Nordic Pancreas and Islet Transplant group

Date: 15th October 2024

Location: Arlanda Clarion conference, Sweden

Participants:

Physical: *Torbjörn Lundgren surgeon Stockholm, Hanne Scholz Islet lab Oslo, Marko Lempinen surgeon Helsinki, Bengt Gustavsson surgeon Gothenburg, Anna Boserup Scandiatransplant, Marko Murreste surgeon Tartu , Christina Andreasson transplant coordinator Uppsala, Bengt von Zur-Mühlen nephrologist Uppsala, Torsten Eich immunology Uppsala and Stockholm, Kristine Fasting surgeon Oslo, Monika Olofsson Storrö transplant coordinator Oslo, Karin Fransson research nurse Huddinge,*

Digital: *Olle Korsgren Islet lab Uppsala, Amir Sedigh surgeon Uppsala, Marie Felldin nephrologist Gothenburg, Lara Aygen Özbay nephrologist Århus, Oleg Slivca surgeon Malmö, Lydia Junebjörk research nurse Uppsala, Shinji Yamamoto surgeon Uppsala, Niclas Kvarnström surgeon Gothenburg*

1. **Welcome, decision on chairperson and secretary for the meeting**
   Torbjörn Lundgren welcomed participants and was elected chairperson for the meeting. Bengt von Zur-Mühlen was elected secretary.

2. **Introduction of participants**

3. **Agenda was approved** with addition of the topic on diagnostics in pancreas transplantation and antifungal treatment

4. **Election of Chairman**

   Presently Hanne Scholz and Torbjörn Lundgren have shared co-chairmanship since 2021, and the Scandiatransplant guidelines say

   "One person is appointed as chairman. A new chairman should be appointed every 3rd year, however it's allowed to be re-elected one time (total 2 x 3 years). Chairman candidates should be announced to all present NπTG members at least one week before the annual meeting"

   Torbjörn contacted Kaj Anker Jørgensen (KAJ), Scandiatransplant to ask if we could continue to have co- chairmanship for our group.

   According to KAJ: In Article 12,1 about the groups in Scadiatransplant it says:

   "Each group constitutes itself, but all member hospitals performing the particular organ transplant must be represented in the group. The group defines its own by-laws, leadership and meeting activity. The group must at all times have a contact person to

the Office and the Association. It is the responsibility of the group to keep the Office updated on who is the contact person."

So the group defines its own by-laws and leadership. For the Scadiatransplant Office it is important to always have one contact person.

- The meeting reelected Torbjörn Lundgren and Hanne Scholz. Torbjörn Lundgren will serve as the contact person to the Office.

5. Minutes from last on-line meeting 16th January 2024

- Waiting list: Torbjörn Lundgren will discuss with Scandiatransplant if all centers have transferred their waiting lists from Medscinet to Yawsa.

6. Short report from centers

Denmark: 1 pancreas, no islets

Sweden: 15 pancreas (Malmö 3, Goth 5, Uppsala 1, Sthlm 6), 2 islets in Uppsala

Norway: 6 pancreas no islets

Finland: 14 pancreas, 1 islet

Estonia: 2 patients on the waitinglist

In Stockholm loss of 2 pancreata, both lost to fungal infection (1 of these patients later died). In Helsink1 2 lost pancreata, 1 fatty donor and recipient reoperated due to compartment and pancreas later removed due to infection, 2nd case calcified vessels, fistula and late infection – removed after 2 months. Gothenburg only SPK no PA. Oslo 5 SPK – one retransplant PA. Malmö only SPK no PA, one case with thrombosis after hematoma. Uppsala – one SPK pancreas lost to thrombosis.

In total approximately 25 % graft loss pancreas. Discussion regarding anticoagulation. Marie Felldin clarified that Klexan is more dependant of renal function than Fragmin (if GFR < 30 50 % reduction vs. 30 % of dose).
There seem to be local variations regarding, for example, how anticoagulants are used that deviate somewhat from the common protocol from 2017.

- The meeting decided that all centers send their local imm supp and prophylaxis to Torbjörn Lundgren with the aim of revising the joint protocol.

7. Allocation of pancreases

Continued discussion from the previous meeting that there are probably more possible pancreases than are being transplanted. The general guide is that pancreases in donors not older than 50 and with a BMI not higher than 30 should be offered within the group including kidney from the same donor if there is a patient waiting for SPK at another center. Payback for the kidney as with any other organ. No pay-back for pancreas.

45 pancreases were sent for possible islet isolation of which 34 were excluded due to ischemia time > 16h and metabolic factors. 7 isolations were released for clinical islet-Tx, 3 lost due to capacity restrictions at Tx-centers, 2 islet batches lost that were planned to be transplanted in hypoimmunization-study.

At the moment there are total 17 patients on the waiting lists. There is a high success rate (70-80 %) if the donor is “clinical-grade”.

Islets for research are also of high value for the Nordic countries.

Discussion that HbA1c is not yet available as an emergency test at all hospitals. Is not done routinely before pancreas tx, but in all donors where the pancreases is used for isolation at the islet labs in Uppsala.

The British waiting list is common for islets and pancreas and their experiences can provide a basis for discussion about better organ utilization.

- Torbjörn L will check if Gabriel Oniscu (prof Stockholm) wants to join and discuss his experiences at the next meeting
- Need for further harmonization of inclusion and exclusion criteria such as BMI (<30) and age (<50) limits. Olle Korsgren suggests that a joint clinic study could be a possible method for this.

8. Pancreases for research.

The Helmsley Charitable trust supports trials with islets with type 1 diabetic donors. Two pancreas have been delivered from Norway.

