Rac1/pSTAT3 expression: 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 differences in expression of Rac1 and pSTAT3 in leucocytes of therapy-naïve IBD patients, IBD patients on immune suppressive therapy and healthy controls.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational non invasive

Summary

ID

NL-OMON50051

Source
ToetsingOnline

Brief title
Rac1 PILOT

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Inflammatory Bowel Disease (IBD)

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 Klinisch;Chemisch & Hematologisch Laboratorium Zuyderland

Intervention

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

Outcome measures

Primary outcome

The primary endpoint is the difference in Rac1 and pSTAT3 expression and

activation in leucocytes of IBD patients on thiopurines and healthy volunteers.

Secondary outcome

The secondary endpoints are the degree of Rac1 and pSTAT3 expression and

activation in different types of white blood cells and the differences in Rac1

and pSTAT3 expression and activation between all study groups.

Study description

Background summary

Despite several new biological treatment options for inflammatory bowel diseases (IBD), conventional 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.
In recent years, an alternative thiopurine, tioguanine, has also been increasingly used in IBD patients who previously failed AZA or MP therapy. Tioguanine has a different metabolism than the conventional thiopurines and

that causes a difference in the therapeutic range of the active metabolites. Nowadays, optimization of thiopurine therapy is performed widely by therapeutic drug monitoring (TDM) and genotyping of the gene encoding the enzyme thiopurine S-methyltransferase (TPMT). Therapeutic drug monitoring of thiopurines is based on blood levels of the pharmacologically active 6-thioguanine nucleotides (6-TGN) whereas 6-methylmercaptopurine ribonucleotides (6-MMPR) are associated with hepatotoxicity and intolerable adverse events.
Furthermore, TPMT plays an important role in the balance of 6-TGN and 6-MMPR formation. Higher activity of TPMT can lead to subtherapeutic concentrations of 6-TGN, whereas low TPMT activity can lead to myelotoxicity due to elevated 6-TGN metabolite levels.
The measurement of these metabolites and TPMT is performed to adjust dosage and to prevent toxicity. However, using TDM and genotyping for optimization of therapy has its limits. Both TDM and genotyping provide pharmacokinetic information, which are of limited, respectively, no use to predict clinical effectiveness.
A pharmacodynamic marker might be more useful to predict clinical outcome of thiopurine therapy. The immunosuppressive mechanism of thiopurines is primarily based on inhibition of the Ras-related C3 tobulinum toxin substrate 1 (Rac1) causing T-cell apoptosis.
The clinical chemical laboratory of Zuyderland MC recently validated a method to measure both Rac1-expression and downstream activity (by means of pSTAT3 expression) in leukocytes.

Study objective

The aim of this study is to explore differences in expression of Rac1 and pSTAT3 in leucocytes of therapy-naïve IBD patients, IBD patients on immune suppressive therapy and healthy controls.

Study design

a prospective observational 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 2 extra tubes of 7 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

- Age between 18 - 70 years old
- Clinical, histological or endoscopic diagnosis of Crohn*s Disease, Ulcerative colitis or IBDU (IBD-unclassified)
- Both hospitalized and ambulant patients are eligible

Exclusion criteria

- current use of systemic corticosteroids
- age < 18 years and > 70 years.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-01-2021
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	17-09-2020
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	29-03-2021
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	NL74446.096.20