Personalized treatment of methotrexate in Crohn*s disease through therapeutic drug monitoring and prediction of clinical outcome: a known drug revisited

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

Summary

ID

NL-OMON50118

Source
ToetsingOnline

Brief title
MTX-PG//CD

Condition

- Gastrointestinal inflammatory conditions

Synonym
'Crohn's disease'; 'inflammatory bowel diesease'

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: MLDS (maag lever darm stichting)

Intervention

Keyword: Crohn's disease, Methotrexate, Personalized medicine

Outcome measures

Primary outcome

The primary study endpoint of MTX efficacy is Step-Up-Therapy-Free-Survival (SUT-FS) in the first 6 months after start MTX therapy. The primary study endpoint of MTX efficacy is Step-Up-Therapy-Free-Survival (SUT-FS) in the first 6 months after start MTX therapy.

MTX-PG levels in red blood cells are the primary outcome measurement for the pharmacokinetic study parts.

Secondary outcome

- Harvey Bradshaw Index (disease activity score CD)
- Faecal calprotectin (stool inflammation marker)
- CRP (blood inflammation marker)
- Hospital admissions
- Quality of life (IBDQ questionnaire)
- Liver and bonemarrow toxicity (blood)
- Gastrointestinal intolerance (MISS questionnaire)
- MTX-PG level in white blood cel (PBMC, at university medical centers only)
- MTX- PG level in colonic mucosa (if additional informed consent obtained)
- Disease activity at coloscopy (if coloscopy for clinical indication, SES-CD

score)

Study description

Background summary

Crohn*s disease (CD) is a chronic autoimmune disease of the bowel affecting 40.000 individuals in the Netherlands. CD patients are commonly treated with thiopurines such as azathioprine, while methotrexate (MTX), another equally effective drug with a better safety profile, is underutilized. The objective of this research is to employ MTX treatment in CD in a personalized fashion so that all CD patients receive the most appropriate therapy. Currently, therapeutic drug monitoring (TDM) is not possible because no stable plasma MTX levels are reached. This may lead to undertreatment and non-response or over-treatment and toxicity. To increase its efficacy and reduce toxicity, individualized MTX dosing based on TDM is needed. We have developed a new assay in red blood cells where MTX accumulates as the metabolite MTX poylglutamate (MTX-PG). We know from studies with reumatoid arthritis patients using MTX that higher MTX-PG levels correlates with good clinical response at three months therapy. There was interindividual variety between RA patients using the same dose MTX, which suggests that measurements of intracellular MTX-PG may be a valuable TDM tool for clinician to individualize MTX treatment in an early phase of treatment, in order to achieve faster disease remission and less (end-organ) damage.
In CD patients not much is known about the pharmacokinetics and pharmacodynamics of MTX. In this study we will obtain this relevant information to make TDM possible in the near future.

Study objective

To personalize MTX treatment in CD through a) therapeutic drug monitoring (TDM) of MTX and b) prediction of MTX efficacy. We will develop TDM by measuring MTX concentrations [MTX-polyglutamate concentration in erythrocytes] and determining their association with clinical efficacy in order to establish a cut-off concentration which discriminates between MTX responders and non-responders. TDM will allow clinicians to determine whether a higher MTX dose or escalation to a different therapy (i.e. biologicals) is necessary to achieve clinical response. We will identify determinants crucial for MTX pharmacokinetics and hence MTX-PG accumulation. We will also develop a prediction model for MTX efficacy before MTX start in order to facilitate clinicians to determine whether MTX is the optimal treatment or additional agents should be implemented (i.e. biologicals).
Secondary objectives includes (a), association of MTX-PG with MTX toxicity (in particular gastrointestinal intolerance with validation of MISS-questionnaire

in adult CD patients) and (b) determination of MTX-PG in different cells/tissue (erythrocytes versus peripheral blood mononuclear cells (PBMCs) versus colonic mucosa)

Study design

Observational.
A multi-center prospective longitudinal study with a follow-up of 12 months.

Study burden and risks

Only those patients for whom the treating physician already wanted to start MTX treatment will be included. MTX is used as in usual clinical care. The effort we ask of participants is filling in questionnaires and collecting extra blood tubes at those moments where blood already would be drawn. We ask to collect faeces for calprotectin, a marker already often used in routine clinical care. This contains no risk, it only costs some time. Besides that, we give participating patients an opportunity to give additional informed consent for an additional rectoscopy and additional biopsies during clinical colonoscopy. The risk of a biopsy during colonoscopy is low (1:10,000) and consist of bleeding and bowel perforation. There is no direct benefit for the participants during the study. However, with the data which we will retrieve from this study we could enable the use of MTX-PG as a TDM tool in CD patients. Optimized and individualized MTX treatment could improve care of CD patients by reducing the incidence of flares and/or use of costly biologicals.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1018 HZ
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1018 HZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Adults (18 years or older) with Crohn's disease starting with methotrexate as primary drug.

Exclusion criteria

- Cotreatment with biologicals at methotrexate start
- Not eligible to receive methotrexate as in usual care

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-05-2019

Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2021
Application type:	Amendment
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
CCMO	NL67718.029.18