Final report of the workshop 'Management of transplant patients with HLA antibodies'

22 March 2023, Copenhagen, Denmark

Programme

10:00 – 10:20	Welcome coffee and Introduction	Søren Schwartz Sørensen | Copenhagen, Denmark
10:20 – 10:40	Demography of sensitised waiting list patients in SCTP	Søren Schwartz Sørensen | Copenhagen, Denmark
10:40 – 11:10	Present options for the highly sensitised patients in SCTP and results	Lars Wennberg | Stockholm, Sweden
11:10 – 11:40	How to optimise the STAMP program	Mats Bengtsson | Uppsala, Sweden
11:40 – 12:10	Delisting antigens in the highly sensitised patients, where to draw the line?	Nizam Mamode | London, United Kingdom
12:10 – 13:10	***Lunch break***	
13:10 – 15:10	Each centre presents their local experience with desensitising patients and bring one case for discussion	All
15:10 – 15:40	Final general discussion where we try to reach conclusion on the following issues: • Are we too cautious transplanting HLAi patients? • What is needed regarding local/national organisation when transplanting HLAi patients? • Where do we go from here?	All

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Attendees

Margrét Birna Andrésdóttir | Reykjavik, Iceland
Mats Bengtsson | Uppsala, Sweden
Alireza Biglarnia | Malmø/Lund, Sweden
Claus Bistrup| Odense, Denmark
Helle Bruunsgaard | Copenhagen, Denmark
Pernille Bundgaard Koefoed-Nielsen | Aarhus, Denmark
Jan Carstens | Odense, Denmark
Christina Dörje | Oslo, Norway
Ilse Duus Weinreich | Scandiatransplant/Aarhus, Denmark
Torsten Eich | Stockholm, Sweden
Sveinn Gudmundsson | Reykjavik, Iceland (remote attendee)
Ilkka Helanterä | Helsinki, Finland
Jan Holgersson | Gothenburg, Sweden
Külli Kõlvald | Tartu, Estonia
Jouni Lauronen | Helsinki, Finland
Ann-Sofie Liedberg | Malmø/Lund, Sweden
Nizam Mamode | UK/Mauritius (remote speaker)
Lars Mjörnstedt | Gothenburg, Sweden
Christian Naper | Oslo, Norway
Søren Schwartz Sørensen | Copenhagen, Denmark
Karin Skov | Aarhus, Denmark
Priit Veskimäe | Tartu, Estonia
Lars Wennberg | Stockholm, Sweden (remote speaker)

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 across the Nordic region.

Welcome and Introduction

Søren Schwartz Sørensen

Presentation

- The ESOT guideline for the management of kidney transplant patients with HLA antibodies outlines an algorithm of treatment options in this patient group, and an important part of the present meeting is to assess how well Scandiatransplant centres fulfils these treatment options
- Increasing 'strength' of donor-specific antibodies (DSAs) is associated with higher risk of graft loss and patient mortality compared to compatible transplantation
    - 'Strength' measured by different crossmatch (XM) methods – complement-dependent cytotoxicity (CDC) XM positive, flow cytometry XM positive and CDC XM negative, or Luminex XM positive and flow XM negative
    - While transplant outcomes in highly sensitised patients are generally worse than in compatible transplanted patients, they are likely favourable to remaining on dialysis on the waiting list
- A calculated panel-reactive antibody (cPRA) value of 100% does not present the same challenge in each patient – dilution of sera in different patients with cPRA 100% has shown that while some will reach cPRA 0% with dilution, others will show very little change in cPRA despite repeated dilution
    - This type of study can give an indication of how difficult a given patient would be to desensitise
- Scandiatransplant has three exchange schemes in place that address the needs of sensitised patients:
    - The Scandiatransplant Acceptable Mismatch Programme (STAMP) – when the patient is ABO compatible with the donor and HLA (human leukocyte antigen)-A, -B, -C, - DRB1, DRB3/4/5, DQA1, DQB1, DPA1, and DPB1 antigens are defined as acceptable
    - Highly sensitised patients (PRA ≥80%) who are HLA-A, -B, and DRB1 compatible with the donor
    - Sensitised patients (PRA ≥10 to <80%) who are HLA-A, -B, and DRB1 compatible with the donor
    - In Scandiatransplant, approximately 20% of kidneys transplanted are exchanged (including payback)

Demography of sensitised waiting list patients in Scandiatransplant

Søren Schwartz Sørensen

Presentation

- Scandiatransplant has developed a gateway for Luminex single-antigen bead (SAB) assay data collected by One Lambda's Fusion software to be imported directly into YASWA (Scandiatransplant's online database)This process is automatic in Sweden, Iceland, Denmark and Estonia, and

includes mean fluorescence intensity (MFI) and final assignment (the listed antibodies for a given patient)
        - Due to data protection rules in Norway, data must be transferred to YASWA manually, but Norway is moving towards automatic data entry
        - Currently, Finland only exports data for STAMP patients, and does not input MFI or final assignment data for non-STAMP patients into YASWA
        - Final assignment data is at the discretion of centres, so may be used to delist antibodies
    - Export of Fusion data to YASWA provides valuable knowledge on the strength and specificity of antibodies in the population served by Scandiatransplant and will aid in tracking outcomes in HLA incompatible (HLAi) transplants
- Eligibility into STAMP is based not on cPRA, but on Transplantability Score (TS), derived from cPRA and blood type, via the formula:
  ((1−cPRA%, expressed as a decimal) × blood type O frequency, expressed as a decimal) × 100
    - Example: cPRA 50% and blood type O frequency 38%
      TS = ((1−0.5) × 0.38) × 100 = 19%
    - Estimated Transplantability Score (eTS) is based on identified antibodies either automatically or manually entered into YASWA
        - A calculation is possible for all Scandiatransplant patients outside Finland
    - Calculated Transplantability Score (cTS) is based on antigens identified as acceptable (final assignment) by single centres and entered into the STAMP module on YASWA
    - It is important to ensure the cPRA field is completed when entering data, otherwise it will be defined as 0% and an incorrect TS will be provided for the patient
    - Within YASWA, there are lists for all antibodies detected in a patient's history and those detected within the last year, both of which can be used to calculate an eTS
        - In the future it would be useful to have a calculator tool which allows clinicians to identify antibodies for potential delisting and provides cPRA and eTS based on this input
- TS can be used to estimate the number of organ offers a patient can expect to receive per year by multiplying by the number of donors available
    - Local acceptable mismatch programmes (LAMPs) will, in theory, yield fewer offers than STAMP, as the donor pool is smaller
- Analysis of eTS and cTS scores in STAMP patients have shown good agreement between the two (N=89, excluding patients from Finland for whom only cTS is available)
- There are currently 101 patients in STAMP:

    - 59% are women
    - Median age approx. 55 year old, though there is one patient below the age of 20
    - n=34 waiting for their first kidney transplant (41 second, 19 third, 7 fourth)
        - Among those waiting for their first transplant, there are 7 patients with TS 0%, all women with pregnancy as their sensitising event
    - n=86 have a cTS below 0.25%, and n=50 have cTS 0%
- The majority of patients in STAMP have spent most of their total waiting time in STAMP, showing that eligible patients are usually quickly entered into STAMP
    - There is a small number of very highly sensitised patients with long waiting times who are outliers, who joined the waiting list before STAMP was created
        - In the past, there was also a minimum waiting time of 1 year before joining STAMP, which contributes to some outliers
    - Patients with lower cTS tend to have a longer waiting time
- There are currently a total of 1077 patients active on the Scandiatransplant waiting list
    - n=533 have cPRA 0%
    - n=374 have cPRA >0 to 90%
    - n=170 have cPRA >90%
    - Waiting times tend to be higher for those with cPRA 0% and very high cPRA (patients in STAMP)
        - Long waiting times in highly sensitised patients are particularly skewed towards those with cPRA >98%

Can we improve STAMP?

