Near-infrared fluorescence molecular imaging of adalimumab-800CW to elucidate the drug distribution throughout inflamed tissue in inflammatory bowel disease and rheumotoid arthritis

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Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON56363

Source
ToetsingOnline

Brief title
Molecular imaging of adalimumab-800CW in IBD and Rheumatoid diseases

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders
- Synovial and bursal disorders

Synonym
inflammatory bowel disease, rheumatoid arthritis, Spondyl arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: AbbVie inc.

Intervention

Keyword: adalimumab, inflammatory bowel disease, molecular imaging, Rheumatoid diseases

Outcome measures

Primary outcome

1. To determine the safety of adalimumab-800CW in IBD and RA/SpA patients by monitoring of vital signs during tracer infusion and evaluating possible (severe) adverse events (SAE & AEs).

2. To determine the feasibility of the (intrinsic) fluorescence signal of adalimumab-800CW as assessed by fluorescence molecular endoscopy (IBD) / wide-field imaging (RA/SpA) for elucidating local adalimumab-800CW concentrations and drug distribution throughout

• The gut mucosa in IBD;

• Synovial joint in RA/SpA.

Secondary outcome

Secondary objectives in the IBD cohort

• To quantify NIR fluorescence signals in vivo and ex vivo using MDSFR/SFF spectroscopy measurements for an *intrinsic* fluorescence signal;

• To correlate and verify fluorescence signals detected in vivo to the histopathology of biopsies;

Secondary objectives in RA/SpA

• To quantify NIR fluorescence signals in vivo using multi-diameter

single-fiber reflectance, single-fiber fluorescence (MDSFR/SFF) spectroscopy

measurements;

• Optionally, in patients that give additional informed consent for

intra-articular MDSFR/SFF measurements and synovial biopsies:

o To investigate the correlation between the detected and quantified

intra-articular fluorescent signal and the histopathology analysis of the

inflamed synovium.

Study description

Background summary

Inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and Spondyl Arthritis (SpA) are all auto-immune diseases that are characterized by chronic relapsing inflammation of respectively the ileocolonic tissue and the synovium. Pathogenesis of the auto-immune diseases is attributed to the proinflammatory cytokine tumor necrosis factor α (TNFa). Adalimumab is a human monoclonal anti-TNF antibody used for treating patients with moderate to severely active IBD, RA or SpA. However, current rates of therapeutic non-responsiveness to this antibody are variable and difficult to predict in advance, whereas patients are potentially exposed to a non-effective treatment and its potential side effects; while clinical deterioration progresses. A key unmet need is the development of a predictive tool for assessment of a therapeutic (non-) response to patients and finding an optimal dose strategy in individual patients before initiating anti-TNF therapy. Unfortunately, we currently lack crucial information about drug distribution of the drug of interest throughout the targeted inflamed tissue itself. Therefore, it remains unknown in IBD/RA/SpA, if the drug reaches its target (in sufficient amounts) and how local drug concentrations are related to therapeutic response. Thus, we linked adalimumab to a fluorescent dye (adalimumab-800CW) in order to create a fluorescent signal of the labelled drug in the diseased tissue that we can visualize and quantify with dedicated optical fluorescence imaging systems. We hypothesize that this tracer will bind to TNFa in the mucosa/synovium and thus create a map of medicine distribution in vivo due to colocalization of the

fluorescent labelled compound. Therefore, the aim of this study is to assess the feasibility of fluorescent molecular imaging of adalimumab-800CW in IBD, RA or SpA patients.

Study objective

We will assess the safety of adalimumab-800CW through the evaluation of both vital signs after tracer administration and possible (severe) adverse events (SAE/AE*s). Importantly, we will determine the feasibility of molecular fluorescence imaging using the GMP-produced near-infrared fluorescent tracer adalimumab-800CW for visualizing medicine distribution in vivo in RA/IBD/SpA patients with dedicated fluorescence imaging systems.

