

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

19 October 2022, Padova, Italy

## Programme

11:00 – 11:10	Introduction	Lucrezia Furian   Padova, Italy
11:10 – 11:30	HLA-sensitised patients: who are they?	Emanuele Cozzi   Padova, Italy
11:30 – 11:50	Desensitisation strategies	Umberto Maggiore   Parma, Italy
11:50 – 12:10	KPD program	Pamela Fiaschetti   Rome, Italy
12:10 – 12:30	Maintenance immunosuppression strategy in HLA-sensitised kidney transplant recipients	Gianluigi Zaza   Foggia, Italy
12:30 – 12:50	Discussion (20 mins)	All
<b>12:50 – 14:50</b>	<b>Lunch break</b>	
14:50 – 15:10	Case Study 1: <i>Combined strategy of desensitisation treatments and Kidney Paired Donation / DECK program to provide the opportunity of transplantation in high sensitised patients</i>	Caterina di Bella   Padova, Italy
15:10 – 15:30	Case Study 2: <i>What should we offer to high sensitised KT recipient?</i>	Roberta Angelico   Rome, Italy
15:30 – 15:50	Case Study 3: <i>Title to be announced</i>	Giacomo Mori   Modena, Italy
15:50 – 16:10	Case Study 4: <i>Desensitisation strategy in highly sensitised patient affected by systemic scleroderma and gastric antral vascular ectasia</i>	Barbara Buscemi   Palermo, Italy
16:10 – 16:30	Discussion and final wrap up (20 mins)	All

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

## Attendees

Roberto Angelico | Rome, Italy  
Elisa Benetti | Padova, Italy  
Barbara Buscemi | Palermo, Italy  
Francesco Cambareri | Reggio Calabria, Italy  
Manuela Cannone | Vicenza, Italy  
Emanuele Cozzi | Padova, Italy  
Caterina di Bella | Padova, Italy  
Paola Donato | Verona, Italy  
Pamela Fiaschetti | Rome, Italy  
Lucrezia Furian | Padova, Italy  
Gabriele Guglielmetti | Novara, Italy  
Giuseppe Ietto | Varese, Italy  
Aida Larti | Florence, Italy  
Umberto Maggiore | Parm, Italy  
Alberto Menegotto | Milan, Italy  
Giacomo Mori | Modena, Italy  
Maria Paola Salerno | Rome, Italy  
Cristina Silvestre | Padova, Italy  
Francesca Valerio | Brescia, Italy  
Gianluigi Zaza | Foggia, Italy

## 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 Italy.

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E: [askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

## Human leukocyte antigen (HLA)-sensitised patients: who are they?

**Emanuele Cozzi**

- Sensitised patients are those with HLA antibodies *or* those with a history of HLA antibodies – these patients may not have antibodies in their current sample
- There are different factors to consider when assessing sensitised patients:
  - The broadness/degree of sensitisation, measured via calculated panel-reactive antibodies (cPRA)
  - The 'strength' of the antibodies, measured by mean fluorescence intensity (MFI)
  - The specificities of the antibodies
- Assays used to detect HLA antibodies have evolved over the last 20 years from low-sensitivity complement-dependent cytotoxicity (CDC) assays, which can only detect lytic DSAs, to flow cytometry and single-antigen bead (SAB) assays, which are highly sensitive and can detect both lytic and non-lytic antibodies
- While SAB assays have several strengths; they are much more sensitive than those used in the past, and can detect allow the detection of antibodies against all loci, as well as permitting a virtual crossmatch (XM), they have limitations:
  - SAB assays use genetically engineered antibodies which may not perfectly match HLA antigens present *in vivo*
    - There is also a risk of antigens on the bead denaturing before they are used for a test
  - The assay consists of approximately 200 beads, while there may be tens of thousands of identifiable HLA specificities
    - With modern populations becoming increasingly international, it becomes more difficult predict which allelic specificities are common in the local donor pool, and should be included in the assay
  - MFI values are semiquantitative
- Risk factors for HLA sensitisation include:
  - Previous pregnancies
    - Risk of sensitisation increases with each pregnancy: after one pregnancy 33% of women have and MFI >1000, after two pregnancies this rises to 62%, and 75% after 3 pregnancies
    - MFI >1000 is a fairly arbitrary cut-off in this instance, and patients with lower MFI may still be considered sensitised
  - Transfusions
    - Number and recency of transfusions impact the likelihood of sensitisation
    - CDC assays may not show positive cytotoxicity in patients who received transfusion(s) a long time prior due to a decrease in antibody titres, but immune memory cells may still elicit a cytotoxic response
    - Ventricular assist devices (VAD) can't directly cause immunisation *per se*, but are usually associated with multiple transfusions
  - Transplants

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Homograft, such as those used to treat arteriovenous fistulae
- Having multiple risk factors can dramatically increase the likelihood of sensitisation
- In the last decade, it has become clear that *de novo* antibody production is most commonly directed against HLA-DQ
- In patients with a previous transplant, even among patients with few HLA mismatches, around half were sensitised, while among those with a greater number of mismatches (6 to 12) this rises to 80% of patients
- Degree of sensitisation has an impact on **waiting list times** – US data show that 10% of patients with cPRA <80% wait more than 5 years; this proportion increases to around 35% for patients with cPRA ≥99% and more than half of patients with a cPRA ≥99.9%
- Pre-existing anti-HLA antibodies also **negatively impact graft survival**, regardless of whether they are donor-specific (DSA) or non-donor-specific (NDSA) antibodies
- In Italy, as of the end of 2021, there were 4,260 patients on the waiting list
  - 51% were sensitised (any HLA antibodies)
  - 12% had a cPRA ≥90%
  - 3.5% had a cPRA ≥90% and had been on the waiting list for ≥8 years
  - 4.3% had a PRA of 100%
- In the 3 years between the end of 2018 and the end of 2021, the total number of patients on the waiting list decreased by ~10%, but the proportion of sensitised patients increased from 45% to 51%
  - This trend has been observed internationally
  - These sensitised patients tend to wait longer, have a higher mortality rate and an increased risk of premature graft failure

## Desensitisation strategies

### **Umberto Maggiore**

- According to recent ESOT guidelines, rituximab, plasmapheresis and immunoglobulin therapies represent standard of care for desensitisation in patients with living donors (LD)
- Studies in the US and UK have shown similar 5-year survival rates among highly sensitised patients who underwent HLA-incompatible (HLAi) LD transplant, but lower survival rates in US control groups of patients who received an HLA-compatible deceased donor (DD) transplant or remained on the waiting list, or those who remained on the waiting list only **Mannok**
  - These data suggest poorer survival for patients on dialysis in the US
  - A Korean study also showed poorer survival for patients on peritoneal dialysis compared with haemodialysis
- In Italy, the pre-COVID-19 mortality rate on the waiting list was ~5%
- US data from Johns Hopkins shows an extended period of increased risk of hospital re-admission among HLAi transplant recipients compared with HLA-compatible recipients

