Relationship between methotrexate polyglutamates in peripheral red and white blood cells with disease activity: towards optimal methotrexate dosing and route of administration in rheumatoid arthritis.

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Primary objective:# What is the relationship between levels of MTX-PGs (1-5) in RBCs vs PBMCs during oral versus subcutaneous MTX treatment? Secondary objectives:# Does subcutaneous administration of MTX induce higher levels of MTX-PGs in RBCs and/...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Observational non invasive

Summary

ID

NL-OMON52447

Source
ToetsingOnline

Brief title
Methotrexate polyglutamates in peripheral blood mononuclear cells

Condition

- Autoimmune disorders

Synonym
rheumatism, Rheumatoid arthritis

Research involving

Human

Sponsors and support

Primary sponsor: Overige Centra
Source(s) of monetary or material Support: Pfizer,Reade;Pfizer.

Intervention

Keyword: methotrexate, PBMC, Rheumatoid arthritis, route of administration

Outcome measures

Primary outcome

1) MTX-PGs accumulation and MTX-PG distribution profiles in PBMCs and RBC from

RA patients following 6 months oral or subcutaneous MTX therapy.

Secondary outcome

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.

4) Validation of a LC-MS/MS based method for MTX-PGs in DBS.

Study description

Background summary

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-PGs). 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 much more relevant to measure MTX-PGs levels in blood cells rather than plasma MTX

concentrations.
There is a highly variable intracellular MTX-PGs accumulation between individuals 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-PGs 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 cells are the ultimate target of MTX, analysis of MTX-PGs levels in peripheral blood mononuclear cells (PBMCs) is more clinically relevant.
Together, to meet shortcomings of RBC MTX-PGs analysis as a tool to predict MTX response or toxicity, novel analytical tools to analyse MTX-PGs in PBMCs and novel molecular knowledge of the determinants of intracellular MTX-PGs 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 objective

Primary objective:
What is the relationship between levels of MTX-PGs (1-5) in RBCs vs PBMCs during oral versus subcutaneous MTX treatment?

Secondary objectives:
Does subcutaneous administration of MTX induce higher levels of MTX-PGs in RBCs and/or PBMCs?
Does measuring MTX-PGs levels in PBMCs correlate stronger with treatment response than MTX-PGs in RBC?
Does aberrant FPGS splicing confer lower MTX-PGs accumulation in RBCs/PBMCs?
Are there other determinants accounting for variabilities in RBC and/or PBMCs MTX-PGn levels (i.e. folate metabolism pathway enzyme polymorphisms)?

Can MTX-PG levels also reliably be assessed in blood samples obtained through finger prick?
validation of a DBS assay
comparison of DBS with erythrocyte assay
comparison of two DBS methods: regular venous EDTA tube and Hem-Col capillary tube on Guthrie cards and Ser-Col filter cards.

Study design

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-PGs 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.

Study burden and risks

Individual participating patients will not benefit from this study, neither will they experience any risks. Patients will only encounter the burden of an extra blood sample of 45 mL at inclusion, after 1, 2, 3 and 6 months, and an extra visit at month 2 and a finger prick at month 3.
Any other risks and benefits of the treatment are not expected, other than standard care.

Contacts

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Selecteer

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Scientific
Selecteer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adults
Diagnosed with rheumatoid arthritis
Able to read Dutch texts
(only prednisolone (and/or triamcinolonacetonide 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: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2018
Enrollment:	40

Type:	Anticipated

Ethics review

Approved WMO Date:	23-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2022
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

ID: 20053
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL63581.048.17
OMON	NL-OMON20053