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

30 November 2022, Paris, France

Programme

11:00 – 11:20	Welcome coffee and Introduction	Christophe Legendre | Paris, France
	SESSION 1	Moderator: Sophie Ohlmann | Strasbourg, France
11:20 – 11:30	HLA-immunization in France	Jean Luc Taupin | Paris, France
11:30 – 11:40	Immune response players: T-B collaboration	Olivier Thaunat | Lyon, France
11:40 – 11:50	Desensitisation: classical approach (PE,IvIg, Ritux): results and limits)	Renaud Snanoudj | Kremlin Bicêtre, France
11:50 – 11:55	Anti-plasmocyte agents	Philippe Grimbert | Créteil, France
11:55 – 12:00	Complement blocking agents	Carmen Lefaucheur | Paris, France
12:00 – 12:05	Imlifidase	Christophe Legendre | Paris, France
12:05 – 12:10	How to set up a controlled trial with few patients	Olivier Aubert | Paris, France
12:10 – 13:00	Discussion	All
13:00 – 14:00	***Lunch break***	

Headquarter

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	SESSION 2	Moderators: Philippe Gatault | Tours, France Nassim Kamar | Toulouse, France
14:00 – 14:05	Local experience	Dominique Bertrand | Rouen, France
14:05 – 14:10	Local experience	Lionel Couzi | Bordeaux, France
14:10 – 14:15	Local experience	Jonathan Visentin | Bordeaux, France
14:15 – 14:20	Local experience	Paolo Malvezzi | Grenoble, France
14:20 – 14:25	Local experience	Antoine Thierry | Poitiers, France
14:25 – 14:30	Local experience	Moglie Le Quintrec | Montpellier, France
14:30 – 14:35	Local experience	Marion Rabant | Paris, France
14:35 – 15:05	Discussion	All
15:05 – 15:15	Wrap-up and Conclusions	Christophe Legendre | Paris, France

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Attendees

Dany Anglicheau | Paris, France
Olivier Aubert | Paris, France
Dominique Bertrand | Rouen, France
Lionel Couzi | Bordeaux, France
Jacques Dantal | Nantes, France
Philippe Gatault | Tours, France
Philippe Grimbert | Créteil, France
Nassim Kamar | Toulouse, France
Carmen Lefaucheur | Paris, France
Christophe Legendre | Paris, France
Mehdi Maanaoui | Lille, France
Paolo Malvezzi | Grenoble, France
Sophie Ohlmann | Strasbourg, France
Marion Rabant | Paris, France
Renaud Snanoudj | Kremlin-Bicêtre, France
Jean Luc Taupin | Paris, France
Olivier Thaunat | Lyon, France
Antoine Thierry | Poitiers, France
Jonathan Visentin | Bordeaux, France
Julien Zuber | Paris, France

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 France.

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SESSION 1, Moderator: Sophie Ohlmann

HLA immunisation in France

Jean-Luc Taupin

Waiting list and transplant activity in France (data from the Biomedicine Agency - ABM)

- As of 01/01/2021, 8,950 patients, 22.2% of whom were highly sensitised (HS) - TGI >85% - were on the active waiting list (without temporary contraindications).
- In 2021, 3,252 transplants were performed, of which only 12% were in HS patients.
- If a living donor (LD) is available:
  - without HLA incompatibility, transplantation can be performed;
  - if anti-donor antibodies (Ab) are detected, several strategies are considered: cross-donation or ABO-incompatible transplantation, which requires preparatory desensitisation.
- In the absence of a LD, the recourse is a deceased donor (DD):
  - via the "Hyperimmunised Antigens Permitted" (HAP) programme;
  - or preparatory desensitisation strategies, including the 'right to forget'.
- It is worth noting that, in France, in 2021, only 15.4% of kidney transplants came from a LD.

LD transplant for highly sensitised recipients (ABM data)

- Living donation: 5.2% of recipients transplanted were HS
- ABO incompatible: 17% of transplants in 2021
  - The number of HS patients who have benefited is not known.
  - In Paris, since 2018, 90 LD ABO incompatible transplants have been performed, of which 10% were in HS patients and 19% were in patients with a TGI between 50 and 84%.
- Cross-donation: only 12 transplants have been performed in France since 2013, none between 2018 and 2021.
  - As of 31/12/21, 18 pairs were pending and 20% of the registrants were HS.

DD grafting for highly sensitised recipients (ABM data)

- HAP programme: almost all HS patients access transplantation via this programme, which represents about 12% of DD transplants.
- Spontaneous / passive disclosures or ‘right to forget’:
  - The HLA antigens (Ag) against which the recipient has progressively "desensitised" themself are changed from "forbidden Ag" status (MFI >2 000 in One Lambda in the patient's serum) to the "grey zone Ag” one as per the software developed by the Biomedicine Agency (CRISTAL).
  - Each team sets the sliders and categories to define the criteria:
    - Waiting time
    - TGI min-max (current and historical)
    - MFI < threshold defining the new status Ag prohibited
    - Time during which the Ab no longer exceeded this threshold

        - ABO blood group of the recipient
    - At the HLA laboratory at the Saint-Louis Hospital, the 'right to forget' has been automated and systematised. The permitted Ag are updated with each serum: if an Ab exceeds the authorised 'right to forget' threshold, the Ag becomes prohibited again and vice versa.
        - In place (gradually) since August 2020 in Paris.

        - 62 transplants (5%) between April 21 and October 22, of which 47 were performed at least 3 months later:
            - 16 recipients (36%) have at least one donor specific antibody (DSA) that exceeds the allowed level of 'right to forget', after a median of 3 months.
            - It would be interesting to analyse the occurrence of rejection to evaluate the effectiveness of this programme, and to improve the follow-up of DSA very early after transplantation to detect possible rebound - a precursor of rejection (e.g. *Burns et al, AJT 2008*).

Post-transplant survival

- Immunisation, whether DSA-related or not, is a risk factor for poor graft survival.
- HLA compatibility, either in Ag or in epitope, must be improved: the more HLA compatible the graft, the fewer complications there are.

Immune response players: T-B collaboration

Olivier Thaunat

Allogeneic HLA molecules can be found in the following situations: transfusion, pregnancy, previous transplants.