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Another Johns Hopkins study showed that 5-year graft and patient survival can be stratified according to donor-specific antibody (DSA) 'strength'
  - Five-year graft survival was: 84% in patients who underwent an HLA-compatible transplant; 80% in those with DSAs detectable by Luminex; 72% in those with DSAs detectable by flow cytometry; 60% in those with DSAs detectable by CDC **Orandi Am J Transplant 2014;14:1573**
  - Five-year patient survival was: 91% in patients who underwent an HLA-compatible transplant; 91% in those with DSAs detectable by Luminex; 87% in those with DSAs detectable by flow cytometry; 81% in those with DSAs detectable by CDC
  - ENGAGE risk stratification also factors in the risk to patients with a history of anti-HLA antibodies, or 'serological memory', which is lower than for those with detectable DSAs, but higher than patients without DSAs or a history of sensitisation
  
- Eculizumab was studied in a clinical trial for the prevention of antibody-mediated rejection (AMR) in patients with living donors undergoing desensitisation
  - Eculizumab plus standard-of-care (SOC) was compared to SOC, showing no significant difference in graft survival during 3 years of follow-up (eculizumab had numerically higher graft survival at 3 years, but very low numbers of evaluable patients meant the difference was not statistically significant)
  
- In sensitised patients with deceased donors, transplantation is an unscheduled procedure, meaning there is a lack of planning time for desensitisation strategies
- Pre-transplant conditioning (during dialysis) for patients on the waiting list for HLAi DD transplant aims to achieve a negative or weak positive XM upon donor offer
  - One protocol investigated was alternating intravenous immunoglobulin (IVIg) and rituximab for 1 month
  - However, importantly, this study raised the threshold for what was considered a positive XM, meaning it is difficult to assess whether the immunosuppression therapy or the adjusted XM threshold led to patients being eligible for transplant
  - The results of the study showed that when patients were stratified as low risk (MFI <5,000 pre-transplant) and high risk (MFI ≥5,000 pre-transplant), the rate of AMR was 12% in low-risk patients compared with 59% in high risk patients, suggesting that in fact, many of these patients may not have been suitable for transplant
  - Analysis of median MFI during IVIG and rituximab treatment showed no notable decrease following therapy, with a largely consistent median MFI
  - By assessing the risk profiles of patients who suffered very early AMR (<6 weeks) and early AMR (6 weeks to 6 months), authors identified that those with <300 mean channel shift flow XM and <30,000 total DSA MFI were at least risk of AMR

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- They developed a risk stratification tool for their protocol, assigning 0 points to patients with no DSAs, 2 points for DSA <5,000 MFI, 5 points for 5,000 to 10,000 MFI, and 10 points for ≥10,000 MFI
- Patients with ≥17 points have a >90% risk of acute AMR
- Based on their experiences with IVIG and rituximab, the same group studied desensitisation therapy with the IL-6 inhibitor clazakizumab
  - Patients were treated with IVIG, then received clazakizumab once monthly for 6 months with the hypothesis that anti-IL-6 therapy would inhibit antibody production
  - Eighteen patients were included in the study, 60% had a cPRA of >99.5% and 45% has received prior desensitisation treatment
  - AMR occurred in 17% of patients and the mean eGFR at 12 months was 58 ± 29 ml/min/1.73 m<sup>2</sup>
  - Despite these promising results, the results have not been replicated in other studies into anti-IL-6 therapies
    - A French group studied anti-IL-6R monotherapy with tocilizumab once monthly for 6 months in 13 patients with cPRA >95% and found only a minimal reduction in MFI for anti-HLA antibodies
- Studies in primates have led to ongoing clinical trials assessing another technique involving costimulation blockade of B7/CD28 or CD40/CD154 pathways
  - The proposed mechanism involves targeting plasma cells via proteasome inhibitors (e.g. bortezomib), which prevents the negative feedback loop provided by plasma cells, leading to rapid germinal centre activation and rebound humoral immunity; a costimulation blocking agent can then be used to inhibit this negative feedback loop, preventing T follicular helper cells from interacting with B cells to cause them to differentiate, and thereby preventing rapid humoral rebound
- Other desensitisation methods which are implemented at the time of transplantation have been studied
  - One protocol studied in patients with a DD offer and negative CDC or flow cytometry XM, but positive Luminex XM (MFI >3,000); patients were transplanted and treated with thymoglobulins, plasmapheresis, IVIG and rituximab every 3 weeks (for three doses)
    - Acute AMR (within 1 year of transplant) occurred in 33% of patients
    - Chronic AMR occurred in 40% of patients
    - Two-year graft failure was 5%
  - Eculizumab has also been assessed as a therapy given at the time of transplantation in an open-label prospective study
    - Patients with a DD offer and positive flow cytometry XM were transplanted, then treated with eculizumab

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- The study showed the regimen was effective at preventing acute AMR, only 3/80 (4%) of patients suffered acute AMR
  - Two-year graft failure was 14%
  - Median MFI for the highest single DSA was >5,000 at baseline, suggesting around half of the patients included were at high risk of acute AMR
- There are two treatment protocols which have been used for desensitisation in patients with positive CDC XM
    - Peri-transplantation immunoadsorption (IA) has been studied using a protocol of one pre-transplant session of IA on organ offer; all patients with CDC negative XM or CDC positive XM that was converted to negative were transplanted and treated with 6 to 11 post-transplant IA session
      - 33% of patients had AMR and there was a (nonsignificant) trend towards higher AMR rates in patients with a positive CDC XM at baseline (41% vs. 30% in negative baseline CDC XM)
      - DSA MFI was significantly associated with AMR; 20% of patients with peak MFI <5,000 had AMR, whereas 71% of patients with peak MFI >15,000 had AMR
      - The protocol studied is challenging logistically and very burdensome to patients, with IA sessions lasting 6 to 9 hours each
    - Imlifidase is a new treatment option which has been assessed in a clinical trial programme in Sweden and the US, with DD (82%) and LD (18%)
      - Imlifidase is an immunoglobulin G (IgG)-degrading enzyme derived from *Streptococcus pyogenes*, which cleaves human (and rabbit) IgG into F(ab')<sub>2</sub> and Fc fragments in a two-step process; this essentially ablates humoral immunity, as the cleaved IgG can no longer activate complement or mediate antibody-dependent cellular cytotoxicity
      - Since imlifidase also cleaves rabbit IgG, thymoglobulin cannot be used concurrently with imlifidase
      - The effects of imlifidase last up to ~2 weeks
      - In one trial, 8 out of 18 patients included had a pre-transplant DSA MFI of >20,000, and 11 out of 18 had >10,000, so a very high-risk population
      - 83% of patients' DSA MFI had decreased to <3,000 by 6 hours post-implifidase
      - 39% of patients had AMR and were treated with plasma exchange/IVIG, immunosuppressants and glucocorticoids; 2 patients received rituximab, 3 received eculizumab, 2 received bortezomib, one had spleen embolization and one had splenectomy
      - Post-transplant immunosuppression must be adapted to avoid thymoglobulins, but included alemtuzumab, rituximab and high-dose immunoglobulins, there have also been discussions around the use of anti-IL-6