Study design

The current study is a non-randomized, non-blinded, prospective, multicenter safety / feasibility dose-finding study. IBD, RA and SpA patients will receive an intravenous bolus injection of a microdose of 4.5 mg adalimumab-800CW 2-4 days before imaging. Before and after administration, the vital signs will be monitored. Imaging will be performed with fluorescence endoscopy (IBD) or fluorescence wide-field imaging and MSOT (RA/SpA) for fluorescence detection. The fluorescent signal will be quantified by MDSFR/SFF spectroscopy. Furthermore, biopsies will be taken from non-inflamed and inflamed mucosa in IBD patients. In RA/SpA patients, fluorescent imaging with spectroscopy measurements and MSOT will be done both before and after tracer administration. Optionally, patients give additional consent for sampling of synovial tissue. An extensive ex vivo procedure in addition to histopathology analysis of the biopsies will be conducted for tracer localization in order to precisely correlate this to the in vivo observed signal. The ex vivo procedure will comprise MDSFR/SFF spectroscopy, immunohistochemistry, fluorescence imaging and fluorescence microscopy.

Intervention

Two to four days prior to the imaging procedure, the subject receives an intravenous injection of the fluorescent tracer adalimumab-IRDye800CW. The first three patients receive 4.5 mg adalimumab-800CW and the second three patients will receive 15 mg adalimumab-800CW. After these six patients, an interim analysis will be conducted based upon safety parameters and target-to-background ratio (TBR)/contrast-to-noise ratio (CNR) of the fluorescence signal. If these factors are considered positive for one of these doses, an additional nine patients will receive the same dose. If not, there will be a dose escalation to 25 mg adalimumab-800CW in the another three patients and the best dose group can then be extended with six patients. Groups and interim analyses will be constructed and performed separately per disease

cohort (IBD/RA/SpA).

Study burden and risks

Risks of adalimumab-IRDye800CW are considered negligible. Before, during and after administration, the subject will be monitored. Subjects will receive a dose of either 4.5 mg, 15 mg or 25 mg adalimumab-800CW 2-4 days prior to the imaging procedure. RA/SpA patients have one or two extra visits to the hospital for the administration and imaging of the tracer. IBD patients, have an extra visit to the hospital for tracer administration; fluorescent imaging of the bowel will be on the same day of their endoscopy, which is a clinical standard procedure. Extra biopsies will be obtained from IBD patients for study purposes. RA/SpA patients can opt for synovial biopsies. No direct benefits are expected for study participants.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Established IBD, RA or SpA diagnosis
• Active disease.
o IBD cohort: clinically active disease of the bowel defined either clinically as at least mild activity using dedicated scoring indices (for definitions of disease activity, see below) or biochemically active disease as defined by a faecal calprotectin > 200 *g/g;
o RA / SpA cohort: clinically active disease of at least one joint of the hand as assessed by rheumatologist;
• Age of 18 years or older and mentally competent;
• Written informed consent.

IBD patients must already have an ileocolonoscopy scheduled due to a clinical indication.

For female subjects who are of childbearing potential, are premenopausal with intact
reproductive organs or are less than 2 years postmenopausal
• A negative pregnancy test must be available (blood or urine)
• Willing to ensure that she uses effective contraception during the study and for 3 months thereafter.

Disease activity scores
Crohn*s disease Ulcerative colitis
CDAI HBI
SCCAI
Clinical remission <150 0-4 <= 2
Mild activity 150-220 5-7
3-5
Moderate to severe activity 220-450 8-16 6-11
Severe fulminant >450 17-100 >= 12

Exclusion criteria

- A potential female subject that is pregnant or provides breastfeeding will be excluded from participation in this study;
- RA / SpA patients with a skin type above type 3 according to the Fitzpatrick scale due to feasibility of the MDSFR/SFF spectroscopy measurements;
- Medical or psychiatric conditions that compromise the patient's ability to

give informed consent.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2023
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Generic name:	RA: an open-air fluorescence camera;a MDSFR/SFF spectroscopy probe and MSOT. IBD: a clinical diagnos
Registration:	No
Product type:	Medicine
Brand name:	adalimumab-800CW
Generic name:	adalimumab-800CW

Ethics review

Approved WMO Date:	06-01-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2023

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-09-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2020-004405-31-NL
ClinicalTrials.gov	NCT03938701
CCMO	NL75246.042.20