Adaptive humoral response

- These proteins are recognised as Ag by allospecific B lymphocytes (B cells) which present them to T lymphocytes (T cells). The latter provide a second allospecific activation signal and activate the germinal centre, and help establish an immunological memory.
- Humoral adaptive memory is complex because it consists of several layers: serological memory and cellular memory.

Serological memory

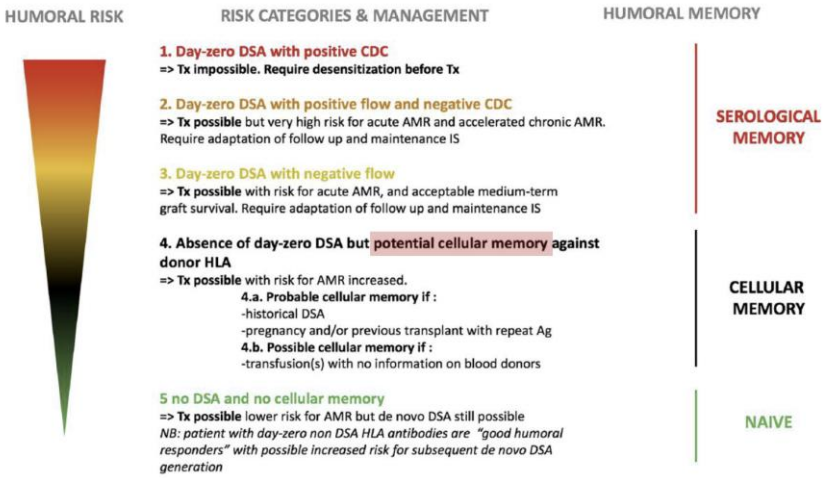
- If the graft contains a DSA already encountered in a previous transplant and if the corresponding Ab is sufficient, the binding of the Ab to the graft endothelium leads to complement activation, destruction of the endothelium and thrombosis, and thus to hyperacute rejection.
- Since the 1960s, the complement-dependent cytotoxicity crossmatch (CDCXM) has been used to avoid hyperacute rejection by detecting these complement-activating anti-HLA Ab in the recipient's serum.
    - This technique is quite effective in identifying patients who will experience acute rejection. An CDCXM(+) is therefore a contraindication to transplantation.

Detection of anti-HLA antibodies

- Increasingly sensitive tests have been developed:
  - Crossmatch by flow cytometry (FXM): detection of anti-HLA antibodies in the recipient's serum in contact with the donor's cells ("real" HLA molecules);
  - Luminex® single antigen technique: detection of anti-HLA antibodies in the recipient's serum in contact with synthetic HLA molecules.
    - Even more sensitive than FXM, but has limitations, including a risk of false positives.
- In contrast to CDCXM, both techniques also detect Ab that do not activate complement. However, the sensitive Luminex® test can be used to assess complement activation: the higher the MFI, the greater the chance that the Ab activates complement.

Risk stratification of humoral rejection in sensitised renal transplant candidates

- Four groups can be defined according to the results of these different tests and the level of risk of humoral rejection:
  - *Group 1*: CDCXM(-), FXM(-), DSA(-): No DSA → Transplantation possible
  - *Group 2*: CDCXM(-), FXM(-), DSA(+) / *Group 3*: CDCXM(-), FXM(+), DSA(+): Presence of DSA but not complement activating →Transplantation possible by adapting induction and maintenance immunosuppression
    - Desensitisation is not necessary
    - The results obtained - not as good as for patients in Group 1 - are considered acceptable (Necker High Immunological Risk Transplant Programme)
  - *Group 4*: CDCXM(+), FXM(+), DSA(+): Presence of complement-activating DSA → Transplantation not possible, unless pre-transplant desensitisation allows the patient to be in Groups 2 or 3
- Studies usually include heterogeneous groups of patients with different profiles and in different proportions.
- Therefore, the ESOT working group – ENGAGE - proposed a new classification with risk stratification according to patient profiles *(Bestard et al, Transpl Int 2021):*



- An HS patient may have memory Ab and/or memory B cells, with a greater risk of humoral rejection in those with only memory B cells.
- It should be noted that memory B cells may be present during a desensitisation or 'right to forget'. However, at present, there is no technique to routinely detect these memory

B cells in a standardised manner.

Perspectives

- A test for memory B cells should be developed to stratify patients more efficiently and adapt induction: rituximab could be interesting in these patients.
- Humoral memory is even more complex with a third layer: the memory follicular helper T cells. Preliminary data suggest that these cells may play a role, especially when present together with memory B cells.

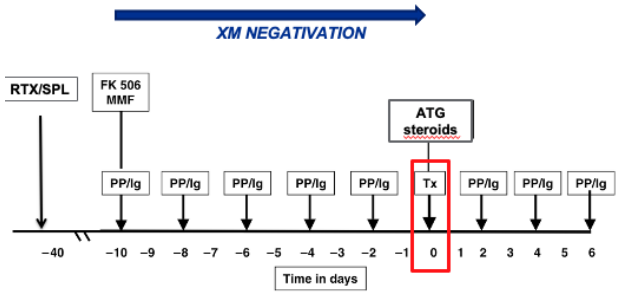
Desensitisation: classical approach (PE, IVIg, rituximab): results and limits

Renaud Snanoudj

Available therapeutic tools

- The different tools available should be combined with a double objective:
  - Remove / neutralise Ab:
    - Plasma exchange (PE) or immunoadsorption
    - Limitations: transient effect, rebound effect, elimination of other plasma proteins (less so with PE)
  - Targeting the cells that secrete the Ab:
    - Maintenance immunosuppression: acts primarily on T cells to block T/B collaboration
    - Rituximab: action mainly on T cells but not on plasma cells
- Intravenous immunoglobulins (IVIg), which allow neutralisation of Ab by their anti-idiotypic effect, are used by some teams at the end of PE to reduce the rebound effect. They also play a role in elimination of Ab, complement blocking and T/B immunomodulation.