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E: [askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Long-term pooled results from all available studies (N=39; median cPRA 99.6%; DD 82%) showed that patients with no AMR had patient survival of 94% and graft survival of 77% at 3 years, and those who had AMR had patient survival of 85% and graft survival of 93% at 3 years

## Italian National Transplant Centre (CIT) Kidney Paired Donation programme

### *Pamela Fiaschetti*

- The number of kidney transplants performed in Italy in 2022 looks set to increase after dropping during 2020 and 2021 due to the COVID-19 pandemic
- Across all organs, as of 31 August 2022, the total number of Italian patients waiting for a transplant was 8292 and 3431 transplants had been performed
  - This illustrates the need for tactics to increase the number of transplants
- One such tactic is greater support for living donation programmes
  - The number of LD kidney transplants has been stable at around 300 per year for several years; in 2021 there were 341, the forecast for 2022 is 278 (though predicted numbers can be unreliable due to late or missing reporting)
  - There is disparity between the regions of Italy in terms of the number of LD transplants conducted, with some regions not performing any in 2021 or 2022
  - Based on the forecasted number of transplants for 2022, the LD transplants per million population will fall to 4.7, compared with 5.7 in 2021
  - A new project aimed at increasing the number of LD transplants was approved at the Regional State Conference in August 2021
    - A survey has been sent to transplant centres across Italy on whether they have accepted the project and started implementation, but to date many centres have not responded, and responses have been mostly concentrated among regions already implementing LD transplantation effectively
- The main goal of the Crossover Programme is to increase the chance of donation for patients with a living donor with whom they are incompatible (ABO or antibodies)
  - Regional crossover programmes have been operating in Italy since 2005, though the CIT Crossover Programme began in 2015 for chains initiated by unspecified donation ('Good Samaritan' donation), but has since expanded to include crossover chains of different modalities, including DECeased donor kidney paired exchange (DEC-K) and incorporate national and international programmes
  - Italian crossover programmes have helped 71 patients receive a transplant since 2005
  - The first Good Samaritan donor in Italy was in 2015, and between 2015 and 2019, there have been 8 Good Samaritan donors, leading to 19 pairs and 26 transplants

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E: [askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092



- Good Samaritan donation was stopped during to the COVID-19 pandemic and some donors have since withdrawn
- The DEC-K programme was introduced at the Padua transplant centre in 2018 and in the first 13 months there were 5 deceased donors, resulting in 9 pairs and 14 transplants
  - Following this early success, the CIT Crossover Programme was modified to include DEC-K
- The subsequent Kidney Paired Donation protocol has been in place since July 2019
  - Donors must have standard or negligible infection and neoplastic risk, and serum creatinine within normal limits to exclude acute kidney injury
  - Donors are excluded from selection if they: require kidney biopsy to assess organ sustainability, are hepatitis C positive, are ≥70 years old, have arterial hypertension with evidence of organ damage, have a positive history of diabetes, are deceased circulatory death (DCD) donors
  - Since 2019, 10 DEC-K donors have resulted in 18 pairs and 29 transplants
- As of September 2022, there were 63 pairs active in the programme, including 7 who are ABO incompatible, 34 who are DSA incompatible and 22 who are ABO and DSA incompatible
  - 139 pairs have left the programme, 46 due to transplants completed within the programme, 45 due to transplants completed in another programme and 48 due to cancellations
  - 26 of the active pairs are currently enrolled in the DEC-K programme
  - As of September 2022 there were 15 recipients in the DEC-K programme, all with a PRA above 80% - 5 have PRA >95% and 7 have PRA 100%
  - Six matching runs have been conducted in the DEC-K programme in 2022
  - One obstacle to DEC-K chains relates to ‘closing’ the chain in a reasonable time – when a DEC-K recipient is selected, the crossover programme is put on hold and pairs in the chain remain on standby; ideally chains should be completed within 3 months, but often this time is exceeded and chains can be broken due to missing or outdated data, development of new antibodies while waiting or a patient in the chain being transplanted via another route in the meantime
- Italy has an agreement for an international crossover programme with Spain; the Italian matching system uses the Spanish software
  - The first match between Spain and Italy was in 2019, and since then there have been 5 match runs resulting in 3 pairs and transplants

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Three match runs were conducted in 2022
- A pilot programme is currently ongoing at one Italian centre (Gemelli) for Kidney Paired Donation collaboration with the United States; if pairs registered in Italy could not be allocated, they can be entered into the match run software for the United States to see if compatible pairs can be formed
  - Once 3 transplants have been carried out in this pilot, it can be rolled out across other Italian centres
  - Due to travel times and cold ischaemia, donors will travel between the two countries, rather than removed organs
  - It is hoped that introducing a genetically different donor pool may help patients who have been waiting for many years find an HLA-compatible donor

## Maintenance immunosuppression strategy in HLA-sensitised kidney transplant recipients

*Gianluigi Zaza*

- Effective pre- and post-transplant immunosuppressive treatment is vital to avoid graft loss in sensitised patients, but there are few randomised clinical trials examining which treatment(s) are most effective, nor does the literature offer much reliable data on optimal therapy
- Immunosuppressive treatment in these patients must balance the risk of AMR with the risk of adverse events posed by immunosuppressive therapies
- Insufficient immunosuppression in sensitised patients can lead to glomerulonephritis in the peritubular capillaries, arterial fibrinoid necrosis, thrombotic microangiopathy and acute tubular injury, which contribute to AMR
- Both clinical and subclinical AMR lead to significantly higher rates of graft loss, compared to kidney transplant patients without AMR
- HLAi has been shown to have a higher risk of early hospital readmission compared with other variables in kidney transplant patients including: ABO incompatibility (ABOi), history of diabetes or cardiovascular disease, age  $\geq 60$  years, BMI  $\geq 25$  kg/m<sup>2</sup>, delayed graft function and acute rejection during index hospitalisation
  - Incidence of early hospital readmission within the first 30 days of discharge was significantly higher for HLAi transplant recipients compared with ABOi recipients and controls
  - Early hospital readmission is significantly associated with reduced 5-year graft survival
- **There are no comprehensive guidelines on maintenance immunosuppression for highly sensitised kidney transplant patients;** the most commonly used strategy is a combination of a calcineurin inhibitor, a cytostatic agent and a corticosteroid