- Marko Lempinen investigates how ethical approvals are going in Finland

9. Studies -ongoing, planned, closed.

a. **Vertex VX880 = *Forward trial*** with the use of pluripotent allogenic stem cells to fully differentiated into islet cells. The Forward trial is no open for part C (part A half dose 2 patients, part B full dose 5 subjects, part C full dose many centers 30 subjects). Data for 12 subjects who received the full dose as a single infusion in Parts B and C were presented on the 60th EASD Annual Meeting . All patients had improved glycemic control and achieved HbA1c < 7%, all had eliminated severe hypo and 11/12 had reduced or eliminated exogenous insulin (7/12 no use of insulin 2/12 70 % reduction). At baseline 49.5 % time in range and > 90 % at M12. Majority of AEs were mild or moderate. No SAEs. On the 9th October the first transplant was performed in Oslo (the stem cell-derived islet cells are produced at Vertex in Boston). An earlier attempt in the same patient was aborted in late August due to no-release of the islet cells product due to failure in quality testing of the cells. Patients developed serum-sickness due to the ATG-induction (the clinical protocol prohibit steroid administration after the first ATG

dose), second attempt in October was therefore selected to be performed with the use of basiliximab induction.

The trial has extensive procedures and reporting. Discussion on whether to increase the number of centers or send patients for any future studies. Future manufacturing may be established in central Europe (The Netherlands). This will be an advantage as the shelf life for the stem cell-derived islet cell product is short (within 3 days of the release of the drug product).

A stem cell source provides more unrestricted access to islet cells but the need for immunosuppression and cost limits the selection of patients. Still only recipients with blood group A and AB

b. **Vertex VX264 = *Upward trial.*** The trial aims to use the same investigational stem cell-derived islet cells but with encapsulation. The devices are implanted in the abdominal wall – in total 6 devices/patient. Phase 3 trials are planned to start next year at many (100) centers

   Olle Korsgren told about previous less successful historical attempts with encapsulation and concerns about sarcoma (the combination of insulin, semipermeable device and inflammation). The pipeline for Vertex seems to be to develop hypoimmune cells, same cells as VX880 but edited to eliminate need for immunosuppressants.

- The meeting concludes that even if there are low hopes regarding the clinical success rate with macro encapsulation, it is valuable that the Nordic network participates in *"cutting edge"* studies. Hanne Scholz communicate on behalf of the Network with Vertex.

c. **NNCIT-02:** Study closed after severe bleeding – see previous minutes.

d. **UP421 / Sana Biotechnology:** Generation of cells that can evade the immune system with generating hypoimmune primary islet cells (HIP islets). The clinical trial is based on solid preclinical data from the Schrepfer lab, in short, the HIP islet cells are produced with genetic modification of primary human islets where HLA I and II are knocked out (depleted) from the cell surface and CD47 is overexpressed (CD47 protects cells without HLA from NK-cells). Uppsala Akademiska Sjukhuset is sponsor of the study with PI Per-Ola Carlsson – Olle Korsgren with the clinical site in Uppsala will perform the islet isolation and im transplantation. The HIP islets are manufactured and released as a drug product at the GMP lab in Oslo (Hanne Scholz) and transported to Uppsala for im transplantation into type 1 diabetic patients For the moment the study has approval for transplanting 2 subjects. A planned recent transplant was aborted due to that the HIP islets did not meet one of the release criteria..

- The meeting supports future attempts to be done with some modification of the protocol such as reduced lenti virus exposure and better sampling method for

less “contaminating” media in the sampling reducing the interference for the analysis of vector copy number..

10. Registries/waiting list

Entering data into the registers is not complicated, so the problem of lack of registration is likely mainly a lack of time.

- Torbjörn Lundgren will double check that the waiting list is up and running in Yawsa and then we can close Medscinet

11. Study to evaluate antifungal prohylaxis

In short: The use of prophylaxis in pancreas recipients differ in Nordic centers, both to which antimicrobial agents are used and how long. In order to evaluate the effect of these changes in prophylaxis in Oslo a retrospective multicenter study wants to examine patients from Oslo university hospital in 2 periods: for fungal infections from 01/01/2012-31/06/2016 vs 01/07/2016-31/12/2024, for bacterial infections from 01/01/12-31/12/17 vs 01/01/18-31/12/24. Furthermore, we will examine the incidence of these infections in other Nordic transplantation units to see if the results vary. Questions to be answered are: How many invasive infections in these periods – bacterial or fungal - have been observed the first month post tx? [From Months 2-6 months? From Months 7-12?] Which and for how long has antimicrobial therapy been used after prophylaxis during the first month after transplantation? Have there been any increase in length of stays after transplantation? Have there been any changes in the number of graft losses or deaths at 30 days post transplantation?

- The meeting supports this trial proposal
- Check how auto-islet Tx protocols include antifungal prophylaxis and inform the investigators

12. Pancreas post transplant monitoring – dd-cfDNA

Donor derived cell free DNA (dd-cfDNA) and the prediction of rejection. In heart transplant a high number of protocol biopsies are performed and there is a need of non invasive alternatives. Torsten Eich asks if there has been a similar demand/discussion in the setting of pancreas transplantation. All tissue labs will be able to analyze this in the future. Marie Felldin reports that Gothenburg have up and running studies for heart and lung transplants and that a kidney study is in pipeline.

Many patients lose large amounts of exocrine tissue without impairing endocrine function. A marker for endocrine tissue would be preferred.

- Torsten Eich to explore more into this topic

13. Next meeting

- Tuesday 8th April 2025, afternoon – digital meeting.

Secretary for the meeting	**Chairman for the meeting**
Bengt von Zur-Mühlen	**Torbjörn Lundgren**