1st strategy: pre-transplant desensitisation, living donors



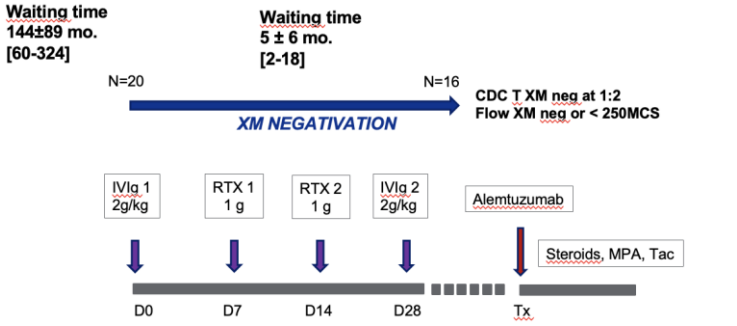
Montgomery RA, Transplantation. 2000 ;70(6):887-95

- This protocol is based on PE combined with small doses of IVIg and the implementation of maintenance immunosuppression. The number of PE was regulated according to immunological risk based on CDCXM or FXM.
- The first studies carried out had very variable definitions of DSA. They found a highly variable acute rejection rate (between 12 and 100%) but a rather satisfactory short-term survival.
- More recent multicentre studies in the US have shown benefits in patient survival at 5

and 8 years vs. dialysis, regardless of immunological risk (CDCXM, FXM, Luminex®) (*Orandi et al, N Engl J Med 2016*). However, they found an increased risk of graft loss, as well as mortality when switching from immunologically safe transplantation to CDCXM, FXM or Luminex® positive (*Orandi et al, Am J Transplant 2014*).

- A similar study in the UK found no benefit or negative effect on patient survival at 5 years (*Manook et al, Lancet 2017*). However, the results showed a decrease in graft survival.

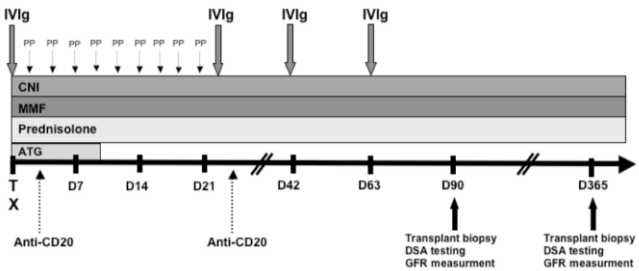
2nd strategy: pre-transplant XM negativity, living/deceased donors



AA Vo et al, N Engl J Med 2008

- This protocol allowed patients to receive a transplant after an average of 5 months, with an "acceptable" XM: CDCXM(-) or negative when diluted to half or FXM(-) or weakly positive.
  - Analysis of the data showed a decrease in PRA from an average of 77% to 44%, and an increase in the number of patients with sub-threshold XM (*Vo et al, N Engl J Med 2008*).
  - These results were confirmed in a cohort of 200 patients, with an acute rejection rate of 22% and a 4-year graft survival of 87% (*Vo et al, Transplantation 2013*).
  - In contrast, another team obtained different results: no or a very small decrease in DSA or PRA (*Lobashevsly et al, Transplantation 2013*).
- Note: this strategy requires priority access to transplantation.

3rd strategy: post-transplant desensitisation, deceased donors



Loupy A, Transplantation. 2010;89:1403-1410.

- Two groups of patients were compared: MFI >3,000 (high risk group) of which 1/3 with

CDCXM(+) vs. MFI <3,000 (control group) *(Amrouche et al, Transplantation 2017*).
  - Graft survival was 78% at 7 years, which is acceptable for these very difficult to transplant patients.
  - The acute rejection rate at 1 year was 32%.
  - Chronic rejection lesions were found at the 1-year screening biopsy in 39% of patients.
- The benefit of rituximab was studied in a meta-analysis of 7 studies (*Zhao et al, Int Urol Nephrol 2014).*
  - A total of 589 HS patients were included, of which 277 were treated with rituximab.
  - The results showed a benefit in terms of frequency of humoral rejection and graft survival for patients receiving rituximab.
  - However, the methodology is questionable, e.g., information on the level of immunisation of patients is missing.

Conclusion:

- All studies include a mixture of immunological risks.
- Living donors: CDCXM and FXM positive are associated with reduced graft survival: they should be limited to the most immune patients.
- Deceased donors: pre-transplant desensitisation requires a short local waiting time or prioritisation to anticipate rebound.
- Post-transplant desensitisation: forgetting the old prohibited Ag should be considered to reduce the risk of humoral rejection, but the long-term outcome remains to be evaluated.

Anti-plasmocyte agents

Philippe Grimbert

The plasma cell is a key cell involved in pre- and post-transplant DSA synthesis, regardless of the mode of activation:

- Follicular helper T cells in the germinal centre inducing the generation of long-lived plasma cells and memory cells
- Generation of short-lived plasma cells in extra-follicular responses

Targeting the plasma cell is, therefore, a prime prospect. Very preliminary data have been obtained in the treatment of myeloma. The available therapies use different strategies.

Proteasome inhibition

- When used in the treatment of the discharge, it induces:
  - increased apoptosis of the cell
  - inhibition of the presentation of class I molecules
  - reticulum stress
- Carfilzomib induces a profound depletion of intramedullary plasma cells but unfortunately a rebound phenomenon appears systematically after 3-4 months (*Woodle et al, Am J Transplant 2021*).

Inhibition of the cytokine pathway

- Cytokines, including the IL-6 pathway and its receptor, are involved in the synthesis of DSAs and the maturation of B cells into memory B cells.
- Anti-IL6-R in desensitisation:
  - Preliminary results from a small study showed complete disappearance of pre-transplant DSA at 3 months extended beyond 12 months (*Vo et al, Transplantation 2016*).
- Anti-IL6-R in the treatment of acute humoral rejection:
  - A meta-analysis of 6 non-randomised studies including a total of 117 patients treated with an anti-IL6-R showed (*Noble et al, Frontiers Immunol 2022*):
    - a significant reduction in the number of DSAs but with a rebound,
    - a reduction in intra-graft inflammation,
    - stabilisation of renal function,
    - no effect on graft survival.