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Even with these strategies, sensitised patients have poorer long-term graft survival than patients without DSA
    - In one study, 8-year graft survival was significantly lower in patients with DSA (67.9%) compared to those without DSA (77.3%;  $p=0.03$ ) when both groups received maintenance immunosuppression with tacrolimus or cyclosporine, mycophenolate mofetil (MMF) and steroids
  - Dosing these drugs appropriately is also critical to avoid AMR
    - One study found that in sensitised patients, a tacrolimus dose of  $<8$  ng/mL at discharge was associated with almost twice the risk (OR 1.84; 95% CI: 1.04-3.25;  $p=0.04$ ) of acute AMR compared to a higher dose
  - In kidney transplantation there is a large inter- and intra-patient variability of tacrolimus exposure influenced by many factors
    - Factors affecting inter-patient variability: drug-drug interactions, race, genetic polymorphisms, underlying disease
    - Factors affecting intra-patients variability: non-adherence, gastrointestinal motility, diarrhoea, food and drug interactions, haematocrit, plasma protein levels, time post-transplant, drug formulation
    - A within-patient coefficient of variation of tacrolimus levels in the blood  $>30\%$  has been significantly associated with the development of *de novo* DSA
    - Higher intra-patient variability of tacrolimus concentration has also been shown to predict accelerated progression of chronic histologic lesions
  - Chronic calcineurin inhibitor use is not without its own problems, and can lead to hyaline arteriosclerosis and fibrosis
- 
- Personalisation of maintenance immunosuppression currently relies on: pharmacokinetic analysis, laboratory tests (serum creatinine, eGFR, proteinuria), DSA and PRA measurement and graft biopsy
  - While some recommendations are in place for classifying AMR (Banff) and appropriate treatments (Transplant Society Working Group), transplant clinicians' interpretation of these in real-world settings has been shown to be inconsistent
    - One study presented 95 clinicians and 75 renal pathologists with 6 common clinical scenarios and asked to select a diagnosis
      - Among clinicians, the largest proportion (30%) only assigned diagnoses that were concordant with the reference standard for half of the cases
      - On average, pathologists assigned a different diagnosis from the reference standard in 26% of the cases, while for clinicians it was 35% of the cases

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- In pathologists, discordance was related to transplant experience (higher in those working at centres performing <100 transplants per year)
  - In clinicians, discordance was related to the size of the transplant centre, C4d positivity and graft function
  - Therapeutic approaches recommended were heterogeneous, but linked to the diagnosis provided
- Protocol biopsy may have an important role in patients with high immunological risk by allowing better classification of subclinical and borderline injury which may warrant treatment
    - However, many centres seem to be moving away from biopsies due to logistics and expertise required, as well as their invasive nature and patient reluctance
  - Therefore, there is a need to identify novel biomarkers for risk stratification, diagnosis and prognosis
    - One potentially useful biomarker which has been studied is cell-free DNA (cfDNA) – fragments of DNA released into the blood by cells damaged by apoptosis or necrosis
    - cfDNA is present in patients with AMR due to graft cell breakdown
    - **The half-life of cfDNA in the blood is very short, around 2.5 hours, and so the test represents the current clinical situation**
      - This method can identify AMR quicker and earlier than existing biomarkers such as creatinine, which only appears as a notable increase once tissue damage has already taken place
    - Research by the Diagnosing Active Rejection in Kidney Transplant Recipients (DART) group has shown that **donor-derived cfDNA levels >1% indicate probable active rejection**
      - The test showed high specificity for both acute and chronic, as well as T-cell-mediated rejection
    - The Trifecta study compared levels of plasma donor-derived cfDNA with histological and molecular microscope analysis, and showed a strong correlation between donor-derived cfDNA and active molecular rejection
      - More recent work from this group showed that combining the fraction of donor-derived cfDNA and total quantity of cfDNA yields more confident results
    - While the literature suggests cfDNA testing is a valuable tool to identify AMR risk, **tests are currently expensive** (reimbursed by Medicare at more than \$2,800 per test in the US, estimated at \$401 per test based on the German Code of Medical Fees) and not used routinely outside of the United States, other countries must negotiate within their healthcare systems for the tests to be introduced

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org/> - T: +393482786092

- MMF has a number of side-effects it is important to consider, including high rates of infection in the first year of use
  - Infectious risk has been shown to be increased in sensitised patients (CDC XM negative, flow cytometry XM positive) compared with CDC and flow cytometry XM negative during maintenance immunosuppression
  - Mammalian target of rapamycin inhibitors (mTORi) is one proposed alternative therapy, but highly sensitised patients have been excluded from all studies to date
  - One study comparing the mTORi everolimus plus low-dose tacrolimus to MMF plus standard-dose tacrolimus which did allow sensitised patients (>20% PRA) yielded conflicting results, as everolimus-treated patients showed higher rates of acute AMR but lower rates of graft loss compared with standard of care
    - Conclusions which can be made for highly sensitised patients are limited even further, as only ~15% of patients included in the study had PRA >20%, and the majority were moderately sensitised, not highly sensitised
  - A single-centre study in Barcelona including patients with cPRA >50% found that 1-year rejection-free survival was significantly better in patients treated with mTORi, tacrolimus and prednisone compared with those treated with mycophenolate, tacrolimus and prednisone
    - However, tacrolimus dose was not decreased in the mTORi group as in other studies; authors suggested tacrolimus dose should not be decreased in this high-risk population
- The costimulation blocker belatacept has been associated with lower graft loss and better renal and cardiac function compared to standard-of-care with calcineurin inhibitors, but resulted in increased incidence of acute rejection
  - Belatacept is contraindicated for patients with high immunological risk in the United States, and not used as first-line therapy in those with low immunological risk
  - Rejection-free survival in the first year post-transplant has been shown to be lower in sensitised patients converting from calcineurin inhibitors to belatacept compared with non-sensitised patients
    - Conversion from calcineurin to belatacept should be done with caution in patients with high immunologic risk
- Corticosteroid withdrawal in sensitised patients has not been widely assessed, significant benefit to graft survival in sensitised patients (PRA >60%) who maintained chronic corticosteroid use compared with those who discontinued corticosteroids before hospital discharge
- In conclusion, there should be continuous follow-up of highly sensitised kidney transplant recipients including drug pharmacokinetics monitoring, DSA measurement and protocol biopsies, where possible; tapering or discontinuation of immunosuppressive drugs should be avoided in this patient population; mTORi can be considered (after careful risk/benefit analysis) as a replacement for MMF (in

