Rac1/pSTAT3 expression: Towards a potential pharmacodynamic marker to optimize and individualize thiopurine therapy in IBD patients

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The aim of this study is to explore intra-individual differences in expression of Rac1 and pSTAT3 in leucocytes of IBD patients before and during thiopurine treatment.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON51798

Source
ToetsingOnline

Brief title
Rac1 longitudinal PILOT study

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Crohn's disease; Ulcerative Colitis

Research involving
Human

Sponsors and support

Primary sponsor: Zuyderland Medisch Centrum

Source(s) of monetary or material Support: enkel voor kosten van de bepaling (materiaal en analist) is onderzoeksbudget gebruikt van het Zuyderland Medisch Centrum

Intervention

Keyword: Inflammatory Bowel Diseases (IBD), pharmacodynamic marker, Rac1, Thiopurines

Outcome measures

Primary outcome

The primary endpoint is intra-individual differences in Rac1 and pSTAT3

expression before and during 4 weeks of thiopurine treatment.

Secondary outcome

The secundary endpoints are:

- Assessment of number of patients with intra-individual reduction of at least

30% of Rac1 corrected pSTAT3 expression in peripheral T cells of thiopurine

derivative initiating adult IBD patients at week 4

- Assessment of number of patients with intra-individual reduction of at least

50% of Rac1 corrected pSTAT3 expression in peripheral T cells of thiopurine

derivative initiating adult IBD patients at week 4

- To measure early inhibition (at week 1) of the Rac1-pSTAT3 pathway after

starting thiopurine therapy in percentual reduction and in number of patients

with at least 30% of Rac1 corrected pSTAT3 expression in peripheral T cells

- To evaluate the correlation between 6-TGN concentrations and Rac1-corrected

pSTAT3 expression at week 1, and at week 4

Study description

Background summary

Despite several new biological treatment options for inflammatory bowel diseases (IBD), thiopurine derivatives, such as azathioprine (AZA) and mercaptopurine (MP), remain the gold standard of treatment. Unfortunately, there is a delayed onset of therapeutic response, as clinical response generally occurs after 3-4 months after initiation of thiopurine therapy. In addition, up to 50% of patients discontinue thiopurine therapy within 2 years due to intolerable adverse reactions or therapeutic resistance mostly during the first months of treatment. Optimization of therapy in the early stage is therefore warranted in order to prevent unnecessary failure due to toxicity and/or thiopurine drug resistance.

Today, optimization of thiopurine therapy is widely performed in two ways: the first is through blood level determinations of the drug. Secondly, genotyping is used, where based on the DNA profile it is checked whether there is a higher risk of getting side effects. Both strategies are recommended in the national guideline and partly help to predict the risk of side effects. However, the effectiveness cannot be predicted with this.

A new so-called 'pharmacodynamic marker', such as the protein called Rac1, could be a predictor of the effectiveness of thiopurines in the future. It has been described in the literature that the Rac1 protein is directly related to the mechanism of action of thiopurines. In a previous study (Deben et al, cytometry 2021) we showed that we can measure this marker in the blood. Subsequently, a PILOT study was performed to investigate whether this marker is useful in IBD patients, by looking at the difference of this marker between IBD patients taking thiopurines and IBD patients taking other drugs. Clear differences were demonstrated (unpublished data), which gave rise to new research questions. In the PILOT study we have already shown that the amount of Rac1 protein changes in patients taking thiopurines. We hypothesize that the amount of Rac1 protein will also change within the same patient when he/she starts thiopurine therapy. We expect that this difference can later be used as an effect measure for the effectiveness of thiopurine therapy.
However, before a large observational study can be set up to compare the amount of Rac1 with the effectiveness, we would like to investigate whether intra-individual differences are indeed visible in the amount of Rac1 before and during the use of thiopurine therapy. Therefore, we have now set up this longitudinal PILOT study to test our hypothesis that there are also intra-individual differences in Rac1.

Study objective

The aim of this study is to explore intra-individual differences in expression of Rac1 and pSTAT3 in leucocytes of IBD patients before and during thiopurine treatment.

Study design

a prospective observational longitudinal PILOT study

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no compensation for the participation in the study. The burden on the subjects is considered to be minimal. Patients are treated in accordance with the applicable national guidelines. The only burden is that 1 - 2 extra tube(s) of 5 ml of EDTA blood will be drawn during the already planned venipuncture to determine additional study parameters. This is the only additional burden on the patient. The patients are not exposed to additional risks. Feedback and recording of adverse reactions are standard in this patient group, so that no additional effort is required from the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Diagnosis of Inflammatory Bowel Disease (IBD) (either Crohn's disease or Ulcerative Colitis)
- Mild or Moderate-to-severe IBD patients who are starting thiopurine treatment
- age between 18 - 70 years old
- both hospitalized and ambulant patients are eligible

Exclusion criteria

- other auto-immune diseases
- previous use of thiopurines within two weeks before inclusion

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-06-2022
Enrollment:	43
Type:	Actual

Ethics review

Approved WMO Date:	28-03-2022
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	24-04-2023
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	NL80556.096.22