Report on the extramural tissue typers meeting, Groningen, the Netherlands
Friday 8th of March, 2019

The extra mural meeting was opened by Sebastiaan Heidt (ETRL).

The first topic on the agenda was an update of the EPT results from 2018, presented by Yvonne Zoet (ETRL). For HLA typing, a discrepancy rate of 1.3% was observed. For cross-matching (all results included) discrepancy rates of 3.9% and 3.0% for respective donor centers and recipient centers were observed. To complete the overview, data from screening detection and screening identification scheme were also shown. For screening detection, a discrepancy rates of 0.7% for HLA class I antibodies, and 1.4% for HLA class II antibodies were observed. For screening identification, CDC and SPA Single Antigen techniques were assessed. In CDC, 17 consensus specificities were found and in SPA SA 311 consensus specificities were found (261 HLA class I and 50 HLA class II). In general, the discrepancy rates for the 2018 EPT were comparable to previous years.

The next subject was the positive cross match inventory, which is related to the upcoming introduction of virtual cross matching in Eurotransplant. Since the beginning of June 2018, recipient centers are asked to comment on positive donor cross match results for their recipients. Approximately 6% of the donor cross matches are positive. Comments on 208 positive cross matches were analysed. Comments were divided as follows:

Comment	Percentage
The presence of autoantibodies	5%
Unacceptable antigens present on this donor had not been entered	17%
Unacceptable DQA and/or DP antigens are present on this donor	20%
Other	58%

The “other” comments were divided as shown below:

Comment	Percentage
No explanation	34%
Proposed for AM program	33%
Possible donor center problem	3%
Recipient is treated with Rituximab	5%
IgM/Non-HLA/Unspecific Antibodies	16%
Difficult recipient, ENIS does not meet the needs	6%
Other	3%

Other results from the inventory are that in more than half of the 208 analysed cross matches the autologous status was not known or not entered in ENIS, and that in 34 cases no unacceptable antigens were entered despite a current and peak PRA above 6%.

The next speaker was Sebastiaan Heidt , who discussed three patient-based cases that were sent to all EPT participants in 2018. Prior to the extramural meeting, a summary of the results was sent to the participants. This summary can also be found on the ETRL website. This year, in one of the patient cases was to assign unacceptable antigens on basis of Luminex SA results together with some other information like immunizing events. The two other cases involved patients with complicated immunological profiles. A discussion took place on how to deal with low level luminex DSA for patients with a very low chance on a donor organ.

The meeting continued with Frans Claas (ETRL), who showed the issues discussed during the TTAC meeting on the 7th of March 2019. He discussed the following issues:

Toward virtual cross matching. In the future ET will skip shipment of sera and crossmatches in the donor centers. There are several requirements in order to be able to do so. First the following requirements must be fulfilled:

1. The degree of sensitization must be fully based on unacceptable HLA antigens and will be reflected by the virtual PRA. % PRA will not be used anymore as a parameter.
2. Proper definition of the unacceptable mismatches is crucial as this will prevent the occurrence of unexpected positive crossmatches.
3. Donors must be typed for more loci: HLA-DQ-A and HLA-DP-A and -B (a new list of alleles to be reported will be made by the TTAC)

Sebastiaan Heidt gave a more detailed explanation on the timeline of introduction of the virtual crossmatch in ET in the afternoon.

Changes in the AM program.

Inclusion criteria: To make sure that the AM program only includes patients with a low chance to be transplanted the future criterion will be a chance of <2% of finding a compatible organ.

Minimal match criteria: Future AM program reduce minimal match to 1 broad DR antigen and for patients with a chance of <0.1% no minimal match at all.

Waiting time criteria: Future AM program: the mean waiting time of the country will be used as minimal time that a patients from that country is eligible to enter AM. A separate but similar approach will be used for pedriatic patients. Only for patients with a chance < 0.01% the waiting time criterion will be omitted.

Blood group compatibility rule will change from ABO compatible to ABO **ET** compatible (see table).

ABO ET Compatible	
Donor	Recipient
O	O, B
A	A, AB
B	B
AB	AB

The unacceptable antigen definition should be in the hands of the recipient center. The ETRL will monitor for changes in the number of registered unacceptable antigens around the time the respective patient becomes eligible for inclusion in the AM program (mean waiting time of the country of residence).

This was followed by a presentation of Marian Witvliet, who will leave the ETRL this year, because of her retirement. She gave her personal view on developments in the AM program over the past years. Frans Claas took the opportunity to thank her for her efforts and commitment.

Next the road towards virtual crossmatching was explained by Sebastiaan Heidt. In short:
Current situation: mandatory serum exchange program for immunized recipients. The donor center has no knowledge of the immunization history of the recipient. Crossmatches can be falsely interpreted as positive (irrelevant antibodies). In donor center crossmatches it is hard to detect HLA class II-specific antibodies, because of low sensitivity. Cold ischemia times are longer, due to waiting for the crossmatch at the donor center.
To improve this situation, Eurotransplant will transition to virtual cross matching. Therefore the following requirements must be met:

- An alternative parameter to measure sensitization (Virtual PRA instead of % PRA) must be implemented. Definition of vPRA: the percentage of potential donors within Eurotransplant to which the patient has made HLA antibodies (Calculated based on the HLA types of the actual Eurotransplant donor population
- Unacceptable antigens must be defined adequately to be able to measure to vPRA.
- Extended donor HLA typing for HLA-A, B, C, DR, DQA, DQB, DPA and DPB is necessary.

The timeline for implementation of vPRA and virtual cross matching:

1. Inventory of positive donor center crossmatches by ETRL: Q3 of 2018

2. Introduction of vPRA as the sole way to indicate whether a patient is immunized: Q1-2 of 2019
3. Possibility to submit extended HLA typing of donor and recipient to Eurotransplant: Q2-3 of 2019
    - Monitor HLA typing progress within Eurotransplant
    - Gather data for vPRAbased on all loci (retrospective data gathering may be required)
4. Minimize the number of positive donor-center crossmatches due to inadequate unacceptable antigen definition
5. Mandatory HLA typing for HLA-A, -B, -C, -DR, -DQA, -DQB, -DPA, -DPB of donors: Q2 of 2021
6. Test phase in which both virtual and physical crossmatches are performed simultaneously: Q3-4 of 2021
7. Introduction of virtual crossmatch in Eurotransplant: Q1 of 2022

This was followed by a short presentation on the upcoming International HLA and Immunogenetics Workshop (IHIWS), which will be concluded with a final meeting in 2021 in Amsterdam. In case you are interested to participate in the workshop, please use the following link: https://www.ihiw18.org/

The final speaker of the day was Dr. Jan Stephan Sanders from Groningen who presented his ideas on personalized medicine in transplantation.

In case you are interested, all presentations are published on the ETRL website: http://etrl.eurotransplant.org/cms/index.php?page=extramuralmeeting.