Methotrexate to suppress immunogenicity to anti-tumor necrosis factor therapy in IBD patients with loss of response

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON48064

Source
ToetsingOnline

Brief title
Immunix

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anti-TNF, immunogenicity, Inflammatory bowel disease, methotrexate

Outcome measures

Primary outcome

A composite primary endpoint will be used: i.e. percentage of patients with:

• Complete disappearance of measurable ADA,

AND

• Measurable IFX or ADL serum concentrations within 6 months after starting MTX

Secondary outcome

- Association of intracellular MTX-Glu1-5 concentrations in red blood cells

(RBCs) with reduction of immunogenicity

- Association of intracellular MTX-Glu1-5 concentrations in peripheral blood

mononuclear cell (PBMCs) with reduction of immunogenicity

- Association of plasma MTX concentrations (extracellular concentrations) with

reduction of immunogenicity

- Correlation of MTX-Glu-1-5 levels between RBCs and PBMCs

- Impact of HLA genotype on therapeutic effect of MTX

- Time to disappearance of ADA after addition of MTX

- Time to regained clinical and biochemical response after addition of MTX

- Proportion of patients in clinical remission at week 2, 6, 10, 14, 18, 22 and

26(defined by HBI <= 4 points, SCCAI <= 5 points)

- Evaluation of adverse events due to MTX treatment (using the PRO-CTCAE questionnaire)

- Proportion of patients in biochemical remission at week 2, 6, 10, 14, 18, 22 and 26, defined by serum CRP level < 5 mg/l and fecal calprotectin levels < 250 mg/kg)

- Percentage of CD patients with quiescent perianal fistulas at week 2, 6, 10, 14, 18, 22 and 26, who had actively draining fistulas at baseline

- Percentage of patients with disappearance ADA (<12 AU/ml) combined with therapeutic IFX and ADL serum concentrations at week 2, 6, 10, 14, 18 and 22 (primary endpoint at week 26)

Study description

Background summary

Up to 20% of IBD patients in the Western world receive treatment with anti-tumor necrosis factor (TNF) agents. TNF inhibitors are among the most powerful agents to treat Crohn's disease (CD) and ulcerative colitis (UC). However, loss of response is seen in approximately 30% of patients, which is often caused by formation of anti-drug antibodies (ADA), and this usually results in increased clearance of the drug and low or even unmeasurable anti-TNF serum concentrations. Immunogenicity might be triggered by specific interactions between human leukocyte antigen (HLA) and the causative drug. Recent studies have demonstrated a genetic association between HLA alleles and susceptibility to delayed drug hypersensitivity of certain therapeutic agents but for anti-TNF agents this has not be investigated so far.[1] There are limited therapeutic options for patients who lose response to anti-TNF agents due to immunogenicity. The anti-TNF dose can be intensified by increasing the dose and/or shortening the treatment interval or patients can be switched to another TNF blocker or to an agent with a different mode of action. An alternative approach to overcome ADA formation is addition or reintroduction of an immunomodulator (i.e. thiopurines or methotrexate (MTX)). Recent work from others as well as from our own group showed that addition of MTX to anti-TNF therapy is often beneficial in these circumstances.[2,3] After addition of MTX, ADA decreased and anti-TNF serum concentrations increased in the vast majority

of patients resulting in recaptured clinical responses. Although MTX seems to be a powerful approach to suppress immunogenicity of anti-TNF agents, available evidence is derived from retrospective studies. Additionally, the minimum required MTX dose that is needed to suppress neutralizing antibodies, resulting in increased anti-TNF serum levels and recaptured clinical responses, remains unknown. MTX is an inexpensive drug that is used for more than five decades to treat various inflammatory diseases, such as psoriasis, rheumatoid arthritis and Crohn*s disease (CD). Although MTX is generally well-tolerated, it can produce (potential serious) side-effects. Therefore, MTX should be administered in the minimally effective dose.

Study objective

The main goal of the proposed project is to compare two MTX dosing regimens to suppress ADA levels in patients with inflammatory bowel disease (IBD) with loss of response to anti-TNF agents, and to relate these findings to clinical and biochemical outcomes.

Study design

We propose to perform a multi-center randomized study in CD and ulcerative colitis (UC) patients with loss of response to IFX or ADL (based on clinical and/or biochemical parameters) due to immunogenicity. All patients will be started on MTX via subcutaneous (SC) injections (i.e. MTX will be added to IFX or ADL). A randomization procedure will be applied and patients will be randomized into two groups in a 1:1 ratio. No blinding will be performed.

Intervention

Addition of methotrexaat to anti-therapy (infliximab or adalimumab) according to standard care (first 12 weeks 25 mg/week, followed by 15 mg/week) or a lower methotrexaat dosing regime (first 12 weeks 25 mg/week, followed by 7.5 mg/week)

Study burden and risks

The aim of the study is to regain clinical response in IBD patients treated with infliximab or adalimumab, who lose response due to the formation of ADA. There are limited therapeutic options for patients who lose response to anti-TNF agents due to immunogenicity. We expect that adding MTX to anti-TNF therapy in these patients, will lead to a significant proportion of patients regaining clinical response. This will postpone the need for switching out-of-class therapy and will postpone the need for a colectomy. The goal is to regain clinical response in order to regain a normal quality of life for each IBD patient.
Blood samples will be taken 5 times on top of standard care with a negligible risk and low burden.

Quality of life will be assessed at every study visit:
o 1 clinical disease activity questionnaire (SCCAI/HBI)
o 1 quality of life questionnaire (EQ-5D-5L)

At week 6 and week 26 (or at early withdrawl):
o patient reported outcome questionnaire (PRO-CTCAE)

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 >= 18 years (both men and women)
- Confirmed diagnosis of CD or UC by endoscopy and histopathology
- Maintenance therapy with IFX or ADL, with or without thiopurines (i.e. azathioprine or mercaptopurine)

- Loss of response, defined by clinical parameters (i.e. HBI >4 points (CD), SCCAI >5 points (UC), and/or patients with actively draining perianal fistula (CD)) and/or with elevated inflammatory biomarkers (i.e. serum CRP >=5 mg/l and/or fecal calprotectin >=250 mg/kg))
- Detectable anti-drug antibodies (ADA) directed against IFX or ADL (>=12 AU/ml) using a drug-sensitive assay
- Sub-therapeutic IFX or ADL serum levels (IFX <3 µg/mL, ADL<5 µg/mL)

Exclusion criteria

- Prior intolerance to MTX
- Pregnancy or planned pregnancy in the coming year (men and women)
- Patients with total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, AST or ALT of more than 2 times the upper limit of normal
- Subjects with evidence of or suspected liver disease, such as primary sclerosing cholangitis or cirrhosis

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Folic acid

Generic name:	Folic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Metoject
Generic name:	Methotrexate for injection
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2018-003594-95-NL
CCMO	NL68115.018.18