Anti-CD38 monoclonal receptor antibodies

- Targeting of the CD38 receptor induces plasma cell death by various mechanisms: complement-dependent, ADCC (antibody dependent cell-mediated cytotoxicity) or phagocytosis. This receptor is also expressed by NK cells, which are involved in certain types of humoral rejection and in T responses. However, anti-CD38 Ab are also thought to act on T cells with an inversion of the T-regulator/T-effector balance to the detriment of the regulatory response, leading to an increased risk of cell rejection. This paradoxical response, therefore, limits their use in the treatment of rejection.
- An anti-CD8 Ab, daratumumab, has been evaluated both (*Kwun et al, JASN 2019*):
  - in an experimental model of humoral rejection in primates:
    - profound depletion of plasmablasts in both lymph nodes and long bone marrow,
    - very significant decrease in anti-HLA antibodies,
    - no significant change in T-cell populations,
    - graft survival benefit but much higher acute cellular rejection in the daratumumab group,
    - rebound phenomenon at 6-8 weeks observed after use of the molecule in induction (probably a transient suspensive effect).
  - in human clinics, in compassionate situations:
    - acute humoral rejection of refractory renal allografts in a cardiac and renal transplant patient with a major risk of death given his cardiac situation, having escaped conventional treatment: significant improvement in renal and cardiac functions, significant drop in DSA and intra-graft depletion of plasmocyte rate on iterative biopsies carried out;
    - desensitisation before heart transplantation in a patient not eligible for transplantation: significant decrease in DSA that allowed the patient to access the transplant.
- These preliminary data prompted the initiation of a phase IIA study, DARDAR, in patients awaiting transplantation for at least 3 years who had escaped or failed a standard desensitisation technique, with a cPRA >95%:
  - Step 1: Safety study testing 3 dosages including 19 patients in 2020

  - Step 2: Evaluation of desensitisation in 13 patients with the highest dose tested (last patient included had completed treatment in June 2022)
    - Primary endpoint: cPRA at 6 months
    - Secondary criteria:
      - cPRA at 12 months (anti-HLA)
      - modification of immune cells
      - infections
      - patient survival
      - renal transplantation
      - safety
  - The first results, which are currently being analysed, show a significant reduction in DSA, especially for class I molecules, except for patients with an MFI >10,000 for whom there is complete failure.
- Two other studies are on-going:
  - NCT04294459 - *A Phase 1b/2 Study to Evaluate the Safety, Pharmacokinetics, and Preliminary Efficacy of Isatuximab (SAR650984) in Patients Awaiting Kidney Transplantation*: study completed in 21 patients, results pending
  - NCT04827979 - *A Mechanistically Driven Therapy to Desensitize >98.0% cPRA Patients: Depletion of Plasma Cells With Anti-CD38 and Prevention of B Cell Activation With Costimulation Blockade (ITN090ST)*: on-going in 15 patients

Complement blocking agents

Carmen Lefaucheur

Rationale

- The complement system traverses all organs and is central to the process of Ab-mediated rejection. Its analysis, therefore, has a diagnostic, as well as a therapeutic and prognostic role in the management of Ab-mediated rejection.
- Experimental models and accumulated experience from hundreds of patients in several organs with different detection techniques have highlighted the association between complement-activating Ab, rejection and long-term prognosis.
- This link is reinforced by a biological rationale that links the ability of these Abs to activate complement to different organ rejection mechanisms and phenotypes: the complement activation phenotype identifies complement inhibition.
- A *post-hoc* study, performed in a randomised trial evaluating the efficacy of the complement pathway inhibitor, eculizumab, in desensitisation showed an effect of complement inhibition on rejection in patients with complement-activating Ab (*Lefaucheur et al, JASN 2018*).

Current place in the therapeutic arsenal for the treatment of humoral rejection

- The inhibitors act at two levels: proximally (C1-INH) or terminally (C5-INH), with favourable arguments *in vitro* and *in vivo*.
- Numerous clinical studies have also been carried out, but overall they are disappointing:
  - no primary endpoint met
  - interruption for various reasons

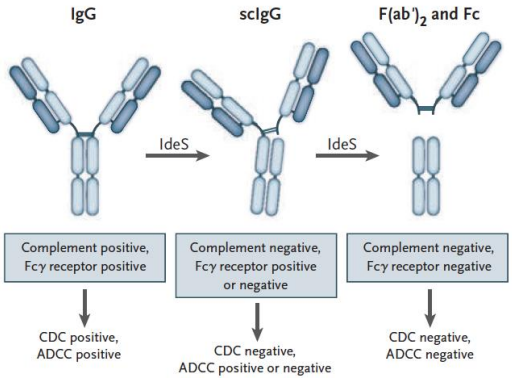
  - questionable methodology
- Nevertheless, experience with the use of these inhibitors has placed complement inhibition among treatments for acute humoral rejection in patients with demonstrated activation (*Schinstock et al, Transplantation 2020*).
- In France, a C1-esterase inhibitor has been granted a temporary recommendation for use.
- Other studies, which will be different in terms of methodology and population selection, are underway to evaluate complement inhibitors in the treatment of humoral rejection as well as in prophylaxis, including the NCT05156710 study evaluating BIVV020.

Imlifidase

Christophe Legendre

Mode of action

- Imlifidase is the first molecule to be authorised in Europe and France for use in desensitisation. It is a cysteine protease derived from an enzyme of *Streptococcus pyogenes*.
- It cleaves IgG into 2 fragments: F(ab')$_2$ and Fc, preventing IgG from activating complement, and inhibiting ADCC. The intermediate step before complete cleavage is *single cleaved* IgG.



Results

- After treatment with imlifidase, a near complete disappearance of IgG is observed within a few hours, regardless of its specificity. IgG then reappears between days 3 and 7 and returns to normal levels around 2 months (*Jordan et al, N Engl J Medicine 2017*).
- Studies show that the molecule should only be used after XM is negative.
- The immunosuppression used by the groups that worked on this topic was ATGAM or anti-CD52 Ab, an imlifidase that cleaves rabbit Ab.
- Imlifidase allows HS patients to be transplanted with relatively good 3-year results and renal function.
- Difficulties in use have been described:
  - Existence of rebound: 30-35% humoral rejection has been found in studies, mostly at the time of rebound (*Jordan et al, N Eng J Med 2017*).
  - Difficulty in using other molecules: with the exception of ATGAM, a delay is recommended before using IVIg (12 hours), alemtuzumab (4 days) or belatacept (1 week) (*Huang et al, Am J Transplant 2022*). Of note, future studies will use a rabbit Ab at D4 and an anti-CD20 at D7.
  - *Single-cleaved IgG*: although their exact role is not known, it would appear that their effect is not neutral. It is, therefore, important that the CDCXM, and not only the FXM, is negative.
  - Existence of anti-IdeS antibodies: variable from one patient to another, their long-term role remains to be defined.

