A clinical study to investigate Interferon gamma (IFN*) signature in patients post HSCT and in patients with impaired HSC proliferation pre-transplant

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HSCT cohort:* -To investigate the relationship between IFNγ levels and IFNγ activity by measuring CXCL9 levels and the risk of graft failure* -To investigate the relationship between IFNγ levels and IFNγ...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Observational invasive

Summary

ID

NL-OMON52048

Source
ToetsingOnline

Brief title
IFNg-study

Condition

- Leukaemias
- Blood and lymphatic system disorders congenital
- Autoimmune disorders

Synonym
graft failure, graft versus host disease and impaired hematopoietic stem cell proliferation

Research involving
Human

Sponsors and support

Primary sponsor: Swedish Orphan International
Source(s) of monetary or material Support: Sponsor: Swedish Orphan Biovitrum AG (Sobi AG)

Intervention

Keyword: IFNg

Outcome measures

Primary outcome

For HSCT cohort: To investigate the relationship between IFNγ levels and IFNγ

activity by measuring CXCL9 levels and

the risk of graft failure

For IHSCP cohort: To investigate the IFNγ levels and IFNγ activity by measuring

CXCL9 levels in patients with impaired HSC proliferation pre-transplant.

Secondary outcome

not applicable

Study description

Background summary

IFNγ has been reported to play a deleterious effect on hematopoietic stem cell (HSC) proliferation. This negative activity is suspected to play a central role in conditions where hematopoietic stem cell proliferation is impaired like when engraftment failure occurs after HSC transplant (1) (2) (3). Initial observational investigations in children who received allogeneic hematopoietic stem cell transplant (HSCT) in patients with various conditions such as hemophagocytic lymphohistiocytosis (HLH), severe aplastic anemia (SAA), erythroid and metabolic disorders, primary immune deficiencies and leukemia have demonstrated a strong association between IFNγ activity measured by elevated biomarker levels (e.g. CXCL9) few days post-transplant and the risk of

primary graft failure (GF) (Sponsor*s data on file and (4)). The same CXCL9 elevation was observed in patients developing secondary graft failure (Sponsor*s data on file). In this condition, IFN* is thought to be produced by activated residual T cells from the recipient against the donor cells. On the contrary, IFNγ activity may also be elevated in patients developing Graft Versus Host Disease (GVHD), where donor T cells act against the recipient organs. Finally, it is also considered that IFNγ may play a role in other diseases where HSC proliferation is impaired like in aplastic anemia (AA) patients (5). Emapalumab, an anti-IFNγ antibody has been recently approved by the FDA for HLH treatment (6), a disease where activated T cells produce abnormal amounts of IFNγ.

Study objective

HSCT cohort:
* -To investigate the relationship between IFNγ levels and IFNγ activity by measuring CXCL9 levels and the risk of graft failure
* -To investigate the relationship between IFNγ levels and IFNγ activity by measuring CXCL9 levels and the occurrence of GVHD
* -To measure exploratory biomarkers associated with GF and GVHD
IHSCP cohort:
* -To investigate the IFNγ levels and IFNγ activity by measuring CXCL9 levels in patients with impaired HSC proliferation pre-transplant
* -To measure exploratory biomarkers associated with impaired HSC proliferation

Study design

This is a multinational interventional non drug study designed to assess IFNγ activity by measuring IFNγ and CXCL9 in serum.
IFNγ activity will be investigated in two cohorts of patients:
-First group will include patients post HSCT at risk of graft failure defined based on their underlying diseases and on the transplant procedure. HLH patients are not part of this cohort since specific protocols are ongoing for the treatment for HLH with emapalumab and data is collected post HSCT.
-Second group will contain patients with conditions where HSC proliferation is impaired (e.g. aplastic anemia) and with respective controls (healthy volunteers (HV)).
These two groups of patients will be called HSCT and Impaired HSC proliferation cohorts respectively. Clinical data and sample collection for both groups might be performed prospectively or retrospectively in case required samples are available at the collaborating center.