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

combination with calcineurin inhibitors) in cases where MMF cannot be tolerated or infectious complications occur

## Management of transplant patients with HLA antibodies – combined strategy of desensitisation treatments and Kidney Paired Donation (KPD) / Deceased Kidney Donor (DEC-K) programme to provide the opportunity of transplantation in high sensitised patients

**Caterina Di Bella**

### Presentation

- Cases can highlight how the immunological risk profiles of individual transplants influence treatment decisions with respect to desensitisation strategies
- One case involved a 55-year-old female patient (“Patient A”) with renal failure secondary to polycystic disease who had already undergone ABOi transplantation her right kidney followed by subsequent removal of the graft 4 years later
  - At first visit:
    - Patient A presented with a large polycystic left kidney and an incisional hernia where the right kidney was removed
    - Patient A attended the clinic with a friend volunteering to become a living donor (“Donor A”)
    - Donor A presented with no clinical contraindications to donation
      - It would again be an ABOi transplant (group A donor, group O recipient) but anti-A titres were acceptable (1:32)
  - Case history:
    - Patient A underwent video-assisted laparoscopic left-side nephrectomy, with no need for blood transfusion, and was discharged 4 days post-operatively with no complications
  - Patient A’s antibody profile revealed the presence of:
    - High-titre antibodies in class A, class B, class 2 in DR and DQ
    - DSAs against Donor A with medium-to-high MFI
      - Anti DQ6 MFI: 7,429
      - Anti B44 MFI: 9,207
      - Anti DR13 MFI: 6,633
- Patient A’s complement-dependent cytotoxicity (CDC) and flow cytometry crossmatch are both positive (B- and T-cell) putting her in the “high risk” category
- The options for a high-risk ABOi/HLAi transplant are:
  - Desensitisation protocols
    - Monoclonal antibodies
    - Apheresis techniques
    - Immunomodulation
  - Kidney Paired Donation (KPD)

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Cross over
- Good Samaritan donation
- DEC-K (deceased donor-KPD)
  - Waiting list for deceased donors
- Given their incompatibility, the most suitable option for Patient A and Donor A was to:
  - Proceed with transplant following desensitisation
  - Enrol them both in the national and international cross-over programme
  - Suggest the DEC-K protocol
  - Add Patient A to the waiting list for transplant from deceased donors
- Patient A and Donor A agreed to participate in all KPD options, including DEC-K, in May 2020
- However, there was a prolonged waiting time in DEC-K or KPD due to Patient A's immunological profile and the impact of the COVID-19 pandemic
- Patient A enquired about her status on the DEC-K list and whether desensitisation might be possible even in cases with deceased donors, having researched this herself
  - Possible desensitisation strategies include:
    - Antibody removal
    - B-cell depletion (anti-CD20)
    - Plasma cell inhibition (proteasome inhibitors, anti-CD38)
    - Anti-cytokine agents (IL-6, BlyS)
    - Complement inhibitors (C5, C1)
  - Possible desensitisation protocols include:
    - Low-dose rituximab with intravenous immune globulin (IVIg) and plasmapheresis
    - High-dose IVIg
    - Bortezomib
    - Eculizumab
    - Imlifidase
- Imlifidase is a new drug indicated for the desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against an available deceased donor
- Conditional approval was granted by the European Commission in August 2020
- The use of imlifidase should be reserved for patients unlikely to be transplanted under the available kidney allocation system, including prioritisation programmes for highly sensitised patients
- Analysis of 4 Phase II clinical studies with imlifidase (N=46), 3-year data (Kjellman, *et al.*):
  - Patient survival at 3 years was 90%
    - 3 deaths occurred between 6 months and 1 year due to
      - 1 death due to influenza

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org/> - T: +393482786092

- 1 death due to cardiac arrest
- 1 death due to unknown causes
- No deaths occurred between 1 and 3 years
- Patient survival at 3 years was:
  - 85% in the antibody-mediated rejection positive (AMR+) group
  - 94% in the antibody-mediated rejection negative (AMR-) group
- Death-censored 3-year allograft survival: 84%
  - 3 grafts losses in the feeder studies:
    - 1 non-IgG mediated hyperacute rejection
    - 2 due to primary non-functioning grafts
  - 2 graft losses occurred between 2 and 3 years:
    - 1 due to reduction of immunosuppression secondary to an infection
    - 1 due to immunosuppression medication non-adherence
  - 3-year allograft survival: 84% (positive crossmatch (XM+) patients)
    - AMR- group: 77% (4 graft losses)
    - AMR+ group: 93% (1 graft loss)

## Discussion

- Imlifidase is potentially suitable for highly sensitised patients like Patient A, because patients with PRA  $\geq 60\%$  often have transplant waiting times of  $\geq 5$  years
  - For example, Patient A has PRA 75% in Class I and 100% in Class II and has been on the waiting list for 5 years
- There was some discussion around whether it would be reasonable to offer imlifidase to Patient A to facilitate DEC-K
  - There was some concern that as the patient had not been on the waiting list for the 8 years required in Italy, it would be seen as giving her priority; however, the patient's situation is urgent and if a chain could be initiated through DEC-K, there would be no disadvantage to those on the waiting list, as we kidney would be donated to the list to close the chain
  - Overall, there was some agreement that it would be, but only because her PRA level is 100%
  - However, it was agreed that overall, that it would not be suitable to proceed unless a DD could be found through DEC-K with a negative CDC XM – though positive flow cytometry or Luminex XM could be acceptable
- Imlifidase is especially valuable when there is an organ available for transplant immediately, but it would not be possible to complete all the sessions of plasmapheresis required, or the patient cannot tolerate plasmapheresis

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092



- In this circumstance, imlifidase acts as an “instant plasmapheresis”, abolishing the antibody barrier so that within hours the patient can undergo the transplant
- Tensions exist between the needs of the individual patient and the rational use of an extremely expensive drug
- Use of imlifidase should be avoided when there is no clear need
  - Imlifidase should only be used for patients in dire need
  - It was universally advised **not proceed with patients who have a positive CDC**
  - The ideal patient would have either a positive flow XM result or DSA and positive flow XM
  - The value of administering imlifidase to a subject with a negative flow XM who has DSA is questionable as the cost of treatment is very high
  - There was some discussion around the use of virtual XM with Luminex in place of a flow XM in centres where rapid flow cytometry testing is not available
    - Some attendees were against relying on a virtual XM, however it was pointed out that antibody delisting is done on the basis of Luminex assays, for which a threshold for ‘acceptable’ MFI values must be established, so why could this not be the case for virtual XM prior to imlifidase administration
- Overall, the idea of finding a standard for efficient management of highly sensitised patients is welcomed and imlifidase is a useful tool in this regard

## Management of transplant patients with HLA antibodies – What should we offer to high sensitised kidney transplant recipients?

