Deep profiling of lipid changes in patients with active ulcerative colitis treated with either tofacitinib or infliximab

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To evaluate the tofacitinib and infliximab treatment-induced changes in plasma lipids and lipoproteins and to provide insight in the underlying mechanism in relation to the inflammatory status in patients with active UC.

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

Summary

ID

NL-OMON55536

Source
ToetsingOnline

Brief title
LIPID study

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
inflammatory bowel disease, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer

Intervention

Keyword: Colitis, Infliximab, Lipids, Tofacitinib

Outcome measures

Primary outcome

Changes in HDL-C and LDL-C concentrations in patients with active ulcerative colitis treated with tofacitinib and infliximab induction therapy

Secondary outcome

- Changes in total cholesterol, triglycerides, Apo-AI, Apo-B and lipoprotein(a) (Lp(a)) following tofacitinib and infliximab induction therapy

- Changes in total cholesterol, HDL-C, LDL-C, triglycerides, Apo-AI, Apo-B and Lp(a) following tofacitinib and infliximab maintenance therapy

- Correlation between lipid changes and inflammatory state (CRP, FCP, SCCAI, Mayo endoscopic subscore)

- Effectiveness of tofacitinib and infliximab with regard to clinical, biochemical and endoscopic response

- Difference between groups with regard to changes in lipid profile following tofacitinib and infliximab therapy

- Safety of tofacitinib and infliximab therapy measured by adverse events (AEs)

Exploratory:

- Shifts in density of the lipoproteins or their subfractions and, as a

potential consequence, alterations in their compositions and functioning

- Effect of treatment on HDL2 and HDL3 composition and functioning including anti-inflammatory function

- Effect op treatment on cholesterol homeostasis including cholesterol absorption, cholesterol synthesis, bile acid synthesis and the formation and role of oxysterol

- Mechanisms underlying the observed changes in lipoproteins upon treatment, focussing on cholesterol metabolism, inflammation, insulin resistance and bile acids

Study description

Background summary

Recently tofacitinib is registered for the treatment of moderately to severly active ulcerative colitis (UC). In the tofactinib clinical development program (OCTAVE), mild elevations in serum lipid levels in a proportion of those receiving tofacitinib were described without further side effects. Mild alterations in the lipid profile are also observed in patients with inflammatory bowel disease (IBD) treated with infliximab (IFX). Although an overall increase in total cholesterol and low density lipoprotein cholesterol (LDL-C) is unwanted, an increase in high density lipoprotein cholesterol (HDL-C) as a result of treatment might protect against cardiovascular events. Moreover, these findings are consistent with the previously observed inverse relationship between active inflammation and serum lipid levels in chronic inflammatory disease including rheumatoid arthritis (RA) and psoriatic arthritis (PA). The mechanisms by which the inflammatory process can lead to these lipid changes are not fully understood.

Study objective

To evaluate the tofacitinib and infliximab treatment-induced changes in plasma lipids and lipoproteins and to provide insight in the underlying mechanism in relation to the inflammatory status in patients with active UC.

Study design

This is a multicentre, prospective, observational, open label lipid mechanism of action study. Patients with active ulcerative colitis will initiate tofacitinib twice daily or infliximab infusions with a follow up period of 52 weeks measuring lipid levels at different time points. Tofacitinib induction therapy 10mg twice daily orally for 8 weeks followed by maintenance therapy of 5mg twice daily. Infliximab induction therapy 5mg/kg at weeks 0, 2 and 6 and subsequently maintenance therapy of infliximab every 8 weeks 5mg/kg

Intervention

One study arm receives tofacitinib film-coated tablets for oral use of 10mg twice daily during the induction phase with a duration of 8 weeks, before continuing to the maintenance phase where tofacitinib will be prescribed twice daily either 10mg or 5mg.
The other study arm receives infliximab intravenously in a dose of 5mg/kg in weeks 0, 2 and 6 following the induction scheme from our protocol, continuing with the same dose every 8 weeks during the maintenance phase.

Study burden and risks

Patients participating in this study will come to their habitual check-ups at the department of Gastroenterology and Hepatology following the protocol of the administered drug. One extra visit will be planned during the induction phase, between week 4 and 6, since the OCTAVE trial showed interesting increase in lipid profile in this time period. As additional burden, they will be asked to collect an extra blood sample in the diagnostic centre combined with fecal testing at home at certain time points during a study period of one year. They will be asked to fill out questionnaires by telephone. In the OCTAVE intervention studies upon which our main study parameters are based, despite increasing cholesterol levels, major adverse cardiac events (MACE) were infrequent and occurred in patients with multiple cardiovascular risk factors.2 These results were similar to those reported for rheumatoid arthritis (RA), a larger study with longer follow-up3 and for other UC agents. Benefits of the proposed therapies are the anti-inflammatory effects on UC disease activity. This study will have direct impact on the management of patients with ulcerative colitis by determining how tofacitinib and infliximab are involved in the cardiovascular risk with regard to the lipid profiles before, during and after therapy. If tofacitinib exerts a similar effectivity on disease activity and a similar mode of action in altering the lipid spectrum compared to infliximab, tofacitinib as an oral drug might potentially be regarded as a first line therapy as well after failure of conventional treatment in the treatment of active UC.

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

- Aged 18 years or older
- Previous diagnosis with ulcerative colitis of at least 3 months
- Moderately to severe disease defined as SCCAI equal or more than 5 and fecal calprotectine more than 250 ug/g
- Refractory disease or intolerance for 5-ASA, thiopurines and/or biologicals
- Body mass index of 20-35 kg/m2

Exclusion criteria

- Absence of written informed consent
- Active or current infection

- Current treatment with biologicals (wash-out 8 weeks)
- Concomitant medication use to be named corticosteroids (except for locally administered or low dose systemic corticosteroids, e.g. prednisone <20mg and budesonide <9mg), lipidregulating agents, supplements with involved in cholesterol metabolism
- Pregnancy and lactation
- Concomitant disease to be named diabetes, hypo- or hyperthyroeidism, liver or renal failure, adrenal failure, hyperlipidemia, hypoalbuminemia, cardiopulmonary disease, malignancy, immunodeficiency, psychiatric illnesses

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-04-2021
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Inflectra
Generic name:	Infliximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeljanz

Generic name:	Tofacitinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23533
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-004587-61-NL
CCMO	NL67752.078.18
Other	TC = 7585
OMON	NL-OMON23533