How to set up a controlled trial with few patients

Olivier Aubert

- In transplantation, the studies performed are survival studies, so it is important to anticipate/limit the loss of follow-up of patients when estimating the number of patients to include.
- Although it is difficult to define "few patients", to reduce the number of patients in a randomised study, several parameters can be adjusted:

Choose the lowest power (0.80 vs 0.90):

The lower the power, the lower the number of patients

- With a high power (e.g. 90%), the probability that the observed difference is significant increases, but this requires a certain number of patients.
- With a lower power (e.g. 80%), the number of patients can be reduced but there is a risk that the observed difference is not significant even though it exists.

Choose an achievable alpha (>0.05):

The higher the alpha, the lower the number of subjects

- The standard cut-off is 0.05, but in a therapeutic study the alpha is sometimes lowered to 0.01 to be sure of the effectiveness of the new treatment. However, such a low threshold requires a larger number of patients.

Prefer unilateral analysis:

Fewer patients are needed for a one-sided analysis

- A two-way analysis is when there is no certainty about the superiority of either of the two treatments being compared. Such an analysis requires a large number of patients to observe significant differences.
- If it is certain that the new treatment will be superior to the comparator, a one-sided analysis requiring fewer patients is recommended.

Choose a higher difference:

The higher the difference, the lower the number of patients

- When the difference is small, the variance around the primary endpoint, which is also difficult to estimate, will be problematic and the number of patients will need to be larger.
- This is to ensure that the new treatment will make a significant difference.

Plan for a longer follow-up period:

The longer the follow-up, the lower the number of patients

- With a longer follow-up, the observed difference will be larger, and thus the variance less problematic, so allowing the number of patients to be reduced.
- However, longer follow-up involves higher costs.

Consider a composite endpoint if possible:

→ *A composite endpoint could help increase the number of events and reduce the number of patients*

- The use of a *surrogate endpoint* could also be interesting.
  - For example, 7-year survival could be estimated from 1-year survival assessment data using iBox, a universal artificial intelligence-based risk prediction tool for renal graft loss (*Loupy, Aubert, et al, BMJ 2019*).

- An online calculator using the iBox scores is used to estimate the number of patients to be included in the study (https://cpath.shinyapps.io/ibox_v3/).

Discussion

Right to forget

- Regarding the 'forgotten' Ag, it should be possible to refine the CRISTAL results to take into account the Ag of the first graft, for example, by using an algorithm.
- The notion of delay is very subjective and depends on the teams: it is up to the transplanter to decide. In the case of active desensitisation, the delay is 0 days. The advantage of waiting is to have several sera, therefore at least two consecutive signals under the threshold if 1 year, to avoid fluctuations or transient immuno-sensitivity.
- Theoretically, global IFM should be more deleterious than individual IFM: one possibility is to be more stringent, i.e. to unblot the Ab that are no longer in the last serum. However, fewer Ab would then be unblotted, which would increase the waiting time for patients and reduce the number of transplants performed, which would mean not using this technique. Few patients have actually been transplanted and there has been a significant rebound, certainly related to B memory. Induction with rituximab could be beneficial for these patients (see study in the Netherlands): a study could be set up to confirm this.
- Although transplants are obtained from local donors for the 'right to forget', a national strategy should be defined to ensure equity of access to transplantation.

Monitoring of memory B cells

- Interest in identifying memory B cells is initially to quantify them and to assess the impact of treatments.
- Memory B cells alone may not be predictive (see European randomised study evaluating biomarkers), but the combination of several biomarkers, i.e., an integrative biomarker, might be. A randomised study is underway by Carmen Lefaucheur's team: 750 patients, including >350 with risk stratification, will be included.
- In addition, progress could be made in the following areas
  - Common method / definition
  - Effective technique followed in every University hospital
  - Common biomarkers with peripheral blood mononuclear cell culture from patients
  - Use in specific patient profiles

Rebound observed with bortezomib

- With bortezomib, the maturation process is not blocked: the cell is destroyed and then regenerated. A combination with other molecules such as rituximab would be relevant.
- The observed rebound varies greatly in duration.
- It is not observed in multiple myeloma because patients are treated in maintenance; this is not legal for patients awaiting transplantation.

Imlifidase

- *How long would it take to abolish the Ab?*
  - This is difficult to say. In practice, a significant decrease is observed especially for

patients with an MFI <10,000 after several weeks. It is then maintained over very variable periods depending on the DSA, over 3 to 6 months.

- *Could bortézomib replace rituximab in the imlifidase protocol?*
  - The majority of patients desensitised before transplantation still have their graft in place. Bortézomib will act on the plasma cells but a rebound will certainly occur. The antigenic mass should be reduced, for example, by adjoining transplantectomy.
- *IdeS presensitisation, risk of non-response or early rejection?*
  - Anti-IdeS Ab can be detected in patients never treated with imlifidase, streptococcus being a fairly common bacterium, but some patients have very high levels.
  - It would be useful to set up a study to detect pre-existing anti-IdeS Ab before starting this new treatment to identify patients with very high levels who may be at specific risk.
  - However, according to the literature, it is not necessary to systematically test for these Ab, as a very small number of patients are affected, and imlifidase also cleaves these Ab.

Definition of a common national strategy

- The problem is that there is currently neither a common approach nor a vision of French practices regarding the transplantation of HS patients.
- It is important to define a national strategy for passive or active desensitisation or treatment of rejection. This would first require agreement on definitions of patient groups and data to be collected. The effort made for imlifidase treatment should be continued.
- The support of the ABM will be necessary to enable the entry of the necessary data into CRISTAL. The Agency is *a priori* in favour of this and even requests it.