**Roberta Angelico**

### Presentation

- Cases can highlight the challenges that arise in matching transplant recipients with living donors due to their immunological risk profiles
- One case involved a 67-year-old male patient (“Patient A”) with renal failure secondary to light chain amyloidosis who had undergone autologous stem cell transplant (ASCT) in 2003 and peritoneal dialysis since 2018
  - Patient A’s clinical history:
    - BMI: 26
    - *In situ* melanoma (2000)
    - Benign prostatic hyperplasia
    - Autoimmune thyroiditis
  - Patient A completed pre-transplant study and was added to the deceased donor waiting list in 2018
- Patient A attended the clinic with his 53-year-old sister “Donor A” who was in excellent clinical condition and requesting to be evaluated for living donation

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Donor A's clinical history:
  - BMI: 25.8
  - Negative PMH
- Donor and recipient were ABO compatible
- In May 2018, an antibody screening found that Patient A had PRA Class I of 18% and Class II of 0% but had identified B7 DSA titre of 11,000 MFI against Donor A:
  - anti-HLA class I: **B7 (11,260)**, B27 (7,769), B42 (11,070), B55 (8,496), B67 (10,048), B73 (1,207), B81 (10,470), B82 (9,758)
- Besides Patient A's history of ASCT, he had not reported any other immunising events such as blood transfusion
- Flow cytometry XM was positive, CDC was not performed, however the positive flow result in conjunction with day-zero DSA and lack of negative CDC XM meant he was "high risk" per ENGAGE criteria
- The team would therefore need to consider how to proceed very carefully:
  - Was it safe to proceed with the living donor?
  - What treatment would Patient A need to prepare for transplant?
  - How would post-operative immunosuppressive therapy be managed?
  - What kind of long-term therapeutic strategy would be required?
  - How to communicate the level of risk to the patient?
- The team decided that looking for a compatible living donor would be the best option, so they proposed cross exchange, however, Patient A was adamant to receive Donor A's kidney or remain on the deceased donor list
- Three years later, Patient A was still waiting on the deceased donor list
- In September 2021, Patient A began to experience peritoneal catheter problems such as recurrent infections
- The team were contacted again by Patient A's nephrologists due to the difficulties with performing peritoneal dialysis
- Patient A then returned to see the team, requesting they re-evaluate Donor A
  - Flow cytometry results came back negative and results showed the patients no longer had DSA
    - The 2018 sample was re-tested and confirmed as positive
- In October, the team requested a second opinion from Professor Maggiore:
  - Advised a repeat test in November which was confirmed as negative once again
- Together with Professor Maggiore, they decided to proceed with the transplant with a living donor kidney from Donor A
- Clinical management:
  - Pre-transplant

---

**Headquarter**

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Considering his previous history of DSA, Patient A started with tacrolimus three days before the transplant to ensure a satisfactory antibody level at the time of the transplant
- Transplant
  - Methylprednisolone at reperfusion
  - Anti-thrombocyte globulins (ATG) starting at reperfusion
- Post-transplant
  - ATG at day 4
  - Immunosuppression: prednisone, tacrolimus, MMF from day 1
  - Cytomegalovirus prophylaxis
- Post-operative DSA monitoring at days 1, 3, 5, 7, 10, 15 and 30
  - All post-operative DSAs were negative
- Protocol biopsy at day 10 to monitor for signs of subclinical rejection
- Non-protocol biopsy in case of signs of graft dysfunction
- Plasma exchange in case of B7 DSA detection
- Post-transplant clinical evolution
  - One year later, Patient A has excellent renal function

## Discussion

- This case suggests there may be value in re-testing for DSAs in patients who have previously been blocked from transplant to evaluate possible changes in DSA status
  - The type of immunising event and clinical history may be indicators
  - Mandatory testing of antibodies every 3 months could be the best solution
- CDC XM should ideally be performed to best stratify risk pre-transplant
- Patient A's PRA was only 18%, which may not warrant high risk strategies to achieve transplant
  - However, the medical history and sensitising event in this case were unusual, and the patient only wanted to accept a kidney from his living donor and was resistant to starting haemodialysis in the meantime
  - The fact that Patient A had a DSA identified at >11,000 MFI with no typical sensitising event, which was undetectable 3 years later could be considered a risk factor in itself, but at a certain point a decision on whether to transplant the patient must be made
  - There was discussion that Patient A's DSA finding may have been an anomaly, perhaps showing an MFI higher than the true strength of the antibodies, and that a different solid phase assay may have shown a different result
  - **Regardless of the lack of DSA on testing at the time of transplant, the fact the patient had a history DSA and positive flow cytometry XM infers some risk per ENGAGE risk stratification criteria (cellular memory)**

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

## Management of transplant patients with HLA antibodies – Learning from failure

**Giacomo Mori**

### Presentation

- The case being reported highlights several misfortunes with the intention that this may offer useful learnings for other clinicians
  - It is a good example of why in this category of patient it is necessary to invest and work to obtain an excellent transplant result in the long term, rather than deciding what to do and how to do it
  
- In 2001, the patient (“Patient A”) was a 27-year-old male with advanced renal failure
- Clinical history:
  - Year of birth: 1974
  - IgA nephropathy (diagnosed 1996)
  - Hypertension
  - BMI: 29.3 kg/m<sup>2</sup>
  - Blood Group: A+
  
- A living donor transplant was suggested, and his 52-year-old mother (“Donor A”) volunteered
  - Immunological profile:
    - Blood Group: A+
    - Match: 3/6 (50% match as expected for mother and child)
    - (1A, 1B, 1DR, 1C, 1DQB)
    - Serum creatinine: 1.6 mg/dL (suboptimal due to a mismatch in size between smaller donor and larger recipient)
  
