk patients
  - All three deaths in the clinical trial programme were in this patient group; all were within 3 months of transplant, although no correlation with imlifidase treatment or AMR has been established
  - Three-year outcomes in this group showed good estimated glomerular filtration rate, but persistently high Class II DSAs, which jeopardises long-term graft survival
- The UK should not try to replicate imlifidase experiences of other countries, but focus on how imlifidase can help transplant highly sensitised patients within the context of the UK system
  - Centres could have a list of patients approved for imlifidase, who have serum samples analysed every month, rather than every 3 months, so there is a current sample readily available in the case of an offer
  - Surgeons are unlikely to be willing to administer imlifidase until the donor kidney has been delivered and they have inspected it
  - Testing for DSA removal after imlifidase administration should happen after 4–6 hours; 2 hours is too soon

## Safe, effective and equitable implementation of an imlifidase-enabled kidney transplant pathway – a four-nation view

**Rommel Ravanan**

### Presentation

- The NHS commissioners for the four home nations agreed that NHS Blood and Transplant (NHSBT) guidance was needed on imlifidase implementation, which they could then use to write policy on imlifidase
  - A national expert group was assembled including clinical and H&I specialists:
    - Seven nephrologists, five H&I experts, three surgeons and two pharmacists
    - Split into two subgroups: a ‘pre-transplant’ group looking at patient selection, and a ‘Day 0’ group looking at the procedure on and following the day of transplantation
  - The guidance produced by the expert group will be reviewed and endorsed by the British Transplant Society (BTS) and British Society for Histocompatibility and Immunogenetics (BSHI)
  - The aim is to have a working draft of the guidance before the end of 2022

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- The four NHS commissioners initially agreed that there should be a national panel of clinical and H&I experts set up to review and authorise each candidate put forward for imlifidase treatment
  - However, one nation has since decided not to participate in this, a final decision on whether to create a panel is yet to be reached
  - Complexities involved with setting up such national panels include reimbursement to members and indemnity protection for decisions made
- In having a national organisation, the NHSBT, the UK is excellently placed to collect registry data on the imlifidase rollout and answer research questions that remain from the imlifidase clinical trial programme
  - The national expert group will also advise on which data should be collected

## Discussion

- NHSBT will not seek to dictate which UK transplant centres will be able to use imlifidase, it will be up to each centre to confirm they have the expertise required
  - This expertise is less about administering imlifidase or the transplant surgery, but managing the patient after an imlifidase-enabled transplant
    - Sequential 'checkpoint' learnings can be derived from early registry data and quickly distributed to transplant centres
- Should an expert panel be established, it may play a role in supporting centres in the management of early imlifidase-enabled transplants
- NHSBT are planning to include an imlifidase 'tick box' exercise during the organ allocation process to enable tracking of outcomes in imlifidase-treated patients
- NHS pricing and tariffs for imlifidase-enabled transplants could impact the equity of access to imlifidase treatment
  - NHS commissioning seems to be moving away from tariffs, so this may be less relevant in the future
- An NHSBT memorandum of understanding for linkage to hospital data, while difficult to achieve, would be a major advantage when setting up a registry

## Pathway to implementation: protocol standardisation and data collection

### Group discussion

- NICE has dictated that patients should be active on the waiting list for at least 2 years before they are eligible for imlifidase
  - This represents the median waiting time in the UK across all kidney transplant patients
  - Patients who are transplanted under Tier A of the Kidney Offering Scheme tend to be transplanted quite quickly, so there may not be much rationale for mandating a longer waiting list time for imlifidase eligibility
- Regular review of unacceptable antigens for potential delisting should be undertaken during these 2 years; for some patients it may be worth waiting longer if they can be offered an acceptable-risk transplant via delisting. Ideally, a consistent approach to this would be applied across all centres
  - Imlifidase is the final step in a tiered approach that first involves attempts to find an antibody-compatible kidney, followed by options for a DSA-positive