Mats Bengtsson

Presentation

- Balance between benefit and risk is key with highly sensitised patients
    - Very strict definitions of acceptable mismatches (AMs) will result in better outcomes but fewer HLAi transplants
    - Less stringent definitions of AMs will result in more possible donors and more transplants in this patient group, but perhaps also higher rates of antibody-mediated rejection (AMR)
- In 2008, prior to the creation of STAMP, >50% of highly sensitised patients had a waiting time of >2 years, and 20% had a waiting time >5 years
    - 80% of non-sensitised patients were transplanted within 2 years during the same period
- Between 1995 and 2006, there was a clear trend of poorer graft survival among highly sensitised patients (PRA >80%) who were transplanted compared to non-sensitised and sensitised patients with PRA ≤80%
- When STAMP was initiated in April 2009, the acceptance criteria were:
    - Waiting time >1 year (except children)

    - PRA >80%, defined recently and repeatedly
    - HLA-A, -B, -DR, or split-level antibodies
- Initially, the following criteria were defined to assess the success of STAMP:
    - Reduced waiting time for highly sensitised patients
    - <10% of shipped kidneys not transplanted to the indicated STAMP patient due to a positive XM
    - Graft survival comparable to non-sensitised patients
- There was some initial success; between 2009 and 2015, 96 patients were transplanted in STAMP, and 5-year graft survival was not significantly different (p=0.309) to sensitised patients transplanted with ABDR-identical donors (n=73)
    - STAMP patients had between 2 and 5 HLA mismatches
    - There were no cases of AMR in the STAMP cohort
- While transplant outcomes were good, STAMP was not able to help all highly sensitised patients
    - In 2015, analysis of the 87 patients listed in STAMP at the time showed that only 23 (26%) had an increased chance of a donor compared to their likelihood without STAMP
    - There were also 75 highly sensitised patients without a STAMP record
    - Despite there being patients with antibodies against HLA-DQ and HLA-C antigens, these were not being typed at the time and were actually manually removed; extended HLA testing has evolved over time in STAMP:
        - HLA-DQ in 2010
        - HLA-C in 2012
        - HLA-DPB in 2019
        - HLA-DRB3/4/5, DQA1 and DPA1 in 2020
        - After testing for all 11 HLA loci was introduced in April 2020, it was shown that 84% of patients in STAMP had antibodies for the newly included alleles
    - Between 2009 and 2018, HLA typing also increased in priority in terms of exchange rules, from priority 5 to priority 1
- Other changes to STAMP included:
    - Introduction of the TS, which combines PRA with ABO compatibility, in 2017
    - Removal of the 1-year waiting time requirement, also in 2017
        - A patient with TS 0% has virtually no chance of an offer, so there is little sense in a mandatory waiting time
    - Acceptance of ABO compatible, rather than identical, donors for STAMP patients, in 2018
        - As these changes, as well as the expansion of HLA typing were introduced, the number of patients entering STAMP, and the number of STAMP transplants increased
- Between 2009 and 2020, there was no significant difference (p=0.2) between death-censored 10-year graft survival for STAMP transplantations vs all other transplantations in Scandiatransplant

- While these outcomes are good, the outlook has not improved since 2015 in terms of the ability of STAMP to increase the number of offers for these patients
    - Recent analysis of 111 patients in STAMP showed that only 4 had a TS >1%
- Higher resolution HLA typing is one way that more patients may be transplanted through STAMP
    - Currently, allele-specific antibodies are not discriminated – if there is a positive antibody against one allele, all will be listed as unacceptable
    - High-resolution HLA typing is now achievable within 4 hours
    - Matching by specific alleles could pair donors and recipients who would not be considered matches under current HLA typing
        - SAB assays require more beads to allow for higher resolution typing
        - The use of extended bead panels can help avoid false positive and false negative results
- The most effective way to increase the chances of an offer for patients in STAMP would be to increase the size of the donor pool
    - Data from the Europe-wide Strategy to enhance Transplantation of highly sensitised patients on the basis of Acceptable HLA Mismatches (EUROSTAM), showed that of 724 patients from across Europe, 195 (27%) would have a higher chance of receiving a transplant in a different European donor pool
    - HLA haplotypes vary geographically, so widening to donor pool to other European regions could introduce more suitable donors for patients in STAMP and vice versa
- Comparing STAMP to the Eurotransplant Acceptable Mismatch (AM) programme suggests that STAMP entry criteria are not too strict and the number of patients being transplanted is good
    - In 2020, 278/10162 (2.7%) of Eurotransplant patients were included in the AM programme, while current data show 150/1373 (10.9%) Scandiatranplant patients are included in STAMP
    - In 2020, 78/2555 (3.1%) of Eurotransplant transplantations were via the AM programme, while current data show 50/972 (5.1%) of Scandiatransplant transplantations are via STAMP
- In 2011, the Collaborative Transplant Study Report was published, which concluded that there was no association between kidney graft loss with HLA antibodies detected exclusively by Luminex SAB assay, stating:
    - “Consideration of HLA defined by this method as unacceptable would do harm by reducing the patient’s chance of receiving a donor kidney that would have resulted in an acceptable outcome”
    - STAMP data supports this – long-term graft survival for STAMP patients with HLAi transplants was not significantly different to sensitised patients receiving compatible transplants, or to all other transplants conducted by Scandiatransplant

    - The key factor is how we define what is an ‘acceptable’ mismatch – altering MFI cutoffs can have a large impact on TS
- A Dutch study of 3237 deceased donor (DD) transplants showed that 10-year graft survival was significantly poorer ($p<0.0001$) in patients with DSAs (60% graft survival) compared with those without DSAs (76% graft survival)
    - Another study showed that long-term graft survival (up to 14 years) was similar for patients without repeated mismatches or DSAs, and those with repeated mismatches and without DSAs; however graft survival was notably poorer in patients with repeated mismatches and DSAs
- All grafts are likely to fail eventually, so it important to minimise sensitisation in the first place
    - Better matching can minimise the impact of sensitisation, using matching via epitope or amino acids, that than traditional HLA matching
        - The number of solvent accessible amino acid mismatches seems to be proportional to DSA formation across HLA loci
- In conclusion, improvements to STAMP could come from:
    - Cooperation with other European AM programmes (patients with TS 0% and long waiting time)
    - Implementation of high-resolution HLA typing
    - Use of extended bead panels
    - Allowing delisting of antibodies in STAMP patients together with desensitisation
    - Use of Modern matching techniques (epitope and amino acid matching)

Discussion

- STAMP graft survival data showed a small number of patients had early graft loss, these were due to surgical issues and venous thrombosis, there were no cases of AMR
- Delisting is permitted in STAMP but the case must then be re-evaluated by the STAMP committee
    - There must be oversight of delisting
- High resolution HLA typing is expensive and will require more funding

Management of transplant patients with HLA antibodies

Lars Wennberg

Presentation

- The best option for transplanting sensitised patients is to use a compatible kidney, however for many sensitised patients this is unlikely to be achievable
    - Avoiding DSAs is preferable but poses several questions:
        - Should all DSAs be avoided, if not, which?