SESSION 2, Moderators: Philippe Gatault, Nassim Kamar

Local experience

Dominique Bertrand, Rouen

Waiting list

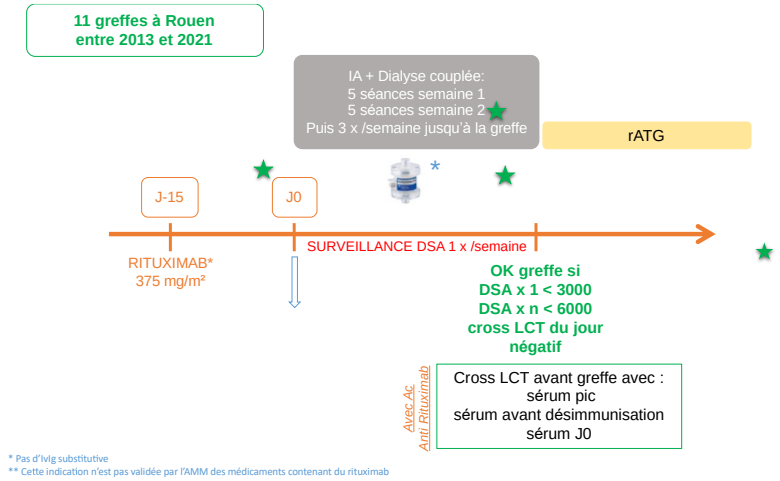
- Out of 553 waiting patients: 16% have HS priority and 5% have a TGI ≥98% and a waiting time >3 years.

Strategy

- In patients for whom LD transplantation is not possible, anti-HLA antibodies are tested in the last serum by Luminex® One Lambda single antigen:
  - In case of a decrease or disappearance of the Ab, the Ab that disappeared are unmarked.
    - Between 2011 and 2021, 37 transplants were able to be performed on patients with historical DSAs but not on the day of transplantation, so reducing their waiting time.
  - In case of persistence of Ab, the last serum is studied again but diluted to 1:10 in class I and class II. If the antibodies decrease, a desensitisation is proposed.

- Note that only patients who request a transplant are tested, depending on waiting time and feasibility of the transplant.

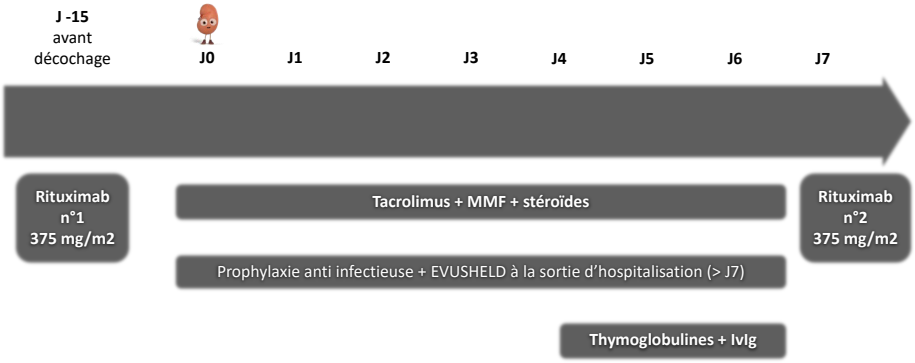
Deceased donor desensitisation protocol



Interest of the 1:10 dilution

- A study in Rouen showed good prediction of the efficacy of class I and II desensitisation of the 10-fold dilution. Conversely, the correlation is not strong with pure serum.

Deceased donor desensitisation protocol with imlifidase



- The strategy is the same, but rituximab treatment is added 15 days before deselecting the Ab which decreased in the 10-fold diluted serum. The protocol proposed by the SFT-SFNDT-SFHI working group is then followed (*http://www.transplantation-francophone.org/images/public/IMLIFIDASE_RecoSFTSFNDT_v5.pdf*).

Patient case treated with imlifidase:

- A 65-year-old patient with nephroangiosclerosis on dialysis since 2015 and enrolled since 2017 with a 100% TGI was treated with imlifidase, PE and eculizumab.
- All specificities with an MFI <5,000 on diluted serum were removed from CRISTAL: the patient no longer had any class II Ab >5,000.
- Comparison of the level of Ab >5,000 just prior to imlifidase infusion and 6 hours post-imlifidase revealed that there were no more Ab >3,000.
- The TGI increased to 58% and the patient was transplanted on 22 October 2022 after 3

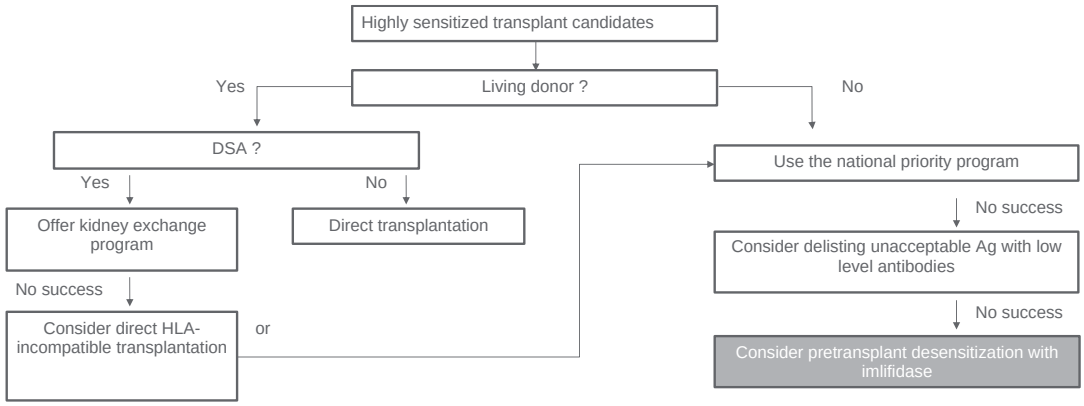
months of waiting with two DSAs, without rebound or rejection.

- However, she had an episode of haemolysis after the transplant with biological stigmata of unexplained thrombotic microangiopathy (TMA), but two biopsies revealed no inflammation of the microcirculation or histological TMA, just endarteritis with a very rapid favourable evolution. In view of the patient's history of miscarriage, an anti-phospholipid syndrome was suspected.
- Another patient is awaiting the same protocol.