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- XM-negative transplant, before a DSA-positive XM-positive transplant should be considered with imlifidase used to convert a positive to a negative XM
- It would be within the remit of the NHSBT expert group to provide recommendations on a national approach to delisting UAs in these patients before imlifidase is considered
  - In the absence of a national NHS panel for imlifidase use, which could oversee this, it would be difficult to ensure centres follow the recommendations
- There is widespread clinical support for an NHS national panel for at least the first year, given the potential issues around equity of access to imlifidase, the cost of the drug, and the potential to gather valuable data on its use
- Experience of treating AMR after antibody removal with PLEX will be valuable in defining clinical management of imlifidase-treated patients with AMR
- Getting the right kidney will be an important factor in imlifidase use
  - High donor risk category (D3 and D4) kidneys are unlikely to be suitable for use in imlifidase-enabled transplantations
  - The increased cold ischaemia time associated with imlifidase use may also have implications for use of donation after circulatory death kidneys in some cases, for example in Belfast, where there is potentially a longer transport time
    - However, in the US the average cold ischaemic time is double that in the UK (22 hours compared with 11 hours)
  - Surgeons widely agree that they must see the kidney in person before the patient receives imlifidase, photos are not sufficient
  - The kidney will need to be able to withstand the expected AMR after an imlifidase-enabled transplant, as well as other health considerations, as patients who might be eligible for imlifidase may have been on dialysis for some time and have other significant comorbidities

## Future potential of T regulatory cell and cytotoxic therapies

**Anthony Dorling**

### Presentation

- HLAi transplant patients suffer higher rates of AMR, but also of T cell-mediated rejection and chronic rejection, despite enhanced immunosuppressive treatment
- With imlifidase, the extended cold ischaemic time could provide opportunities to manipulate the graft to improve outcomes, while the period post-transplant when the graft is exposed to low titres of DSA which could be used to enhance protection of the graft
- PhD work at King's College showed that in a sample of cells from 30 transplant pairs, donor-specific IL-17 responses were only seen in sensitised individuals, and among the 14 pairs who were transplanted, the three episodes of rejection all occurred in recipients with donor-specific IL-17 responses
  - This suggested that IL-17 could play a role in risk stratification
  - Further work showed that expanded T regulatory cells completely suppressed in vitro IL-17 responses to HLA proteins against which the patients had DSAs, in five of six patients

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- In other assays, we have defined the phenotype of the subpopulation of Tregs that mediate endogenous suppression of IL-17. This subpopulation is expanded during *in vitro* culture to generate polyclonal Tregs.
  - A small feasibility study known as the GAMECHANGgER trial is currently recruiting and will assess whether expanded T regulatory cells can suppress cytokine responses in patients with IL-17 or interferon gamma production to potential donor proteins
- Studies have shown improved renal function and reduced T cell sensitisation in grafts perfused with 'cytotoxic' anti-complement drug mirococept, which is currently being studied for delayed graft function in the EMPIRIKAL trial
  - Mirococept could also be studied in grafts that are at risk of AMR
- 'Cytotoxic' thrombin inhibition with cyclosporin in rodent heart grafts has been shown to completely prevent AMR
  - Consequently, a cytotoxic direct thrombin inhibitor (PTL060) has been developed
    - *In vitro*, it stays tethered to cells for 24 hours before being internalised
    - *In vivo*, the biological effects (e.g. inhibiting chemokine production by vascular cells) have been observed for more than 1 week after a single intravenous dose in a murine model
    - The drug has completed preclinical testing, but a Phase 1 clinical trial failed to secure funding
- Both of these classes of investigational drugs could play a therapeutic role during the period of low DSA levels after imlifidase administration to protect the graft while antibody titres are rising, and perhaps reduce the incidence of AMR
  - The imlifidase rollout in the UK is an opportunity for these, and other, techniques to be studied in highly sensitised transplant patients via an investigator-led, adaptive platform trial
    - Other interventions that could be studied include: machine perfusion vs static cold storage, pre-emptive PLEX/IVIg during the first week post-transplant to maintain low IgG levels, and extracorporeal photopheresis immunomodulation
    - However, before such a trial could be designed, protocols need to be standardised across centres, including some agreement on procedures for: induction and maintenance immunosuppressive agents used, HLA antibody monitoring, AMR and T cell-mediated rejection therapy, biopsies, and collection and reporting of data
    - Access to existing baseline and outcome data would also be required to assess feasibility of design and to power such a trial