- The transplant was performed successfully on 30/01/2001 in another centre with the kidney in the right iliac fossa
- The clinical course after transplantation went well for about ten years, until:
  - 2011: Non-ST-elevation myocardial infarction (NSTEMI)
    - Treated with percutaneous transluminal coronary angioplasty and 3 stents
    - Did not affect the kidney transplant
  - 2016: Graft failure due to chronic allograft nephropathy
    - On 20/12/2016 haemodialysis was commenced due to right arteriovenous fistula
  
- On 8/6/2017 Patient A was waitlisted for a deceased kidney transplant
- His weight had increased by this point:
  - BMI: 30.8 kg/m<sup>2</sup>
- A second living kidney transplant screening was performed with his younger sister (born in 1982) as the potential donor (“Donor B”)
  - Immunological profile:
    - Complement-dependent cytotoxicity (CDC) crossmatch:
      - T-cell negative

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- B-cell positive
  - No preformed donor-specific antibodies (DSA)
  - Calculated panel reactive antibodies (cPRA):
    - Class I: 15%
    - Class II: 0%
  - Living kidney donor profile index (LKDPI): 19%
- Donor B would have been the optimal donor considering her age and LKDPI of 19%, and considering that Patient A was still sensitised from his first transplant
  - However, Patient A was reluctant to accept a kidney from his younger sister so the transplant did not go ahead
- In 2017, when Patient A was relisted, he had class I preformed antibodies and no class II antibodies
- The patient is suspected to have had some transfusions when restarting dialysis that were not documented in his medical history, and in 2018, after a year and a half on the list, an event happened that significantly sensitised him to a stable class II and his PRA rose from 65% to 99%
  - The precise nature of the immunising event could not be traced in his clinical history due to the lack of documentation
- After a year and a half on the deceased-donor transplant list, a potential donor became available:
  - A 54-year-old female woman (“Donor C”) who died of a cerebral haemorrhage and ruptured aneurysm, with no other pathologies and above all with optimal matching:
    - DBD
    - No clinical history
    - Match 4/6
    - 1A 1B 2DR and 2DQB
    - Kidney donor profile index (KDPI): 55%
- At this point Donor B was no longer a good option due to the detection of microhaematuria so Donor C was chosen as the deceased donor
- Patient A was transplanted with the kidney from Donor C:
  - Induced with rabbit anti-thymocyte globulin
  - Cold ischaemia time: 9 hours 20 minutes (optimal)
  - Warm ischaemia time: 45 minutes
  - No DSAs against Donor C
  - CDC: negative
  - No flow was performed
- Unfortunately, a number of complications ensued after the operation, and Patient A returned from theatre with:
  - Anuria
  - Insufficient drainage
  - Pain
  - Hypotension
- CT revealed a haematoma

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Patient A returned to theatre for a vascular review:
  - He was probably predisposed to this haemorrhage due to calcification of the iliac axes, together with a venous thrombosis, for which he had thrombectomy of the anastomosis
  
- He left theatre with a perfused kidney which, however, on serial Doppler monitoring showed inversion of the flow.
- Then he had re-thrombosis of the transplanted renal vein on the fourth day leading to transplantectomy
- Patient A's wife ("Donor D") volunteered as a potential living donor, while the patient's sister (Donor B) was re-evaluated following his further sensitisation event
- Both potential donors had negative CDC XM, positive flow cytometry XM and DSAs were identified for both donors with high MFI
- In particular, the DSA A2 locus that both donors shared, had an MFI between 18,000 and 25,000
  - Donor B (Patient A's sister)
    - 38 y, A pos, Match 4/6 (1A, 1B, 2DR, +2DQA,+2DQB,+2DPA)
    - CDC XM neg B-cell and T-cell
    - Flow cytometry XM pos T-cell (median channel shift [MCS] 457) and B-cell (MCS 377)
    - DSA A2 (MFI 24,981), Cw6 (MFI 3,000)
  
  - Donor D (Patient A's wife)
    - 36y, 0 pos, Match 0/6
    - CDC XM neg B-cell and T-cell
    - Flow cytometry XM pos T-cell (MCS 784) and B-cell (MCS 675)
    - DSA A2 (MFI 18,185), B35 (MFI 5,143) Cw4 (MFI 7,846), DRB3\*03:01 (MFI 18,520)
  
  - Patient A
    - 103 kg, BMI 31.4 kg/m<sup>2</sup>
    - 1st transplant in place right iliac fossa, reconstructed left iliac vessels
    - Following explant of the DD kidney, class I PRA has risen from 15% to between 91 and 96%
  
- Due to the extremely high MFI single antibody levels, as well as the cumulative sum of preformed antibodies, Patient A was not considered a good candidate for desensitisation and enrolled in DEC-K at the end of 2020
  - While waiting, Patient A's BMI increased further to 32 kg/m<sup>2</sup>
  - Then in June 2022, the patient's wife (Donor D) was diagnosed with breast cancer and he had to withdraw from DEC-K
  - The patient's sister (Donor B) begins re-assessment
  - The patient then suffered a second NSTEMI
    - During coronagraphic imaging he became unstable, with symptoms of angina and suffered a critical haemodynamic event
    - Despite being a candidate for heart surgery, the patient was stented

---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- The current picture for this patient is stents, a double integration and a review to be done in December

### Discussion

- The case highlights the importance of timing and taking advantage of opportunities when they present themselves
  - A missed LD transplant with favourable conditions could irreversibly alter a patient's trajectory
    - In this case the patient was reluctant to receive a kidney from his younger sister, even though this could have been the optimal treatment option for him at that moment
    - Completing the screening for Patient A's sister to evaluate her microhaematuria and investigate any potential familial nephropathy could have given offered this patient a different path, before he was further sensitised and became an unsuitable candidate for desensitisation
- Sometimes strategies such as paired donation or desensitisation might not be enough alone, and innovative and combined strategies should be considered to offer patients with complicated situations the best care
  - Young patients with complex immunological profiles should perhaps be given priority on the waiting list
- Patient A was not particularly adherent to dialysis, and it was discussed that he may have been removed from anti-rejection drugs too early by the centre initially treating him
  - Withdrawal of MMF and tacrolimus must balance the risk of AMR with that of side-effects such as infectious complications (e.g. sepsis)
  - Corticosteroid treatment tends to be maintained for longer, even when MMF and tacrolimus are tapered or withdrawn
    - One attendee suggested that they did not believe cortisone 4 mg offered much protection against antibody rebound or acute-on-chronic rejection in younger patients
    - Others added that they see little point in maintaining corticosteroids in young patients in an attempt to avoid future explant, if MMF and tacrolimus are withdrawn
- Both doctors and patients can be reluctant to return to dialysis after transplant, but delaying dialysis when needed can add further complications down the line