Local experience

Lionel Couzi and Jonathan Visentin, Bordeaux

Strategy



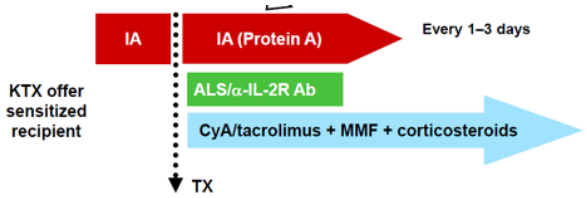
Adapted from Mamode, Transpl Int. 2022 Aug 10;35:10511

Cross donation

- American data (no French data) show that cross-donation is rare: only 1 to 3% of transplants for a TGI >90%, 6% between 80 and 89% and 4% for a TGI <80%. The probability of finding a donor is indeed very low.
- In Bordeaux, enrolment in the cross-donation programme is only considered if a transplant with an incompatible donor is possible in cases of failure of the cross-donation. The aim is not to unnecessarily use the time of the coordinating nurses and medics.

Grafting with desensitisation

- It is considered for patients with a DSA(+), FXM(+), CDCXM(-) or DSA(+), FXM(-), CDCXM(-) profile.
- Passive desensitisation, 'right to forget':
  - Anti-HLA Ab with MFI <2,000 in FXM, in accordance with ABM rules for HS patients, are deleted.
  - NB: access to local grafts only.
- Clinical desensitisation protocol:



Bartell, American Journal of Transplantation 2010; 10: 2033–2042
Niederhaus Transplantation2011;92: 12–17

NB: An emergency pre-operative apheresis session may exceptionally be performed when a FXM(+) is suspected.

- In Bordeaux, 910 patients were on the waiting list in 2021 and 2022, of which 16% were HS with a TGI >85%. 30% of the transplants were performed in patients with at least one historical or current DSA (MFI threshold >500) in the file.

Active desensitisation strategy with imlifidase

- Out of 96 patients with a TGI ≥98%, 52 were eligible according to the criteria defined by the SFT-SFNDT-SFHI working group, including 37 without temporary contraindications.
- After virtual Ab deselecting using an American tool, the cPRA had fallen below 95% for about ten of these patients, a less impressive result than that obtained in Rouen. The patients for whom the decrease in TGI was disappointing probably had a lot of saturating Ab, so the MFI did not decrease.
- In order to choose which of these ten eligible patients to enrol for imlifidase treatment, other comorbidities (obesity, high cardiovascular risk, etc.) were also assessed. Three patients were identified: one is on hold and the other two have been enrolled.
- NB: requests for imlifidase are nominative because in the framework of AP2, the patients included must be documented. However, the product is not allocated to a specific patient but to the UHC. The hospital is not obliged to order for as many patients as there are requests. Hansa Biopharma delivers the number of vials requested by the Pharmacy (without exceeding the total number of nominative requests made) and can deliver additional vials within 48 hours.

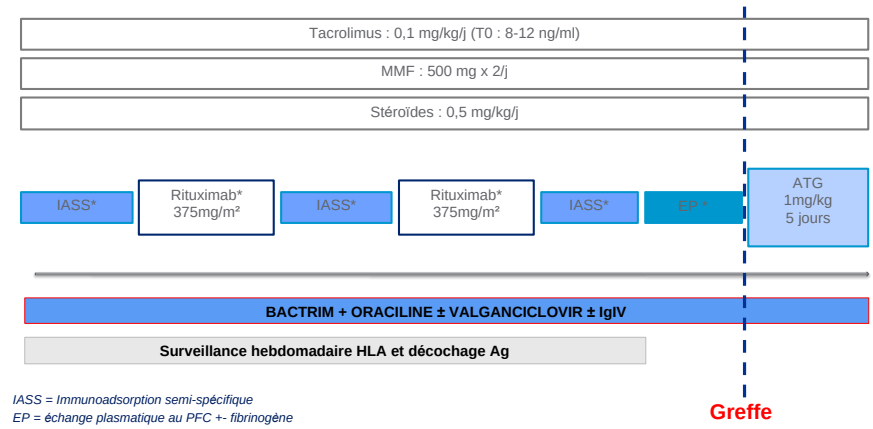
Local experience

Paolo Malvezzi, Grenoble

Strategy:

- Ab with an XM immucor <3,000 are unblocked for all patients.
- Desensitisation is discussed for all patients meeting the following criteria:
  - Age <70 years
  - Minimum waiting period of 3 years (deceased donors)
  - TGI >95% (deceased donor)
  - Motivated and informed
  - No significant cardiovascular comorbidities
  - Pre-vaccination prophylaxis

Deceased donor desensitisation protocol



A DFFP (plasma filter) column is added to remove other factors including complement.

Cohort of deimmunised patients

- Since 2016, 25 transplants have been performed with a DD: patients were relatively young, on average 9 years on dialysis, with an extremely high TGI (99% vs 62.5% for LD).
- Rejection was observed (36% acute rejection and 16% histological active chronic rejection) but with good overall recovery of renal function.
- However, 5 graft losses and 3 deaths due to infectious complications were reported.
- Comparison of patient survival or graft loss data censored on death between patients with an TGI >85% vs <85% showed comparable results.

Discussion

- *Use of imlifidase:*
  - No patients have yet been treated with imlifidase. The team would like to participate in the European PAES study.
  - There is as yet no consensus as to how to manage the bounce with imlifidase that is expected to occur.
- *Pre-transplant immunoadsorption:*
  - A 10-fold dilution is performed but, in the team's experience, it is not so predictive. One week of immunoadsorption can sometimes, surprisingly, result in XM negativity. If the immunoadsorption does not result in a decrease in Ab, the protocol is stopped.
- *Average waiting time for patients with DD once they have started the circuit:*
  - It is very variable because the graft is local, the longest being 9 months.
  - The treatment is intensive on the first month, then reduced and monitoring is implemented: it is intensified according to the rebounds.
- *Infection rates during dialysis:*
  - The team observed two cases of severe infections but no deaths. In particular, the protocol had to be interrupted in a patient who was not on rituximab following a digestive perforation, but despite multiple transfusions in the intensive care unit, he did not re-immunise and was able to be transplanted without further desensitisation.
- *Proportion of CDCXM(+) in deimmunised patients:*

  - In DD recipients, 60% were CDCXM(+) with historical serum but all were negative on the day of transplantation (a condition for performing the transplant). In contrast, FXM can be positive retrospectively.
- *Failed desensitisation in six patients:*
  - It is difficult to describe their profile: 2nd transplants, women immunised at a very young age and after 2nd transplants or class II (even in never transplanted patients).