        - How many DSAs should be avoided in patients with multiple antibodies
        - What is the critical MFI level, and should it be for single antibodies or the total level?
    - Should all positive XMs be avoided, or just some types?
    - What should the HLA-matching parameters be for allocation rules?
- Between 2009 and 2020, 278 transplants were performed via STAMP, equating to about 23 per year
- Another option for sensitised patients (as well as ABO incompatible [ABOi] and those with other incompatibility such as age or size) is the Scandiatransplant Exchange Programme (STEP)
    - Between 2019 and 2022, there have been 11 match runs, 4 re-runs and 49 transplants performed, equating to about 12 per year
- While the numbers of transplants via STAMP and STEP is small, they represent important options for highly sensitised patients
- Correlation between DSA MFI values and XM results are not strong
    - Especially for class II antibodies
    - DSA with MFI >10000 usually correlates to a positive CDC XM (though this correlation is less clear for class II antibodies)
    - The correlation is often even more obscure for class I antibodies against HLA-C, which often yields negative XM using both CDC and flow cytometry
    - There is a summative effect in patients with several DSAs, multiple antibodies with low MFI values can lead to a positive XM (particularly flow cytometry)
        - However, a positive CDC XM is usually caused by a dominant DSA with higher MFI
    - Patients with a positive CDC XM tend to have more pronounced DSA rebounds post-transplant and more active AMR
- At the Karolinska institute, between 2001 and 2012 (before Luminex was introduced), there were a small number of flow cytometry XM positive transplants carried out using desensitisation, based on experience with ABOi transplants
    - Select patients only (N=24), 11 were ABO compatible and 13 were ABOi
    - Desensitisation was performed with apheresis and rituximab
    - Graft survival at 9-years was poorer in both groups compared with other non-sensitised patient groups with a negative XM (ABO compatible living donor [LD], ABOi, and DD transplants)
        - The combination of positive flow XM and ABOi had the worst graft survival
        - Patients with a positive CDC XM were not selected for transplantation
    - These results lead to the conclusion that transplantation should be avoided in patients with a positive flow XM, particularly those who are ABOi, even with desensitisation via apheresis and rituximab

- Between the introduction of Luminex, in 2012, and 2022, 1513 patients were transplanted at Karolinska, 48 of these were in XM positive patients
    - There was no structured programme or set patient selection criteria
    - No desensitisation was performed
    - n=8 XM positive with DSAs
        - n=2 positive CDC XM
        - n=6 positive flow XM
        - All but one of these 8 patients had good long-term outcomes (mean follow-up 44±31 months)
        - There was one patient with AMR; this was a difficult patient, with 3 DSAs who was treated with imlifidase as part of the clinical trial and had significant immunosuppressive treatment. This patient did, however have good renal function at the last follow-up (93 months)
    - n=40 XM positive with non-donor-specific antibodies (sensitised, but not against the donor)
        - Among patients with a positive CDC XM who were sensitised (n=6), results were largely good, with one case of chronic AMR 22 months post-transplant, and one case of T-cell-mediated rejection 1 month post-transplant. Most had good kidney function at last follow-up (mean 42±22 months)
        - Among patients with a positive flow XM who were sensitised (n=7), there were no cases of AMR and all patients had good kidney function at last follow-up (35±26 months)
    - Although the sample size is small, these results suggest that it is possible to achieve good transplant outcomes in patients with a positive XM without desensitisation, in selected low-risk patients
        - No DSAs or one DSA with low MFI
        - Low PRA
        - Flow XM or CDC XM B-cell positive
    - Risk factors for AMR and poor outcomes in this cohort were:
        - Positive CDC XM (particularly T-cell)
        - >1 DSA
        - High MFI
        - High PRA
- The generally accepted standard-of-care for desensitisation in Scandiatransplant is apheresis and rituximab (possibly with intravenous immunoglobulin G [IVIG])
    - Splenectomy and eculizumab have also been used
- Karolinska has been involved in a clinical trial of immunoglobulin G (IgG) degrading agent idefirix for the desensitisation of adult patients has been completed and a paediatric study is ongoing
    - Patients with DSAs and positive XM (CDC or flow)

- Karolinska is also going to be involved in a clinical trial of a complement inhibitor (BIVV020) for the treatment of acute AMR in patients transplanted with DSAs with an MFI ≥5000 and a positive CDC XM
- The Scandiatransplant Nordic Kidney Group presented a preliminary protocol for idefirix use in 2022, but the protocol has been temporarily withdrawn for updates and should not be used at this time
    - Recommendations are based on limited experience using idefirix and are based on the knowledge and experiences of Scandiatransplant clinicians involved in the idefirix clinical trials
- Idefirix converts a positive XM to a negative one in most patients within 24 hours, usually with a single dose
    - A second dose may be given 4-6 hours following the first, if required
    - If XM is repeated too soon after the first dose, these is a risk of a false positive result as idefirix cleaves IgG in a two-step process
        - This also results in the need for another XM test to be performed, prolonging cold ischaemic time
- In the EU, idefirix is indicated for the desensitisation of highly sensitised adult kidney transplant patients with a positive XM against a DD, and who are unlikely to be transplanted through other kidney allocation programmes
    - In Scandiatransplant, this likely represents patients in STAMP with TS ≤0.5%
    - However, it is also important to consider other factors in patient selection for idefirix treatment, including capacity to tolerate:
        - Transplant surgery
        - Induction therapy
        - Intensified immunosuppression
        - Treatment of AMR
        - Complications, infections
    - Patients with DSAs against a high frequency HLA with MFI 5000 to 10000 (or perhaps even higher for class II DSAs) who are flow XM positive and CDC XM negative may be patients who could gain access to a DD transplant using idefirix
    - When considering candidates for idefirix treatment, it is also important to consider HLA frequencies within the DD population
    - Prolonged cold ischaemic time and elderly DDs with multiple comorbidities should be avoided in idefirix-enabled transplants to minimise the impact of delayed graft function and difficult-to-detect early rejection
        - Donation after circulatory death organs should probably also be avoided
- AMR may occur as a consequence of DSA rebound in idefirix-treated patients
    - Patients with high MFI DSAs pre-transplant are more likely to require treatment for AMR
    - In idefirix clinical trials, DSA rebound usually peaked between 7 and 21 days post-surgery

    - AMR occurred in 30% of patients in the idefirix clinical trials (and in 39% of those with a positive XM pre-transplant)
    - However, AMR was successfully treated with standard-of-care treatment in all of these patients
        - Methylprednisolone 500 mg IV for 3 days
        - Anti-thymocyte immunoglobulin 1.5 mg/kg bodyweight IV for a minimum of 4 days
        - Plasma exchange until DSA MFI <3000 to 5000
        - Eculizumab 600 to 1200 mg IV weekly (until DSA levels have resolved)
        - Following decline of DSA levels: rituximab 375 mg/m^2 IV and IVIG 2 g/kg bodyweight over 48 hours
- Patient and graft survival data at 3-years post-transplant with idefirix are "encouraging"
    - Patient survival is slightly lower in patients who suffer AMR even as compared to patients with cPRA ≥99.9% and positive XM
    - There is also a pattern of lower estimated glomerular filtration rate (eGFR) in patients with AMR over the same time period
- A number of outstanding questions remain to be discussed regarding the use of idefirix within Scandiatransplant:
    - Should sensitised patients always be prioritised over non-sensitised, especially given the long-term outcomes and costs involved
    - Which patients should be selected for idefirix treatment?
    - Is idefirix cost-effective?
    - How should we go about collecting more data on idefirix use and gaining more clinical experience

Discussion

- Idefirix as it is currently used will not increase the overall number of transplantations, but it could were it to be available for use in LD transplants
    - This does raise questions about the ethics of LD transplants being prioritised for patients likely to have a worse outcome, but for many of these patients the alternative may be no transplant

Delisting antigens: where to draw the line?