## Discussion

- The Phase 1 trial for PTL060 was rejected for funding in part due to a primate model failing to show an effect on the rate of AMR, although the drug did inhibit thrombin as intended
- Machine perfusion in liver transplantation with OrganOx has increased the viability of organs to 24 hours; trials are underway with kidneys with similar outcomes targeted

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- An investigator-led, adaptive platform trial into new interventions for highly sensitised patients could enhance our understanding of immunological processes in a way that benefits the wider transplant community
- Interventions that could be protective after imlifidase-enabled transplantation would be beneficial given the effect of imlifidase on commonly used induction therapies

## Management options for treating AMR post-implifidase

*Michelle Willicombe*

### Presentation

- In imlifidase clinical trials, 28% of patients had AMR in the first month and 38% had AMR in the first 6 months, rebound DSAs were common and minimal inflammation was a common feature on biopsies
  - However, treatment of AMR was inconsistent across centres included in the trial
  - Rates of AMR appeared similar between different induction strategies, although the low number of patients limits conclusions, and it would be useful to study this further
- For post-implifidase monitoring, creatinine will likely be useful in patients with graft function, but biopsy will be required for those with delayed graft function
  - It is unlikely routine biopsy will be approved as part of any monitoring protocol
  - Histopathology partners will be important in the monitoring of these patients and should be involved ahead of time by centres planning to use imlifidase
- Histopathologists and clinicians have shown poor concordance on the diagnosis and cause of AMR
  - Poor concordance generally leads to differences in AMR treatment
  - The chronicity of rejection will be important to understand in imlifidase-enabled transplants
- Based on experience in HLAi transplants, it is likely that early acute and acute (<6 months to 1 year) AMR will be most common with imlifidase-enabled transplants
  - Establishing criteria for defining AMR and treatment protocols based on those criteria will aid learnings from early imlifidase-enabled transplants
  - Biopsy criteria for the initiation of treatment of acute/active AMR could be based on the Banff 2019 classification
    - This might enable further collaboration within the Banff group and investigation of: molecular microscope biopsy testing, implementation of iBox follow-up and potential validation of data from the French iBox cohort, and use of novel activity and chronicity scores for rejection
- There are no up-to-date BTS guidelines on the treatment of AMR, and survey data show different approaches across UK centres
  - Consensus would be useful, particularly for centres that have less experience in treating acute AMR
  - Certain potential therapies, such as complement inhibitors and rituximab, are currently not commissioned in the UK for use in kidney transplantation, but their inclusion in a potential adaptive platform trial could perhaps be negotiated

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## Discussion

- Although patient selection for imlifidase may vary in other countries, protocols for diagnosing and treating AMR in this patient group are likely to be similar, opening the door to international collaborations
- Intervention based on the rapid return of antibodies alone might not always be necessary, as a rebound is expected; the wider clinical picture should be considered and ideally biopsy would be used to determine AMR and the need for intervention
  - Patients with delayed graft function are likely to be the most challenging to manage as they will require an early biopsy
  - Intense antibody monitoring may not be possible owing to funding, and this will require consensus on the best time points to conduct antibody testing post-implifidase
    - This will be developed based on experience with other HLAi transplants and early experiences with imlifidase
- The imlifidase protocol to be used in France has been finalised, but not yet published, and a Nordic working group is currently working on a protocol, both of which may be of interest to the UK national expert group
- An estimate of 5-year graft survival in imlifidase-treated patients, based on the 3-year survival seen in the imlifidase clinical trials and HLAi living donor transplants who have undergone PLEX, might be approximately 75–80%
  - This could be a figure to use to counsel potential early imlifidase patients
  - It is important to note that the amount of risk that patients are willing to accept varies widely
- There may be an opportunity for imlifidase-eligible patients to start immunosuppressive treatment while they are waiting for a kidney offer
  - Some centres already occasionally do this with complex HLAi living donor cases, although induction treatments used and protocols differ between centres
- In terms of which patients to select for imlifidase-treatment: those with low immunological risk would ideally wait for a compatible organ offer through usual routes, and those with very high immunological risk would be likely to be too high-risk for imlifidase-treatment until enough experience is gained and learnings can be applied, meaning that those with medium immunological risk, whose only current option is to wait on the list, are likely to be the ideal candidates for an imlifidase rollout
- Some centres may be less willing to change their tried and tested protocols for HLAi patients to accommodate an imlifidase protocol
  - Coventry, for example, does not use any induction treatment apart from basiliximab and relies on close post-transplant monitoring to treat as needed, with good results
  - Adding too many investigational protocols to the imlifidase rollout could obscure or alter the perception of how imlifidase performs in this real-world population
    - Building in protocols to answer these research questions as experience is gained with imlifidase may be a preferable approach
  - Different centres have access to different immunosuppressive agents, with nuances in what is permitted for induction use and what is reserved for

