Preservation and Transfer of Hepatitis B Virus Immunity after Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation in Adult Sickle Cell Disease Patients.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	-

Summary

ID

NL-OMON23265

Source
NTR

Brief title
Protect Study

Health condition

Sickle cell disease

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: N/A

Intervention

Outcome measures

Primary outcome

The proportion of SCD patients with a preserved anti-HBs response following non-myeloablative allogeneic HSCT with an HBV naive matched sibling donor (cohort 1) at 12 months post-transplantation as compared to SCD patients without HSCT (cohort 2).

Secondary outcome

- The proportion of SCD patients with a preserved anti-HBs response following non-myeloablative allogeneic HSCT with an HBV naive MSD (cohort 1) at 3-, 6-, and 24 months post-transplantation as compared to SCD patients without HSCT (cohort 2).
- The proportion of SCD patients with an adoptive transfer of anti-HBs response following non-myeloablative haploidentical HSCT with an HBV vaccinated donor at 3-, 6-, 12- and 24-months post-transplantation (cohort 3a).
- The proportion of SCD patients with an adoptive transfer of anti-HBs response following non-myeloablative MSD HSCT with an HBV vaccinated donor at 3-, 6-, 12- and 24- months post-transplantation (cohort 3b).
- Serum total IgG level and peripheral blood T-lymphocyte subset counts (CD3+, CD4+, CD8+), B-lymphocyte subset counts (CD19+) and NK cell count, at 3-, 6-, 12- and 24-months post-transplantation as compared to counts before the start of (pre-)conditioning.

Study description

Background summary

Rationale: Sickle cell disease (SCD) is an inherited hemoglobinopathy, characterized by chronic hemolytic anemia and microvascular occlusions leading to pain attacks and progressive deterioration of organ function. As a result, SCD patients have a significantly reduced life expectancy. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only available curative treatment for SCD. Recently, a mild non-myeloablative conditioning regimen for HSCT with alemtuzumab (1mg/kg) and low dose (3Gy) total body irradiation (TBI) has been developed for adult SCD patients with a matched sibling donor (MSD) and been implemented in the Netherlands since 2018. The post-transplant setting of SCD patients treated with the alemtuzumab/TBI regimen differs greatly from that in other transplantation regimens usually used as treatment for malignant hematological diseases. Because of its mild character, the conditioning regimen typically results in mixed chimerism. In most patients, stable T-cell donor chimerism of around 50% is achieved. Thus, approximately half of the adaptive immunity is still patient-derived. However, whether these patients preserve their immune response after the transplantation, is not known.
Another promising development is the improvement of HSCT conditioning regimens for adult SCD patients with an haploidentical related donor. At the Amsterdam UMC, haploidentical HSCT has been implemented in 2020 using antithymocyte globulin, fludarabine, cyclophosphamide, thiotepa and low-dose (2Gy) TBI as conditioning regimen and post-transplantation cyclophosphamide (PTCy) as in vivo T-cell depletion. Besides improved engraftment rates, this conditioning regimen is also associated with a reasonably swift immune reconstitution. Unlike the conditioning with alemtuzumab/TBI in MSD HSCT, the

