Relationship between methotrexate in red and white blood cells with disease activity: towards optimal methotrexate dosing in rheumatoid arthritis.

No registrations found.

Ethical review	Positive opinion
Status	Other
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20053

Source
Nationaal Trial Register

Brief title
MEMO

Health condition

Rheumatoid arthritis, methotrexate therapy, PBMC, therapeutic drug monitoring

Sponsors and support

Primary sponsor: Reade Reumatology, Amsterdam
Source(s) of monetary or material Support: Pfizer, Noyons grant, Reade Reumatology grant

Intervention

Outcome measures

Primary outcome

Is there a relationship between levels of MTX-PGn (1-5) accumulation in RBCs vs PBMCs after oral MTX treatment and is this associated/correlated with DAS-28 scores.

Is any inter-patient variability in MTX-PGn accumulation in RBCs and PBMCs associated/correlated with specific FPGS splicing alterations.

Secondary outcome

Are there other determinants accounting for variabilities in RBC and/or PBMC MTX-PGn accumulation:

Socio-demographic parameters (age, sex).

Medication adherence, assessed via the compliance questionnaire for rheumatology (CQR), pill/syringe count and refill rate.

Intracellular folate levels, FPGS and ABC transporter gene polymorphisms, age, and MTX dose.

Clinical variables (e.g., BMI, smoking), kidney function and co-medication.

Study description

Background summary

Rationale

Low-dose methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA), both as mono- and combination therapy with other chemical and biological disease-modifying anti rheumatic drugs (DMARDs). Moreover, its convenience, tolerability, safety and low costs contribute to the clinical and socio-economic benefits of MTX. In order to have a therapeutic effect, MTX should be converted into MTX-polyglutamates (MTX-PGn). MTX monoglutamate is poorly retained and extruded from cells and rapidly cleared from plasma within 24 hours. Thus, for assessment of clinically active levels of MTX, it is more relevant to measure MTX-PGn levels in blood cells rather than plasma MTX concentrations.

There is a highly variable intracellular MTX-PGn accumulation that is largely unexplained but some of the variation may be associated with intracellular folate levels, ABC-drug efflux transporter and folylpolyglutamate synthetase (FPGS) gene polymorphisms, MTX dosing and route of administration, BMI and age. Recently, it was also demonstrated that aberrant pre-mRNA splicing of FPGS could constitute a plausible basis for loss of FPGS activity and consequently decreased MTX-PGn levels.

Furthermore, it should be taken into account that red blood cells (RBCs) do not have nuclei

and intracellular organelles to control folate and MTX homeostasis as immune-effector cells do. Since immune effector cells are the ultimate target of MTX, analysis of MTX-PGn levels in peripheral blood mononuclear cells (PBMCs) is more clinically relevant.

Together, to meet shortcomings of RBC MTX-PGn analysis as a tool to predict MTX response or toxicity, novel analytical tools to analyse MTX-PGn in PBMCs and novel molecular knowledge of the determinants of intracellular MTX-PGn accumulation (e.g. aberrant FPGS splicing) are now available to aid and improve MTX drug dosing and individualize MTX treatment to reach the optimally effective intracellular dose.

Study design and study population

In this pilot study, we will prospectively follow 40 consecutive RA patients in whom MTX therapy is initiated (20 treated with oral MTX and 20 treated with s.c. MTX). RBCs and PBMCs samples will be obtained at 0, 1, 2, 3 and 6 months. MTX-PGn and folate levels will be measured with Liquid chromatography tandem-mass spectrometry (LC-MS/MS). FPGS pre-mRNA splicing profiles in PBMCs will be determined in a multi polymerase chain reaction (PCR)-based approach.

Main study parameters/endpoints

1) MTX-PGn accumulation and MTX-PG distribution profiles in PBMCs and RBC from RA patients following 6 months MTX therapy.

2) Profiles of FPGS pre-mRNA splicing aberrations in PBMCs from RA patients following 6 months MTX therapy.

3) Clinical disease parameters, folate levels and impact of MTX on disease activity.

Study objective

In this study, the primary objective is to compare MTX-PGn levels in PBMCs of RA patients with levels in RBCs and serum and to determine the correlations with clinical response.

The secondary objective is to investigate route of administration-related determinants of MTX-PGn accumulation in PBMCs.

Finally, a tertiary objective is to examine at a molecular level whether aberrant FPGS pre-mRNA splicing is a contributing factor to variability in MTX-PGn levels in PBMCs.

Study design

5 timepoints (baseline, 1 month, 2 months, 3, months and 6 months)

Intervention

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Contacts

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Eligibility criteria

Inclusion criteria

- Adults

- Diagnosis of rheumatoid arthritis

- Able to read Dutch text

- Only prednisolone (and/or triamcinoloneacetonide i.a./i.m.) is allowed as co-medication and no other DMARDs.

Exclusion criteria

- Rheumatic autoimmune disease other than RA, e.g., systemic lupus erythematosus (SLE),

mixed connective tissue disease (MCTD), scleroderma, polymyositis

- Subjects who have received an investigational drug within 30 Days prior to the screening visit, known sensitivity to any component of the study drug or previous hypersensitivity reaction or other clinically significant reaction to s.c. medications, any clinically significant hepatic, renal, cardiac, pulmonary, gastrointestinal, metabolic or endocrine disturbances, other medical or psychiatric condition, or clinically relevant abnormal values on any investigation, which in the opinion of the investigator, could make the subject unsuitable for the study, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study.

- History of substance abuse or alcohol abuse.

Study design

Design

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

Recruitment

NL

Recruitment status:	Other
Start date (anticipated):	01-05-2018
Enrollment:	40
Type:	Unknown

Ethics review

Positive opinion

Date:	16-04-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52447
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL6961
NTR-old	NTR7149
CCMO	NL63581.048.17
OMON	NL-OMON52447

Study results

Summary results
N.A.