Nizam Mamode

Presentation

- Many kidney allocation schemes will not offer a kidney to a patient if they have antibodies against the donor HLA antigens

- In the UK, sensitisation is expressed via calculated reaction frequency (cRF), which represents the percentage of the last 10000 DDs which the patient has antibodies against
    - 10000 DDs represents approximately 7 years of transplant activity in the UK
- The wait list time in the UK has been steadily falling since 2009, helped by an increase in DDs during this time, but is now starting to level off
    - This is thought to be due to the fact that immunologically “easy” patients are transplanted successfully relatively quickly and remaining waiting patients tend to be sensitised
        - The number of HLAi transplants has been decreasing in the UK
        - Patients with cRF 95-100% have a 15% chance of receiving a transplant, compared to those with cRF 0-84% and those with 85-94% (both groups have a 46% chance of being transplanted
        - At Guy’s Hospital, the proportion of the waiting list made up of highly sensitised patients has increased since 2010
- Differing definitions add complexity:
    - Cutoffs for MFI values vary between different labs
    - The cRF cutoff used to define ‘highly sensitised’ varies from 85% up to 100%
    - Different prioritisation schemes have different cRF entry and allocation requirements
- Considerations for transplanting highly sensitised patients include:
    - Will the patient have a low risk of obtaining a transplant?
    - How much does the patient want a transplant?
        - Some patients are more willing than others to remain on dialysis to avoid transplants that carry increased risk
    - What is the risk of transplantation vs the risk of dialysis?
        - The comparison made for these patients should be of higher risk transplant vs remaining on dialysis, since a low risk transplant will never be possible for most of these patients
        - UK registry data shows that patients who received an HLAi transplant had similar long-term (96 months) patient survival to those who remained on the waiting list on dialysis
        - This UK registry data may be more representative of the situation in Europe than a US study which showed increased mortality on dialysis, and means the choice is more a quality of life issue for patients
        - However, the UK registry has also showed that long-term patient survival on dialysis drops considerably with age, to around 30-40% at 5 years in patients aged ≥65 years (which is worse than many major cancers)
- In the UK DSA positive, flow XM negative transplants are commonly performed with LDs
    - Usually stronger induction therapy with alemtuzumab or antithymocyte immunoglobulin (ATG)

    - With DDs, kidneys are not offered if there are DSAs
    - Delisting involves ‘pretending’ that some of these DSAs are unimportant and ignoring them
- While there is broad correlation between total class I DSA MFI and positive T-cell flow XM, there are outliers whereby patients with >30000 total MFI have had a negative XM and patients with <10000 total MFI have had a positive XM
    - It isn’t necessarily possible to predict XM results based on MFI values, and a test should ideally be conducted
- Approaches to delisting include:
    - Defining all antibodies below a certain MFI threshold as unimportant or total MFI below a certain threshold
        - Then accept a kidney and perform a flow XM test – if negative, proceed and treat as if it were a flow XM negative, DSA positive LD transplant (stronger induction therapy)
    - Plasmapheresis prior to transplant
        - Perform a test with flow XM and SAB assay to analyse DSAs both before (baseline) and after plasmapheresis, use this to delist antigens for which MFI drops below threshold level
        - When a kidney is offered, perform flow XM using stored post-plasmapheresis samples; proceed to transplant without plasmapheresis if the baseline sample is negative or, if the baseline sample is positive but post-plasmapheresis is negative, proceed to transplant with plasmapheresis
    - Idefirix prior to transplant
- Data on delisting in the NHSBT LD kidney sharing scheme (n=6) and DD (n-10) showed a
  1-year graft survival of 81% for DD transplants, with 3 grafts lost within the first few days post-transplantation
    - The DD cohort was difficult-to-transplant – multiple comorbidities and median time on dialysis of 10 years (some >15 years)
    - Two of the three patients with graft failure were treated with double filtration plasmapheresis pre-transplant and suffered multi-organ failure leading to death
        - This led to a cessation of desensitisation using plasmapheresis immediately prior to transplant
- Idefirix dramatically reduces HLA antibodies 6 hours after treatment, as shown by MFI data
    - In a clinical trial, 17 out of 18 XMs were converted from positive to negative
        - Three patients required 2 doses
        - Median cPRA at baseline was 99.83%
    - DSA rebound occurs 1 to 2 weeks after transplantation

    - AMR was seen in 39% of patients, suggesting that pre-transplant idefirix has similar AMR rates to other HLAi transplantation, but importantly it has allowed these patients to receive a transplant
- A post-approval efficacy study is underway in DD recipients with a positive XM
    - In most allocations this would require delisting to attain organ offers
- Idefirix-enabled transplantation is unlikely to solve the problem of chronic AMR, and early aggressive AMR is also seen due to DSA rebound 7 to 10 days post-transplant (often above baseline levels)
    - The only way to effectively treat this is with eculizumab
- The ESOT guideline for management of kidney transplant patients with HLA antibodies indicates that highly sensitised patients without a LD should enter prioritisation or AM schemes
    - If they do not receive an offer in 1-1.5 years, delisting unacceptable antigens with low level antibodies may be considered
    - If this is also unsuccessful, more aggressive approaches such as desensitisation with idefirix or plasmapheresis may be considered

Discussion

- Are HLA-C and -DP antibodies of much importance or can they be delisted?
    - Some clinicians have experience transplanting patients with HLA-C antibodies up to 20000 MFI without problems
    - HLA-DQ and -DP antibodies are usually of interest at Guy's, but HLA-C could potentially be ignored and/delisted unless it was an extremely high MFI value
        - Very high MFI HLA-C antibodies are rare in isolation and usually occur along with other DSAs that are of more concern
        - Some UK transplant centres do not place much importance on HLA-DP
        - There has been discussion in the UK about incorporating the perceived lower impact of HLA-C and -DP antibodies into allocation scheme rules, but this has not happened yet
- There should be less caution around LD HLAi transplantation
    - This would increase the number of transplants possible and LDs allow for better planning
        - Number of transplants is perhaps less important than providing a path to transplant to those patients unlikely to receive and organ offer who want a transplant and are willing to accept the increased risk associated with HLAi transplantation
    - These challenging highly sensitised patients will likely not receive any organ offers and their alternative is dialysis

- While UK data shows no difference in survival between HLAi transplantation and remaining on dialysis, this could be interpreted as there being no survival benefit to HLAi transplantation
    - The interpretation of this data is that there is no survival disadvantage to HLAi transplantation, so the discussion centres around patient quality of life, patients choice, and selecting the right patients
- Considering the UK experience of 3 patient deaths with pre-transplant plasmapheresis, it's possible that idefirix will help reduce increased stresses that pre-transplant plasmapheresis and immunosuppression places on these already highly medicated and at-risk patients