above-mentioned conditioning for haploidentical HSCT results in full donor chimerism. Patients losing their immune response due to HSCT might benefit from the transfer of protective immunity from the stem cell donor. Two previous studies have demonstrated the adoption of immunity against hepatitis B virus (HBV) by transplant recipients. However, transplant recipients are also at high risk of gradual disappearance of protective antibodies. In contrast to our study patient population, these studies were conducted in mostly heavily pretreated patients with malignant hematological diseases undergoing myeloablative conditioning regimens. Currently, it is common practice to revaccinate all patients post-transplant according to the revaccination schedules used for other allogeneic HSCT recipients. However, revaccinating might not be necessary in SCD patients undergoing non-myeloablative HSCT, as they might either preserve their immunity (mixed chimerism after alemtuzumab/TBI conditioning) or benefit from transfer of immunity (haploidentical HSCT)). We hypothesize, that patients ending with mixed mononuclear chimerism after HSCT will preserve their immune response to vaccinations administered prior to the transplantation and will therefore not need to be revaccinated. Furthermore, we hypothesize, that SCD patients after haploidentical HSCT can benefit from adoptive transfer of immunity from their donors. To test the first hypothesis, we will vaccinate patients undergoing the alemtuzumab/TBI HSCT with a hepatitis B virus (HBV) vaccine before the transplant. To test the second hypothesis, we will vaccinate haploidentical and matched related donors prior to stem cell donation against HBV. Neither the patient nor the donor may previously have been immunized against HBV in all cohorts. Post-transplantation, we will be able to evaluate whether SCD patients preserve their pre-transplant immune response in the post-transplantation period. Furthermore, we will determine whether donors transfer their immunity to HSCT recipients with SCD disease.
Objectives: Primarily, to investigate whether recipient immunity is preserved and how fast it reconstitutes after non-myeloablative MSD HSCT resulting in mixed chimerism in adult SCD patients. Secondly, to investigate whether donor immunity is transferred to SCD patients after non-myeloablative haploidentical and MSD HSCT.
Study design: Prospective observational cohort study. Six SCD patients will be vaccinated with a recombinant HBV vaccine before allogeneic HSCT and followed until 2 years post-transplantation (cohort 1). Six SCD patients not undergoing allogeneic HSCT will be vaccinated as controls (cohort 2). Six haploidentical donors and six matched sibling donors of unvaccinated receivers will be vaccinated against HBV before stem cell donation (cohort 3a and 3b, respectively). All vaccinated patients and the receivers of stem cells of vaccinated donors will receive a booster vaccination at 12 months post-transplantation.
Study population: Adult SCD patients undergoing a matched sibling donor or haploidentical non-myeloablative allogeneic HSCT. HBV naive SCD patients not undergoing HSCT will serve as controls.
Main study parameters/endpoints: Primary endpoint: proportion of SCD patients with a preserved anti-HBs response following non-myeloablative HSCT with an HBV naive MSD. Secondary endpoints: proportion of SCD patients adopting their donors anti-HBs response following non-myeloablative HSCT. Immune reconstitution as expressed by serum total IgG levels and peripheral blood T-lymphocyte subset counts (CD3+, CD4+, CD8+), B-lymphocyte subset counts (CD19+) and Natural Killer (NK) cell counts at 3-, 6-, 12- and 24-months post-transplantation as compared to baseline (pre-transplantation) values.

Study objective

We hypothesize, that SCD patients ending with mixed mononuclear chimerism after non-myeloablative HSCT with alemtuzumab/TBI conditioning will preserve their immune response to vaccinations administered prior to the transplantation and will therefore not need to be revaccinated. Furthermore, we hypothesize, that SCD patients after haploidentical HSCT can benefit from adoptive transfer of immunity from their donors.

Study design

Before (baseline) and 3-, 6-, 12- and 24- months post-transplantation.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age 18 or older
- High performance liquid chromatography (HPLC) confirmed diagnosis of SCD (not applicable to participating donors).
- An indication for and a planned matched sibling or haploidentical donor non-myeloablative HSCT at the Amsterdam UMC, location AMC (not applicable to patients in cohort 2 (control group) and participating donors)
- Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- History of either cleared, chronic or active HBV infection (positive HBsAg, anti-HBs, anti-HBc and/or HBV DNA)
- History of auto-immune diseases and/or use of immunosuppressive drugs
- History of HIV infection
- Known hypersensitivity to yeast of any vaccine constituent
- Donor with a history of HBV infection

Study design

Design

Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	08-07-2021
Enrollment:	24
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	26-08-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL9684
Other	METC AMC : METC2021_091

Study results