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

## Management of transplant patients with HLA antibodies – Desensitisation strategy in a highly sensitised patient affected by systemic scleroderma (SSc) and gastric antral vascular ectasia (GAVE)

**Barbara Buscemi**

### Presentation

- This case report is about a 56-year-old female patient (“Patient A”) with systemic scleroderma/sclerosis (SSc) and gastric antral vascular ectasia (GAVE)
- SSc is an autoimmune connective tissue disease characterised by immune dysregulation and progressive fibrosis that typically affects the skin, with variable internal organ involvement:
  - Vascular damage
  - Tissue injury
  - Inflammation
  - Autoimmunity
  - Fibrosis
- There is renal involvement in 60–80% of cases, such as:
  - Scleroderma renal crisis (SRC)
  - Chronic forms:
    - Vascular fibrosis
    - Accumulation of interstitial collagen
    - Glomerulonephritis
    - Anti-neutrophilic cytoplasmic autoantibody-associated vasculitis
- SSc is often associated with systemic diseases such as:
  - Autoimmune diseases
  - Liver cirrhosis
  - Chronic renal insufficiency
  - Cardiovascular disease
- GAVE (also known as “watermelon stomach”) is a rare but significant cause of upper gastrointestinal (GI) blood loss:
  - Hyaline thrombosis
  - Fibrin hyalinisation
  - Spindle hyperplasia
  - Endoscopic findings:
    - Parallel red stripes
    - Angiomatous lesions at antral mucosal folds
  - Iron-deficiency anaemia secondary to occult blood loss:
    - Melena
    - Haematemesis

---

#### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E: [askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092



- The aetiology of GAVE has not been fully explored and remains controversial, however it is often associated with either SSc and/or renal failure
- Patient A's clinical history was very unfavourable:
  - SSc:
    - Arthralgia of the fingers
    - Raynaud's phenomenon
    - Anti-nuclear antibodies (ANAs): ANA, ENA
    - Interstitial lung disease, fibrosclerosis, pulmonary arterial ectasia
    - Mild-severe mitral regurgitation with restrictive pattern of left ventricle
  - Diabetes mellitus (DM):
    - Diabetic nephropathy
    - End-stage renal disease
    - Dialysis for 7 years
    - End-stage vascular access (exhausted definitive access options)
      - No more arteriovenous fistula
      - No more veins available for catheter placement due to thrombosis (internal jugular vein, subclavian vein and femoral vein)
    - Internal jugular vein thrombosis due to central venous catheter
    - Anticoagulation not tolerated due to GAVE
    - Pancreatic transplant
  - GAVE:
    - Anaemia secondary to GI bleeding
      - Argon plasma coagulation
      - Endoscopic band ligation
    - Regular blood transfusions were required which gave rise to allosensitisation
- The patient was highly sensitised:
  - Panel reactive antibodies (PRA): 90% class I, 10% class II
  - Calculated PRA (cPRA): >90%
- As she had 7 rather than 8 years of dialysis, Italian regulations prohibited Patient A from enrolment in the Italian hyperimmune programme
- Furthermore, due to her highly unfavourable clinical history, nephrologists would call the team stating that Patient A would not be called from the waiting list
- The team sent continuous serum samples collected from Patient A during her frequent blood transfusion appointments (more than twice per week) which confirmed her high PRA

---

**Headquarter**

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E: [askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- Since Patient A's haematological situation would only get worse because of the frequency of her blood transfusions, the team applied to the National Transplant Centre for an exemption, attaching clinical studies and a description of the situation
  - Emergency registration was granted and expecting an imminent transplant, the patient was started on rituximab for desensitisation
    - Once rituximab was initiated, the patient's gastric bleeding due to GAVE stopped, anaemia improved and transfusions were reduced, lung function also improved
  - The patient received an offer of a DD transplant with 0 mismatches and no DSA
  - Flow cytometry crossmatch was low positive, so plasmapheresis and low-dose immunoglobulin were also used cautiously as this was considered the patient's last chance at a transplant
  - Her immunosuppressive treatment included:
    - Thymoglobulin
    - Tacrolimus
    - Mycophenolate mofetyl (MMF)
    - Methylprednisolone
- Post-operative course was characterised by slow but successful recovery of renal function however, Patient A needed high-dose furosemide for mitral regurgitation
  - Patient A maintained a blood glucose level of approximately 1.6–1.7 mmol/L because she had to take high doses of diuretics due to her cardiovascular condition
  - Another dose of rituximab was given to treat her SSc
- Unfortunately, Patient A died during the COVID-19 pandemic due to acute cholecystitis
  - She was treated with antibiotics in her local hospital in Messina
  - She unable to be transferred to the centre in time

## Discussion

- Prioritisation for kidney transplantation allowed the patient to receive an organ before further deterioration of her clinical condition
  - SSc and GAVE would have led to a worsening of her clinical condition
- The need for blood transfusions placed her in a condition of marked selective disadvantage for renal transplantation
- Rituximab conferred additional benefits in terms of:
  - Symptoms related to SSc and GAVE
  - Quality of life
  - Results of transplantation
- Immunologists are often reluctant to proceed with desensitisation protocols for transplants in patients with unfavourable clinical histories

---

### Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092

- However, there can be clear advantages in giving priority to certain patients whose transplant window is very short even when there are clinical situations that create a clear disadvantage
- Patients in this category are often exposed to therapies which render them susceptible to complications even after a successful transplant
- Both pre- and post-transplant management must therefore remain as centralised as possible in treatment centres so that teams are prepared to manage all potential complications
  
- Death due to cholecystitis or diverticulitis after organ transplants is not rare:
  - For many years cholecystectomies, hemicolectomies or diverticula repair have been proposed as part of pre-transplantation management
  - Early diagnosis and correct treatment of complications can dramatically alter the clinical course, for example:
    - The mortality rate for complications such as cholecystitis or diverticulitis indicates that Patient A may not have died from acute cholecystitis if she had been transferred to the centre in time
  
- Adequate management is not always possible in local hospitals, sometimes colleagues are unable to send patients to treatment centres soon enough
  - Pre- as well as post-transplant networking and avoidance of too much decentralisation for these patients is important to avoid negative outcomes
    - The COVID-19 pandemic also played an important factor in the disruption of care in many cases

*This workshop was kindly supported by*



---

Headquarter

ESOT Office  
Riviera dei Mugnai 8/24 – 35137 Padova (IT) - E:[askme@esot.org](mailto:askme@esot.org) - W: <https://esot.org> - T: +393482786092