Centre experiences: Gothenburg

Lars Mjörnstedt, Jan Holgersson, Margrét Birna Andrésdóttir

- HLA analysis in Gothenburg:
    - PRA:
        - Luminex screening for waiting list patients, if positive SAB analysis
        - Flow cytometry
        - CDC
    - XM:
        - LD: CDC, flow, virtual (SAB)
        - DD: CDC and virtual (acute), flow (not acute) when PRA positive
- For DD there is a local priority list for patients with high cPRA and expected/actual waiting time longer than non-sensitised patients
    - Patients with TS <2% can enter STAMP
- For LD there is STEP
- Positive results for different XM types (roughly) correlate to the MFI values seen for DSAs, this means there can be different interpretations for what and ~~d~~ 'acceptable' MFI cutoff is
    - In the past, when only CDC XM was available, the threshold was easy to define – a negative result (corresponding to DSAs below ~8000 MFI)
    - With the advent of flow XM and SAB assays, for which positive results correspond to lower MFI values (between approximately 1000 and 8000), knowing how define unacceptable antigens is more complicated
    - Differentiation between T- and B-cell positivity in XMs adds further complication
    - And there are many other factors to consider which may impact risk:
        - PRA%
        - HLA class/specificity
        - IgG subclass
        - C1q binding
        - Historic, peak and current DSA strength
        - Immunising event

        - DD or LD
        - Immunosuppressive protocol
        - Desensitisation
- In Gothenburg, acceptable mismatches are defined as:
    - LD recipients: DSAs with MFI <2000 (those with >2000 enter STEP)
        - There is discussion around relaxing this threshold
    - DD recipients with expected/actual waiting time similar to non-sensitised patients: No DSAs accepted
    - DD recipients with expected/actual waiting time longer than non-sensitised patients:
        - STAMP if TS <2%
        - Discuss increasing TS by accepting higher MFI (up to 5000) as acceptable on certain DSAs based on individual risk assessment
- Gothenburg has not performed desensitisation in the last 10 years

Case study 1: HLAi transplantation with desensitisation

- The patient was a participant in a study of eculizumab for the prevention of AMR in patients undergoing desensitisation
    - The patient was in the control arm
- Female, 54 years old, IgA nephritis, two pregnancies
- Previous (first) kidney transplant was from an unrelated LD
- Pre-treatment PRA:
    - CDC 0%
    - Flow cytometry
        - Class I: 84%
        - Class II: 95%
- Pre-treatment XM:
    - CDC: negative (local), positive (Leiden, enhanced?)
    - Flow: positive T- and B-cells
    - SAB DSA (MFI): B7 (13000), B60 (13000), DQ5 (3000)
- Desensitisation/immunosuppression protocol:
    - Plasmapheresis x5 followed by IVIG
    - ATG induction
    - Tacrolimus, mycophenolate mofetil (MMF), prednisone
- Outcome:
    - AMR on day 7, successfully treated with plasmapheresis x3, steroids and two doses of eculizumab
    - The graft is functioning after 10 years, eGFR 35-40 ml/min/1.73m^2
        - Protocol biopsy after 1 year found light glomerulitis – everolimus treatment added

- Biopsy at 3 years due to decreased graft function found signs of low-grade chronic rejection but there were no DSAs or complement component 4d (C4d) – IVIG treatment added
- Biopsy at 9 years also showed signs of chronic rejection, but again no DSAs were detected
- No DSAs have been detected in the patient since the resolution of the early AMR

Case study 2: HLAi transplantation without desensitisation

- Male, 45 years old, IgA nephritis
- LD transplant 23 years previously
- Now a candidate for DD kidney
- PRA:
  - CDC:
    - T-cell: 57%
    - B-cell: 50%
  - Flow cytometry:
    - Class I: 68%
    - Class II: 0%
- XM:
  - CDC: negative
  - Flow: T-cell positive, B-cell not accessible
  - SAB DSA (MFI): A24 (12478)
- Immunosuppression:
  - Tacrolimus, MMF, basiliximab
  - Rituximab after positive flow XM
- Outcome:
  - Functioning graft after 9 years, serum creatinine 120 µmol/L
  - No rejection
  - Persisting DSA after 3 months: A24 (4000 MFI)

Discussion

- The cases show the difficulty in deciding how to manage highly sensitised patients
  - The patient in case 1 underwent desensitisation and had no detectable DSAs at any stage post-transplant, but suffered acute AMR and showed signs of chronic rejection
  - Meanwhile, the patient in case 2 had no desensitisation, showed persistent DSAs post-transplant but had no clinical signs of rejection (acute or chronic)
- In the future, patient selection for desensitisation should consider patients who:
  - Have an unacceptable expected or actual waiting time despite inclusion in exchange and/or AM programmes, and attempts to improve transplantability

by increasing the number of acceptable mismatches (after individual risk assessment)
    - Can tolerate the desensitisation treatment protocol
- The two cases shown are patients who had good HLAi transplant outcomes without idefirix
    - It will be important to select the right patients for idefirix:
        - TS 0%, high MFI
        - But probably patients with a negative CDC XM
- A Dutch study which performed retrospective Luminex analysis of samples from CDC XM negative LD transplanted patients showed that there was no difference in graft survival at 10 years between those with and without DSAs pre-transplant
    - LD HLAi transplantation has excellent outcomes in patients with a negative CDC XM
    - Without STEP it is likely that higher DSA MFI levels would be accepted in LD transplants, but STEP increases the chances of these patients getting a matching organ
- Other centres have not had any patients with such good outcomes following desensitisation (as performed in case 1)
    - Some patients do not respond to desensitisation, or have a very fast DSA rebound that doesn't respond well to plasmapheresis

Centre experiences: Copenhagen

Søren Schwartz Sørensen and Helle Bruunsgaard

- Luminex has been used at Rigshospitalet in Copenhagen since 2014
- Risk stratification using flow XM for LD transplantations which are DSA positive on Luminex was introduced in 2017/18
- Between 2013 and 2021, 61/780 (8%) of transplantation were HLAi, 6 of these were HLAi and ABOi
    - In 30 of these patients, IVIG, rituximab and basiliximab were used as induction treatment
    - In 31 patients, various other combinations of rituximab, IVIG, thymoglobulin and plasmapheresis were used
        - The last use of plasmapheresis for desensitisation was in 2017
    - Current strategy:
        - DD: accept DSAs up to 3000 MFI, with thymoglobulin induction therapy
        - LD: accept DSAs up to 3000 MFI with negative B- and T-cell flow XM (flow XM is only routinely used in LD transplants)
        - LD HLAi + ABOi: try to avoid
- A past PhD study gave access to frozen sera from all transplant recipients from 2009 to 2015 (a timeframe which spans both pre- and post-Luminex availability at the centre)

  - Retrospective Luminex analysis of these samples for DSAs were compared to death-censored graft survival outcomes, and showed there was significantly higher (p=0.0111) graft failure in patients with DSAs compared to those without at 12 years post-transplant, HR=1.73 (95% CI 1.13–2.66)
    - A numerical difference in survival can be seen in the first year
  - There was not, however, any difference in patient survival for the same cohort (p=0.6935)
    - Overtreatment of rejection of a kidney which cannot be saved could pose a risk of harm to the patient
  - Multivariate analysis showed the same results