Local experience

Antoine Thierry, Poitiers

Patients at the centre

- 212 patients are on the waiting list, of which 19% are HS patients enrolled in the HAP programme.
- 4 patients are eligible for imlifidase but are not yet registered.

Strategy

- Pending imlifidase, the current strategy is based on passive desensitisation. Ab with an MFI in the last serum of <3,000, if the patient has been enrolled for >3 years, or <5,000, if enrolled for >5 years, are desensitised.
- Although there is no desensitisation protocol in Poitiers, transplants with pre-formed DSAs (<1,500 in Luminex® One Lambda) are nevertheless performed, depending on individual criteria: waiting time, graft quality, motivation, etc.:
  - Anti-C, anti-DP, anti-DQ_A: peak and sum of MFI
  - Peak and/or DSA sum >10,000: stop
  - Peak and/or sum DSA >6,000 and <10,000, with CDCXM of the day negative:
    - EP (5 in 10 days), rituximab, IVIg (1g/kg/dr x 2 days, 3 courses)
    - FXM (but not on site, in Tours, 8 days delay so no discrimination between group 2 and 3), renal biopsy M3
  - Peak and/or sum <6,000: IVIg

Interaction between IVIg and rituximab

- Small doses of IVIg were often added after each PE, as one study showed that rebound came later. However, as the level of evidence is low, this practice is no longer performed in Poitiers.
- Another study showed that the concomitant use of IVIg and eculizumab (and certainly rituximab) induced a decrease in the efficacy of eculizumab by saturating Fc receptors.
- The combination of eculizumab + rituximab allowed a more rapid reconstitution following the loss of cytotoxic activity of complement. Thus, in neuromyelitis optica, eculizumab reduced the depleting efficacy of rituximab by 90%, which is truly a complement-dependent antibody.

Local experience

Marion Rabant, Paris

Patients at the centre (example in 2017)

- Out of 220 transplants, 94 patients (43%) were HS (no details on MFI, DSA criteria):
  - Imlifidase protocol: n=2
  - ABO incompatible: n=3
  - Pre-transplant desensitisation: n=2
  - Atypical haemolytic uraemic syndrome on eculizumab: n=1
- Characteristics of the transplanted HS patients were:
  - 36% had already been transplanted
  - 23% received a graft from a LD, 34% from a marginal donor
  - Cold ischemia was 21 hours on average
  - 5-year follow-up:
    - 13 deaths (15%) after an average of 2.5 years
    - 4 returns to dialysis, including two early de-transplants

Biopsy analysis

- A total of 219 biopsies were performed, i.e. 2.5 per patient [0-5].
- Screening biopsies:
  - 135 biopsies were performed: at 3 months in 83% of patients and at 1 year in 70% of patients.
  - 24 patients have only one screening biopsy.
  - 8 patients did not have a screening biopsy but a biopsy for cause.
- Biopsies for cause:
  - 84 biopsies were performed in 67% of patients, 44% of which were performed within the first 3 months.
  - 19 had more than one biopsy for cause.
  - 29 patients did not have a biopsy because of this.

N=219	Biopsies avant M3 N=37 chez 31 patients	Biopsies M3 N=73	Biopsies M12 N=62	Autres biopsies N=47
INDICATION				
RRF	5 (13.5%)			0
stagnation	10 (27.0%)			0
IRA	21 (56.8%)			25 (53.2%)
Protéinurie	0			4 (8.5%)
Contrôle	1 (2.7%)			18 (38.3%)
DIAGNOSTIC				
LNS	21 (56.8%)	45 (61.6%)	20 (31.7%)	11 (23.4%)
FIAT	5 (13.5%)	18 (24.7%)	36 (57.1%)	22 (46.8%)
ABMR	6 (16.0%)	2 (2.7%)	3 (4.8%)	5 aABMR / 4 cABMR (19.1%)
TCMR	0	1 (1.4%)	0	0
Rejet mixte	1 (2.7%)	1 (1.4%)	0	2 (4.3%)
Borderline	2 (5.4%)	0	0	0
V isolé	1 (2.7%)	0	0	0
Fibrose inflammatoire	0	5 (6.8%)	3 (4.8%)	1 (2.1%)
BKVN	1 (2.7%)	1 (1.4%)	0	2 (4.3%)

Headquarter

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In total:

- 57 patients did not reject during follow-up (65%).
- 2 early de-transplantations.
- 22 patients had at least 1 episode of rejection (25%):
  - 13 active ABMR (on average at 13 months of transplantation), of which 2 evolved into cABMR
  - 2 cABMR at diagnosis (at 2 years of transplant)
  - 2 mixed rejections at 5 years of transplantation (non-compliance)
  - 1 early MRCT within the first 3 months
  - 2 chronic MRCT at 1 year
  - 2 borderline (within 1er months)
- 3 patients had a BKVN.
- 6 patients have inflammatory fibrosis which is occasionally treated, and which appeared to improve on follow-up biopsies.
- 2 returns to dialysis and 13 deaths (14.7%) were reported, 8 of which were due to infectious causes, including COVID-19.

Discussion

- Almost all patients had received IVIg +/- PE. Only 4 patients had induction with rATG and conventional immunosuppression without IVIg and PE.
- Patients with a positive historical CDCXM but negative on the day of transplant are considered to be at high immunological risk:
  - In case of historical DSA: HRI protocol with rATG and standard immunosuppression
  - If DSA D0 score 6-8: reinforced protocol by EP
- When the XM is negative, some of the teams present give a course of IVIg - in case of doubt - to avoid a rebound. The other teams, if the historical DSAs are no longer detectable on the recent serum, simply monitor at D10.
- When the biopsy is very early, inflammation is sometimes observed: how can we distinguish reperfusion ischemia from immunological mechanisms?
  - These cases are usually treated as humoral rejection, although this may not always be the case, and they progress quite well.
- It is interesting to note that the rate of TCMR is higher than expected: this is probably related to T-memory.
- Subclinical humoral rejection was observed in 3% of patients at M3, but these were probably patients who already had humoral rejection.

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