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treatment of AMR – this may make a standardised induction protocol challenging

- If a protocol dictates that a centre uses an agent that they are unfamiliar with, it adds unnecessary complication
- An adaptive platform trial could be used to expedite comparisons of existing induction protocols between studies to decide on a preferred regimen
  - This would allow centres to roll out imlifidase without needing to amend their existing protocols in a challenging new patient population

### Key messages

- External quality assessment of UK H&I labs generally shows good performance. However, differences in interpretation of assay results, defining UAs and approaches to delisting lead to large disparities in cRF scores, which could have significant impact on chances of an organ offer for highly sensitised patients
- The 2019 Kidney Offering Scheme prioritises highly sensitised patients and has resulted in more transplants to highly sensitised recipients, fewer highly sensitised patients on the waiting list and shorter waiting list times for these patients. For recipients in general there is improved ‘quality’ matching between donor and recipient
  - Patient and graft survival at 12 months are unaffected compared with the previous allocation scheme
  - Future revision to how cRF is derived should consider more granular definitions of cRF 100%
- Risk stratification of highly sensitised patients will play an important role in selecting appropriate patients for imlifidase treatment
  - Much of the current literature on risk stratification for HLA incompatible (HLAi) transplantation is based on living donors, and it remains to be seen how this applies to deceased donors
  - Novel and qualitative methods may allow for more granular and accurate risk stratification of highly sensitised patients
- The patient population in the imlifidase clinical trial programme does not necessarily represent the likely candidate pool for imlifidase use in the UK and identification of appropriate candidates should be contextualised by the transplant system in the UK
- NHSBT has assembled a national expert group to provide guidance on the rollout of imlifidase in the UK
  - NHS commissioners for each of the four nations of the UK are discussing whether to set up a national panel of clinical and H&I experts to review proposed imlifidase candidates and provide expert support in the management of these cases
- Regular review of listed UAs for potential delisting will be crucial to identifying patients for imlifidase treatment; ideally a national protocol for delisting would be established and used by all UK centres
- Getting the ‘right’ kidney will be key to successful imlifidase use – D3 and D4 kidneys are unlikely to be suitable, and AMR is expected to be common with imlifidase-enabled transplants, requiring that patients and grafts are suitable for AMR treatment

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- Logistical matters such as increased cold ischaemia time and surgeons wanting to inspect the donor organ in person before administration of imlifidase must be factored into the transplant procedure
- The rollout of imlifidase in the UK provides opportunities to answer important research questions via an investigator-led, adaptive platform trial
  - Manipulation of the graft during the cold ischaemic time and treatment during the period of low DSA titres following imlifidase treatment using novel treatments such as expanded T regulatory cells and 'cytotoxic' therapies may enhance outcomes
  - Other interventions that could be studied include: machine perfusion vs static cold storage, pre-emptive PLEX/IVIg during the first week post-transplant to maintain low IgG levels, and extracorporeal photopheresis immunomodulation
- There is inconsistency in the diagnosis of AMR which leads to varying treatment approaches
  - Experience with other HLAi transplants and early imlifidase experiences will help inform best practice for post-transplant monitoring and AMR treatment protocols
  - While some UK centres may be reluctant to subscribe to an AMR treatment protocol, the imlifidase rollout could be used to compare practices to improve clinical management
  - International collaboration may also be possible to further investigate monitoring tools

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