Case study 1

- Male, 42 years old, blood type O
- Previously transplanted in 2007
  - Previous mismatches: HLA-A11; -B18,61(40); -Cw7; -DR14(6); -DR52; DQ6(1)
- Highly sensitised
  - CDC PRA 95% (B-cell panel)
  - Luminex cPRA 100%
- Potential LD
  - Male 66 years old, unrelated to the recipient
  - ABO identical
  - 1 HLA-A*02 mismatch
  - No repeated mismatches
  - 1 DSA (A2)
- Luminex analysis in 2020 showed HLA-A2 DSA with MFI 13000 (class I cPRA 100%), while repeated analysis in 2021 showed MFI 5000 (class I cPRA 99.7%)
  - HLA class II antibodies decreased from cPRA 92% in 2020 to 72% in 2021
  - Positive flow XM and negative CDC XM was also consistent on historical sera
- Crossmatching:
  - Positive virtual XM (DSA HLA-A2)
  - Positive flow XM (B- and T-cells)
  - Negative CDC XM (B- and T-cells)
- So far the patient has been in STAMP since 2019 and has taken part in one STEP run, with no organ offer to date

Discussion

- Specifically in Denmark, there is and private initiative funding patient and donor participation in paired donation in in Toledo, USA. Presently Danish Transplant Centres are not involved in this

    - This is apparently only available once patients have participated in 2 runs in STEP
    - Attendees questioned the ethics surrounding this scheme, but due to the private nature of its funding, Danish centres have no control over patients' participation
        - Additionally, if the best offer in Denmark is a DD HLAi transplant, it may be a better option for patients to seek a LD in the US exchange programme
- Dutch data has shown excellent 10-year graft survival in CDC XM negative HLAi transplants, regardless of DSA positivity on Luminex, which suggests this patient would have good outcomes with a transplant
    - However, this hypothesis doesn't fit with Rigshospitalet's own data which shows poorer graft survival in patients with DSAs
        - There is no flow XM data available for these historical samples
        - Even in Luminex positive, flow XM positive, CDC XM negative patients, Dutch data shows only slightly worse outcomes compared to patients without DSAs
    - It is highly unlikely that another donor for this patient will be found
        - The centre had hoped that the patient would be a candidate for iderfirix, but the indication did not include LD transplants
- Attendees largely agreed that accepting the LD was the best option for this patient
    - With a negative CDC XM, desensitisation may not be necessary, it may not even decrease the MFI much below the current level of 5000, though it may lower the intensity of post-transplant DSA rebound
        - The patient's DSA is class I, and rebound of class I antibodies is generally easier to treat than that of class II
        - Treating rejection with class I antibodies is also usually more straightforward than with class II
    - Desensitisation could be attempted to reduce DSA MFI to 3000 in the hopes of achieving a negative flow XM
        - Early AMR is usually more simple to treat compared with late-onset AMR

Case study 2

- Female, 24 years old, blood type O
- Previous HLA mismatches: HLA-A3; B15; B40; Cw9; Cw10
- CDC PRA 0%, Luminex cPRA 82%
- Potential LD
    - 49 years old
    - ABO identical
    - 2 AB mismatches and 1 DR mismatch, no repeat mismatches
    - 2 DSAs

- DSAs
  - HLA-B44 MFI 6000 and HLA-DR7 MFI 4000
- Crossmatching
  - Positive virtual XM (HLA-B44 and -DR7)
  - Flow XM
    - B-cell positive
    - T-cell negative
  - Negative CDC XM (B- and T-cells)

Discussion

- Some attendees suggested STEP for one or two runs may be the best first option for this patient, while others said they would proceed with the LD transplant
- This patient was a lung transplant recipient who entered STEP due to the risk posed by immunosuppressive treatment required for an HLAi transplant, and a match was made in the first round from a chain initiated by an altruistic donor in Sweden

Centre experiences: Aarhus

Karin Skov and Pernille Bundgaard Koefoed-Nielsen

- Aarhus stopped performing desensitisation in 2015 after the introduction of STAMP and STEP
  - The aim of their desensitisation programme was to attain a negative flow XM
  - Few patients were transplanted following desensitisation

Case study

- Male, born 1995
- In 2001, developed nephrotic syndrome and chronic kidney disease
- Received a DD transplant in 2002 with good primary graft function
  - HLA mismatches on HLA-A*03*11; -B*07*35; -C*05,07
  - No DSAs
  - Negative CDC XM
  - In 2004 developed hydronephrosis, no reflux; insufficient bladder emptying
- Immunosuppressive treatment with tacrolimus and MMF
- Renal function was stable until 2012 when the patient developed severe hydronephrosis treated with reimplantation of the graft ureter and trained in selective intermittent catheterisation
  - However, the patient (who was 17 years old at the time), quickly became noncompliant and also lost compliance with his medication regimen, as well as failing to attend many appointments
- In 2015, there was decreased graft function and a biopsy showed Banff classification grade 1B and chronic AMR

    - Dialysis was started
- The following year, the patient's mother was evaluated for LD retransplantation
    - No DSA
    - Repeat mismatch on HLA-C*07
    - CDC XM negative
    - However the mother was a mismatch against the Caucasian super haplotype
        - This mismatch would exclude a large portion of the donor pool
- The transplant was performed in December 2016 with standard immunosuppression
    - Multiple rejection episodes in 2017
    - Limited drug compliance continued and there was loss of graft function in 2019, the patient returned to dialysis
        - Immunological re-evaluation following the second graft loss revealed new class I and II HLA antibodies
- In 2023, the patient's father came forward as a potential donor for a third transplant
    - Also a haplotype mismatch
    - Repeat mismatch on HLA-C*07 and -DQA1*05
    - DSA: HLA-A68 (11000 MFI), -B18 (26600), Cw7 (30700, repeat mismatch), -DQA1*05 (30800, repeat mismatch), -DR12 (25200), -DR52 (28100, repeat mismatch), -DQ7 (28600)
    - CDC XM positive (B- and T-cells)

Discussion

- The discussed options around delisting will have no impact on a patient like this as the MFI values are too high
- Due to the level of sensitisation, the chances of the patient finding a match in STAMP are extremely low and the chances of finding a match by entering STEP with his father are "non-existent"
- Desensitisation with plasmapheresis is unlikely to have sufficient effect
- Desensitisation with idefirix is possible, and likely the only way for this patient to receive another transplant, but the risks posed by potential DSA rebound is very concerning as management would be very challenging
- The patient's long history of noncompliance makes him much more suited to receiving an acceptable mismatch transplant rather than desensitisation with idefirix
    - In this case the best option is likely to remain in STAMP and wait for an acceptable mismatch kidney
    - There may be a higher chance of receiving a kidney if the patient could be included in the Eurotransplant AM programme due to the larger donor pool
        - A larger donor pool that includes different geographical areas has more phenotypes with more diversity of antigens

