Fluorescence Imaging for the Evaluation of Disease Activity in IBD and Rheumatoid Arthritis using the fluorescent tracer OTL38 targeting the folate B receptor: a single-center pilot study.

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General- To determine the safety of OTL38 in IBD and rheumatoid arthritis patients by monitoring of vital signs during tracer infusion and evaluating possible (severe) adverse events (SAE/AEs).RA- To determine the feasibility of molecular...

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

Summary

ID

NL-OMON48394

Source
ToetsingOnline

Brief title
Fluorescence imaging of disease activity in IBD and rheumatoid arthritis.

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Crohn's disease, reumatoid arthritis, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: unrestricted research grant GSK

Intervention

Keyword: Disease activity, Fluorescence, IBD, OTL38, rheumatoid arthritis

Outcome measures

Primary outcome

General

- Evaluating vital parameters, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) for safety assessment.

RA

- Macroscopic fluorescence signals (target-to-background ratio) for detection of inflammation tissue, high disease activity, during imaging using a wide-field fluorescence camera.

IBD

- Macroscopic fluorescence signals (target-to-background ratio) for detection of inflammation tissue, high disease activity, during endoscopy using fluorescence endoscopy

Secondary outcome

RA

- Correlation between fluorescence imaging to the clinical disease activity score (DAS28-score).
- Quantification of in vivo fluorescence signals and optical properties through analysis of MDSFR/SFF spectroscopy measurements.

IBD

- Quantification of fluorescence in vivo and ex vivo through analyses of MDSFR/SFF spectroscopy measurements;
- Standard histopathological examination to correlate fluorescence and non-fluorescence signals detected in vivo with histology using in vivo obtained biopsies;
- The localization and distribution of the OTL38 fluorescent signal at cell level observed in vivo by CLE.
- Correlation between fluorescence imaging to the clinical disease activity score, the Mayo and SCCAI score, for ulcerative colitis.
- Correlation between fluorescence imaging to the clinical disease activity score, the CDAI and SES-CD score, for Crohn*s disease.
- Fluorescence microscopy to correlate fluorescence to localization of inflammatory cells and especially macrophage infiltration.

Other study parameters

- Patient characteristics (age, BMI, sex, medical history, blood pressure, pulse and temperature before and after tracer administration)

Study description

Background summary

Rheumatoid Arthritis (RA) and inflammatory bowel disease (IBD) are both inflammatory diseases caused by a persistent chronic inflammation. A chronic inflammation is caused by the absence of the inflammation response resolution. Currently, diagnosis and disease activity measurements are based on symptom-based scores or on anatomical imaging devices. Both methods are unable to detect both early stages of the disease and early changes in inflammation as a reaction to treatment. Objective, early measures of inflammation could improve diagnosis and in the future therapeutic outcomes by identifying early therapy responders and non-responders. In this feasibility study, we aim to evaluate the safety and feasibility of the NIR tracer OTL38 for monitoring disease activity in inflammatory diseases rheumatoid arthritis and inflammatory bowel disease. We hypothesize that OTL38 will accumulate in inflamed tissue due to the increased presence of activated macrophages expressing the folate beta receptor, enabling better visualization and monitoring of the inflammation. We believe that this approach can improve treatment and diagnosis of patients with inflammatory disease.

Study objective

General
- To determine the safety of OTL38 in IBD and rheumatoid arthritis patients by monitoring of vital signs during tracer infusion and evaluating possible (severe) adverse events (SAE/AEs).

RA
- To determine the feasibility of molecular fluorescence imaging using the tracer OTL38 targeting the folate β receptor on activated macrophages for the evaluation of disease activity in patients with rheumatoid arthritis.

IBD
- To determine the feasibility of fluorescence molecular endoscopy (FME) and MDSFR/SFF spectroscopy using the tracer OTL38 targeting the folate β receptor on activated macrophages for the evaluation of disease activity in patients with ulcerative colitis.
- To determine the feasibility of fluorescence molecular endoscopy (FME) and MDSFR/SFF spectroscopy using the tracer OTL38 targeting the folate β receptor on activated macrophages for the evaluation of disease activity in patients with Crohn*s disease.

Study design

RA
Rheumatoid arthritis patients will be imaged using a near infrared (NIR) wide field camera (figure 1). Both hands (affected and/or unaffected) will be imaged with the SurgVision intraoperative camera in combination with the Vault system, a black box, to provide a standardized measurement environment. Both the palmar and dorsal side of the hands will be imaged. Furthermore, MDSFR/SFF spectroscopy measurements will be performed on three joints per hand as visualized in the DAS28-score.

Optionally: patients will be asked to have the fluorescence imaging and MDSFR/SFF measurements each hour after the end of tracer infusion with a maximum of 6 hours (in consultation with the patient) after the tracer infusion has stopped. If not, fluorescence imaging will only take place once after 2-3 hours.