Participation in this study is not intended to change the routine treatment that patients receive as determined by their prescribing clinicians* all treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician. No additional visits to the

clinic will be required for the purposes of the study.

For HSCT cohort, the following sampling time points are required: on day -7, pre HSCT on day 0, 1, 3, 5, 9, 13, 17, 21, 28, 31, 38 and one additional sample at the time when primary or secondary GF is suspected if not on the planned schedule. In addition, the following time points are recommended: day 7, 11, 15, 19, 24, 35, 42. It is also suggested to collect a sample when GVHD is diagnosed during any visit that the patients will attend as part of his/her standard treatment during the first 100 days post-transplant. The patient will be followed up until around day 100 post-transplant. This follow up will consist of capturing HSCT outcome information from patient hospital records around day 100.

For IHSCP cohort pre-transplant, it is recommended that, one sample (2 mL of blood) per patient at the time of diagnosis (if possible not more than 1 week from the date of diagnosis) is collected. Age/sex matched control samples should be collected from healthy volunteers or malignant patients outside of this protocol after appropriate consent. The matching will be performed per age categories in three groups: < 18, >= 18 - 60 <, >= 60. Control samples for IHSCP will be obtained from existing commercial biobanks of HV or malignant patients matching age and sex of patients participating in the study.

Study burden and risks

Blood samples will be taken several times during the study from a vein (or finger) with a disposable needle. The risks associated with taking blood samples include local irritation, bruising, bleeding and inflammation of the area of needle insertion. Whenever possible the blood will be drawn from an existing venous access to avoid multiple needle insertions through the skin. In addition, numbing creams may be used to decrease the pain level.

Participants will not receive any direct benefits from this study. However, participation in the study will help to learn about the relationship between the measured proteins in the blood (INF* and CXCL9) and GF or conditions where HSC proliferation is impaired. Information gathered blood samples may help to predict the risk of GF and may guide the administration of treatment helping the successful engraftment in the future. In addition, it can also help to develop new treatments for conditions where proliferation of HSC is impaired

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)

Inclusion criteria

• The patient must have consented to the use of their clinical data and biological samples for research investigations.
• In HSCT cohort:
- Patients with underlying:
I. non-malignant hematological disease (e.g. autoimmune and metabolic disorders, aplastic
anemia, Sickle cell anemia, Fanconi anemia, Diamond-blackfan anemia, thalassemia,
osteopetrosis, Wiskott-Aldrich syndrome, severe combined immunodeficiency) or
II. malignant disease with higher risk of GF, i.e. Acute Myeloid Leukemia (AML) and Acute
Lymphoblastic Leukemia (ALL) with primary induction failure, second partial remission or

relapse* Chronic Myeloid Leukemia (CML) in blastic phase (circulating blast or blast above 5%
in biopsy)* Non Hodgkin and Hodgkin Lymphoma and multiple myeloma with primary induction failure, second partial remission or relapse, myelodysplastic syndromes (MDS) and
myeloproliferative disorders (MPD) with splenomegaly, myelofibrosis with portal hypertension pre-transplant, MDS/MPD overlap syndromes
- and who received allogeneic HSCT and are at higher risk of graft failure based on at least one of the following criteria:
I. Having received reduced intensity conditioning (RIC) or non myeloablative conditioning (NMA)
combined with a non-malignant disease or having received graft from Bone Marrow (BM)
II. Ex vivo T cell depleted graft
III. Graft from mismatched unrelated donor or
haploidentical donor
IV. Graft from Umbilical Cord Blood (UCB)
• In the IHSCP cohort:
- Patients with IHSCP pre-transplant (e.g. aplastic anemia)

Exclusion criteria

• HLH patients
• Body weight < 10kg

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO Date:	05-05-2022
Application type:	First submission
Review commission:	METC NedMec

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
CCMO	NL78341.041.21