Centre experiences: Helsinki

Ilkka Helanterä

Case study: Idefirix-enabled transplant

- Male, born 1990s
- End-stage kidney disease due to congenital urinary tract abnormalities
- First kidney transplant as a teenager, graft loss after 2.5 years due to polyomavirus-nephropathy and subsequent AMR after immunosuppression reduction
- Listed for transplantation again in 2014, cPRA 80%
- Has been on the LAMP list since 2015
- Transplantectomy in 2016 due to clinical rejection in the non-functioning graft
    - Following this, cPRA increased to 100%
- Since 2017 there has been a local 'hit-tray' prioritisation scheme
    - All blood group compatible DDs undergo CDC XM using sera samples from patients in the hit-tray
    - Since its introduction, there have been approximately 420 ABO compatible transplants at the centre
    - For this patient, >250 potential donors were XM tested, all were positive
- The patient was included in STAMP in February 2019 and in December 2019 antigens with antibodies <3000 MFI were deslited
- By this time, the patient was experiencing increasing psychiatric burden, particularly in relation to the long time spent on dialysis
- In June 2021, the patient was given a one-off approval for treatment with idefirix
    - A protocol was drafted with experts from Sweden and finalised in September 2021, and the nursing staff, transplant surgeons, transplant co-ordinators, and pharmacist were trained on the protocol
    - After consultation with experts in Sweden and the US desensitisation treatment was caried out, consisting of two doses of rituximab 500 mg in October 2021 and IVIG 140 g twice in October and November 2021
    - In May 2022, the patient was assigned a special LAMP listing for acceptable antigens from all Finnish donors, based on the idefirix clinical trial protocol
        - All HLA-DP and -C DSAs were deemed acceptable, but all other DSAs with MFI >5000 should be avoided
- In August 2022, the patient received an offer
    - 4 DSAs: HLA-A2 (MFI 6425), -A26 (2641), -DP3 (21793), -DP4 (2062)
    - CDC XM positive (B- and T-cells)
- Idefirix administered and after 4 hours there was still a weak positive CDC B- and T-cell XM, so another dose was given
    - 4 hours after the second infusion CDC XM was negative and the patient proceeded to transplant
    - Approval for idefirix use was given during the kidney procurement operation, as soon as it was confirmed the organs were acceptable for transplantation

        - Due to the requirement of a second idefirix dose and delays due to operating theatre capacity, the total cold ischaemia time was 24 hours 54 minutes
- There was immediate post-operative graft function
    - Immunosuppression therapy:
        - Tacrolimus twice daily, trough target 10 12 µg/l
        - Mycophenolate mofetil 1 g twice daily
        - Solu-medrol 250 mg IV on days 1 to 3, 125 mg IV on day 4, methylprednisone 16 mg once daily from day 5
        - Rabbit ATG on days 4 to 6, dose 1.5 mg/kg per infusion
        - Rituximab 1000 mg on day 7
        - IVIG 1 g/kg on day 10
    - Creatinine was 113 µmol/L on Day 7
        - There was a slight increase in creatinine on Day 10, a biopsy showed signs of acute tubular necrosis but no inflammation and C4d was negative
        - Solu-medrol 500 mg IV was administered for 3 days
- Idefirix treatment resulted in a dramatic reduction in DSA MFI values, though there was not much difference seen in MFI values between the first and second dose
- There was a slight DSA rebound seen between days 7 and 10 for DP antibodies (which had the highest pre-transplant MFI value)
- 3-month protocol biopsy:
    - Mild peritubular capillaritis
    - Glomerulitis
    - Acute tubular necrosis
    - C4d negative
        - Suggestive of AMR-related changes
        - Treatment with pulse steroids (methylprednisolone 500 mg IV for 3 days) and IVIG 30 g (single dose)
- Graft function was stable at 150 days follow-up; creatinine 105 µmol/l, no proteinuria
    - DSAs have remained undetectable
    - A large lymphocele was detected during rejection treatment, causing high deep vein thrombosis in the femoral vein
        - Drainage was required, anticoagulation with tinzaparin was started, operative treatment was considered
    - Psychiatric comorbidity had been present for years pre-transplantation, after the last course of pulse steroids there was a worsening in the patient's condition and they have been on the psychiatric ward since December 2022

Presentation

- In Helsinki, the LD desensitisation protocol was defined 2018

    - Eligible patients must have high MFI DSAs but negative CDC XM (B- and T-cell)
        - Flow XM not currently available
    - The protocol mimics the ABOi protocol
        - Rituximab 4 week pre-transplant
        - Immunosuppression with tacrolimus, MMF and steroids started 2 weeks pre-transplant
    - Plasmapheresis or immunoadsorption started 7 to 10 days pre-transplant for 5 to 7 treatments, and continued postoperatively for 3 to 5 days
    - Basiliximab or rabbit ATG induction
- Two patients have been treated under this protocol
    - Both have good graft function
    - One patient suffered AMR treated with another course of immunoadsorption

Discussion

- Although the 5000 MFI cutoff used for the LAMP listing for the case study patient would be considered quite low for a positive CDC XM, the treating clinicians were quite confident of a positive result, as the patient's stored sera had already produced >250 positive CDC XM results via the hit-tray screening
    - In addition, HLA-A2 DSAs were measured at <5000 MFI using the patient's historical sample, but analysis at the time of transplant showed >6000 MFI for this antibody
- Virtual XM was not used in DD transplants until recently and the centre is currently retrospectively analysing the cases with DSAs to assess the to assess outcomes of patients with DSAs versus those without
- The LAMP programme has the same criteria as STAMP, but may accept patients with TS >2%, or on the basis of allele-specific antibodies
    - Since virtual XM has not been available until recently, between patients without DSAs and those with DSAs below 5000 MFI, priority is typically given to those who have been waiting the longest
    - When transplanting patients with DSAs close to 5000 MFI, ATG is added to the usual immunosuppressive induction regimen
- With the advent of Luminex, so much information is available on patients that the decision to transplant becomes a very grey area
- The experience in Helsinki suggests that induction with ATG in very highly sensitised patients have much milder acute AMR that is much easier to manage

Centre experiences: Malmö

Alireza Biglarnia and Ann-Sofie Liedberg

- Tissue typers play a key role in Malmö in selecting and presenting recipients

    - Virtual XM is always documented and communicated to the transplant surgeon
- For patients on the waiting list <2 years:
    - Negative virtual XM, defined as no DSAs with MFI >1000
    - Higher MFI (<2000) is accepted for HLA-Cw, -DP, and -DRB51/52/53 antibodies
    - CDC XM with fresh sera is always performed pre-transplant for highly sensitised patients, including those in STAMP/LAMP
- Guidance has been discussed for patients on the waiting list >2 years, the proposal is:
    - HLA-A, -B, -DR, -DQ: accept MFI <2000
    - HLA-Cw, -DP, DRB51/52/53: accept MFI <5000
    - C1q+ DSAs: not accepted (current and historical sera)
    - Repeat mismatch DSAs: not accepted
- High risk is defined as MFI >5000

Case study

- Historical case study from 2011
- Male, 52 years old, renal disease of unknown origin
- First transplant was an ABO compatible LD transplant from the patient's half-brother in 1992
    - There were several rejection complications but these were managed clinically and the graft was functional for several years
- The patient returned to dialysis in 2007 due to chronic rejection
- By this time, the patient was very highly sensitised
    - ABOi A to O (1:64 anti-A baseline titres)
    - DSAs (with 1:25 dilution):
        - Class I: HLA-B60 (8000 MFI), - A11 (5000)
        - Class II: HLA-DQ6 (06:02 and 06:04) (15000 MFI)
        - Other DSAs were present at lower MFI
    - CDC XM positive (B- and T-cells)

Discussion

- Attendees agreed this patient would not be a good candidate to proceed with LD transplant
- In reality, the patient did receive a LD offer and proceeded to transplant
    - ABOi and CDC XM positive class I and II
    - Pre-transplant immunosuppressive therapy with rituximab, bortezomib (2 doses), immunoadsorption and IVIG
    - Induction therapy with basiliximab and steroids
    - Class I CDC XM was still positive on the day of transplant