IBD
IBD patients will be imaged during a standard colonoscopy procedure using NIR endoscopy. First, high definition white-light (HD-WL) endoscopy will be performed. During HD-WL all suspicious, inflamed tissue will be identified according to standard clinical care. For both UC and CD, both a clinical and endoscopic disease activity score will be calculated. For the ulcerative colitis group, the Mayo score and Simple Clinical Colitis Activity Index (SCCAI) will be used and for the Crohn*s disease group the Crohn's Disease Activity Index (CDAI) and Simple Endoscopic Score for Crohn Disease (SES-CD). Second, molecular fluorescence endoscopy (FME) will be performed. All inflamed areas identified with HD-WL will be visualized again for fluorescence signals, as well as possible additional fluorescence areas. MDSFR/SFF spectroscopy will be performed in vivo, to quantify the inflamed and normal colon mucosa. These spectroscopy measurements are essential since despite the use of NIR excitation and fluorophores, tissue specific differences in the optical properties of the colon have shown to have strong influence on the amount of fluorescence signal that is measured under wide field illumination endoscopy. Last, confocal endomicroscopy will be performed on both inflamed and normal mucosa. In addition, biopsies will be taken from normal mucosa and inflamed mucosa.

Intervention

RA
Score - the disease activity will be scored according to the symptom-based scoring method used in rheumatology (DAS28-score).
Wide-field fluorescence imaging - Fluorescence imaging will be performed using the SurgVision F2 multispectral fluorescence imaging system combined with the SurgVision Vault system. The hands of the patient will be placed one by one inside the black box and multiple fluorescence images and videos will be taken. Both the palmar and distal side will be imaged of both hands.
MDSFR/SFF spectroscopy - MDSFR/SFF spectroscopy will be performed using the system from the Erasmus MC including a fiber. Measurements will be taken from

one unaffected joint if possible (both palmar and dorsal side of the joint. And of a maximum of three affected joints per hand and if present one unaffected joint (both palmar and dorsal side of the joint).

IBD
The disease score will be assessed according to the HD-WL images. The Mayo and SCCAI score will be used for ulcerative colitis patients and the CDAI and SES-CD score for Crohn*s disease patients.
First, HD-WL endoscopy will be performed to identify and localize the inflamed area. Then FME will be performed to assess fluorescent signals in inflammation tissue and normal tissue. MDSFR/SFF spectroscopy will be used to quantify the fluorescent signals. Last, confocal endomicroscopy will be performed on both the inflamed and normal mucosa. After endoscopic observation, biopsies will be taken to a maximum of 28 biopsies. A maximum of 4 biopsies will be taken from normal tissue, a maximum of 16 biopsies in an inflammation area. If a difference between low and high activity areas can be defined based on the white light images, biopsies will be taken from both areas. A maximum of 8 biopsies can be taken from additional areas. Biopsies will be only taken if judged safe by the gastroenterologist.

Study burden and risks

For the participating patients, there is no diagnostic or treatment benefit related to the study. Participation may possibly produce useful scientific data for the future. Risks related to the administration of OTL0038 are described in the IMPD (version May 16th 2019) and section 6.4 of this document. The investigational procedures are extensively described in section 3. The risks of fluorescence endoscopy are comparable to a clinical ileocolonoscopic, very minimal. The biopsies take at both fluorescence endoscopic procedures have a small risk of causing superficial bleeding. Most bleedings coagulate spontaneously. If not, which is very uncommon, the gastroenterologist will coagulate the small bleeding.

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

Rheumatoid arthritis cohort
• Start first treatment or treatment switch to (another) biological(s) in a patient diagnosed with active Rheumatoid Arthritis (RA) by their physician in one or both hands.;
• Age >= 18 years;
• Written informed consent.,

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
• Willing to ensure that she or her partner uses effective contraception during the study and for 3 months thereafter.

IBD cohort
- Patient diagnosed with clinical active ulcerative colitis or Crohn*s disease and therefore scheduled to switch to (another) biological(s);
• Age >= 18 years;
• Written informed consent.

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
• Willing to ensure that she or her partner uses effective contraception during

the study and for 3 months thereafter.

Exclusion criteria

Rheumatoid arthritis cohort
• Received methotrexate and/or folic acid less than 7 days before tracer infusion;
• Skin type above type 3 according to the Fitspatrick scale;
• Primary failure (no response) within the first 12 weeks after start with any anti-TNF agent;
• Prescribed disease modifying anti-rheumatic drugs (DMARDs) at a higher dose than 10 mg and/or no stable dose for at least 4 weeks prior to inclusion;
• Prescribed oral corticosteroids at a higher dose than 10 mg, and/or no stable dose for at least 4 weeks prior to inclusion;
• Use of intramuscular or intravenous corticosteroids within 4 weeks prior to inclusion;
• Prescribed non-steroidal anti-inflammatory drugs (NSAID) with no stable dose for at least 4 weeks prior to inclusion
• Concurrent uncontrolled medical conditions according to treating medical physician;
• Patients with a history of anaphylactic reactions or severe allergies;
• Patients with a history of allergy to any of the components of OTL38, including folic acid;
• Treatment with any investigational drug within the previous 3 months.
• Pregnancy or breast feeding.

IBD cohort
• Concurrent uncontrolled medical conditions;
• Patients with a history of anaphylactic reactions or severe allergies;
• Patients with a history of allergy to any of the components of OTL38, including folic acid;
• Treatment with any investigational drug within the previous 3 months;
• Pregnancy or breast feeding.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2021
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Generic name:	RA: a open-air fluorescence camera and a MDSFR/SFF spectroscopy probe. IBD: a clinical therapeutic e
Registration:	No
Product type:	Medicine
Brand name:	OTL38
Generic name:	OTL38, a fluorescence tracer

Ethics review

Approved WMO

Date:	07-01-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	29-11-2019
Application type:	First submission
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	EUCTR2018-004770-10-NL
ClinicalTrials.gov	NCT03938701
CCMO	NL68577.042.18