        - Class II CDC could not be judged due to the use of basiliximab
- Results were good, creatinine dropped to around 400 µmol/L
    - Protocol biopsy showed signs of acute tubular necrosis, treated with plasmapeheresis but no signs of rejection
    - At Day 8, there was a slight rise in creatinine, biopsy again showed signs of acute tubular necrosis and a stable level of antibodies
        - A third dose of bortezomib was given alongside 2 sessions of immunoadsorption
    - Following this there were signs of cellular rejection (Banff 2a) – but no AMR
        - After another biopsy the patient was treated with ultrafiltration and thymoglobulin
    - Class I CDC XM was positive throughout the first month post-transplant
- However, the kidney functioned well for approximately 10 years
    - After 10 years, the patient started on dialysis and biopsy showed interstitial fibrosis and tubular atrophy score of 3, indicative of chronic AMR
        - DSAs were not detectable
- This case represents probably the most high-risk transplant conducted at Malmö, and the patient had good graft function for 10 years
- The protocol and thresholds used for the post-transplant CDC XM tests is not known
    - When separating B- and T-cells, it is very difficult to get completely pure populations, and it is possible there was some T-cell contamination in the B-cell population and the B-cell XM would have otherwise been negative
    - CDC XM can be difficult to interpret in the 2 weeks post-transplant
- Attendees agreed that this type of transplant would not occur today, as the level of risk would be deemed too high

Centre experiences: Oslo

Christina Dörje and Christian Naper

- Oslo has not performed any desensitisation in the last 15 years
- Management of high risk and sensitised patients has been via LAMP, STAMP and STEP, and in some cases HLAi transplantation

Case presentation

- Middle-aged female with IgA nephropathy
- First kidney transplant, patient has not yet started dialysis
- Two friends have come forward as potential LDs, both CDC XM negative
    - Donor 1
        - Minor ABOi, O to A
        - HLA mismatch 1-1

        - DSA: HLA-B57 (MFI 2400), the donor is homozygous for HLA-B57, so MFI equates to 4800
    - Donor 2
        - ABO compatible
        - HLA mismatch 3-2
        - DSA: HLA-B7 (MFI 5600), -A24 (2400)
    - Luminex cPRA 99.7%, CDC PRA 0%
    - Allele-specific antibodies for HLA-B*27:08 (MFI 3800) – self HLA-B*27:02 and -B*27:05
        - Likely antibodies against Bw6
- Flow XM is not routinely conducted

Discussion

- Clinicians at Olso think LD 1 is the better option
- STEP has low chances of a match due to the patient's class I antibodies
- STAMP has low chances of an HLA compatible match
    - TS 0.35%
        - Some attendees agreed that while the chance was low, TS is not 0, so there is some chance of a match via STAMP
- In these types of cases, it would be interesting to understand the immunising event to have a better understanding of which antigens it may be possible to delist
    - Antibodies that form after previous transplant or pregnancy are considered more high risk for delisting
    - In this case, then immunising event was pregnancy, however it is likely that even multiple pregnancies could not be responsible for antibodies against all the antigens this patient exhibits
        - The local healthcare teams for the patient (who lived in a remote area) could not provide any history around other potential sensitising events such as blood transfusion
- Flow XM would probably not add much value in this case
- Proceeding with LD transplant with donor 1 is likely the best option

Presentation

- Inclusion criteria for LAMP:
    - cPRA >80%
    - TS <5 to 10% (some patients have many unacceptable repeat mismatches without high cPRA)
    - Allele-specific antibodies not accepted on STAMP
- Between 2009 and 2014, 1632 patients were transplanted (LD and DD) at Oslo
    - n=127 DSA positive
    - 61.4% female

    - 24.4% retransplants vs 7.6% first transplants
- Cox regression analysis of uncensored graft loss showed a significantly higher hazard ratio (2.79, 95% CI 1.70-4.60) in patients with DSA MFI >6000 for any one specificity
    - Similarly, death-censored graft survival was also significantly poorer in patients with DSA MFI >6000
        - The data were limited by the small number of patients with MFI >6000, most of the sensitised patients included had MFI values between 1500 and 3000

Discussion

- The Oslo DD immunosuppression protocol includes IVIG, rituximab and Simulect at the same time may result in some of the effects “cancelling each other out”
    - It may be better to separate the administration of IVIG and rituximab by 1 to 2 days
    - It also may not be necessary for all patients to receive such an aggressive protocol

Centre experiences: Uppsala

Mats Bengtsson

Case study

- Male, 44 years old, kidney disease of unknown origin
- On dialysis, but compliance problems
- Non-Caucasian HLA type, so limited chance of finding a HLA compatible donor in the local donor pool
- First transplant in 2015 with a donor homozygous on class I
    - Negative CDC and no DSAs, so low risk
    - 2 days after transplantation there was decreased blood flow to the graft and it was explanted due to what was later deemed autolysis
- A second donor was found with HLA mismatch 3-1, no DSAs
    - Again a low-risk transplant
    - Urinary output during the operation is not known, but there was low urinary output following the operation which ceased around 6 hours post-operation
        - Low blood flow was confirmed by ultrasound
        - The graft was explanted due to a rupture
    - ABO typing, flow XM and CDC XM were repeated to confirm no errors were made pre-transplant and all results were the same as pre-transplant
    - Testing for major histocompatibility complex class I related chain A antibodies was also negative
- In an attempt to find answers, data for patients with a similar history was collected and analysed for autoantibodies to look for any trends

    - SAB assay, some antigens are organ-specific (kidney, heart, lung), while others are more general inflammatory markers
    - No trends were identified in 24 out of 25 patients
        - This autoantibody assay is unlikely to provide answers for these patients and is not applicable to daily practice
        - The assay was designed based on non-transplanted patients
- Complement testing yielded normal results
- The patient is now being treated as high-risk (usually treated with rituximab and thymoglobulin) in search of a third transplant

Discussion

- One explanation for this case may be that the patient has Duffy antibodies
- Some cases have been described in the UK of acute unexpected rejections which were attributed to either HLA class III and endothelial antibodies
- Other centres have had experience of early humoral rejection in LD transplantations with no HLA antibodies which tested positive for AT1 receptor antibodies

Final discussion

- Are we too cautious transplanting HLAi patients?
    - Attendees generally agreed that yes, the current approaches are too cautious
    - Norway and Finland accept higher MFI values than other countries
        - Finland has delisted DSAs up to 3000 MFI in STAMP, but an explanation must be provided
- What is needed in local and national organisation to transplant more HLAi patients
    - Will it be possible to expand the STAMP donor pool?
        - Frans Claas, at Leiden University Medical Center, applied for European Union funding via the Horizon 2020 scheme to implement a wider Europen donor pool scheme, but it was rejected as transplantation was deemed to be an area with too few patients
        - ESOT guidelines state that cooperation between different organ sharing organisations is the best path forward
        - This should be achievable without external funding, but requires resolutions to data sharing difference across borders
        - Every year, >10000 bone marrow transplants are carried out across borders, which shows it is possible
        - The EUROSTAM project has already proven the advantages of expanding the donor pool
    - Proper recording of data on HLAi transplants in Scandiatransplant systems is essential to get reliable outcome data

    - More cross-functional meetings (like the present one) including clinicians and tissue typers will be beneficial
- Where do we go from here?
    - Lots of good data exists in Scandiatransplant, but perhaps more follow-up data as standard for HLAi transplant patients would be useful
        - Use YASWA to pull out as much relevant data as possible and reconvene in 1 to 2 years to discuss progress and how practice has changed
    - New drugs are being develop to manage acute and chronic AMR and if effective and approved for use, these could change the way high risk HLAi transplants are approached
    - A new protocol for delisting in STAMP is possible but should not be done *ad hoc*
        - A formal written proposal should be developed and put forward to the STAMP committee to discuss and implementation

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