Immunomonitoring of rheumatoid arthritis patients receiving methotrexate therapy

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• To evaluate the response to an in vivo immune challenge (KLH) in RA patients in responders versus non-responders to MTX therapy.• To evaluate the immune status of RA patients before and after the start of MTX therapy using an ex vivo immune...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON57191

Source
ToetsingOnline

Brief title
Immuno-monitoring of RA patients

Condition

- Autoimmune disorders

Synonym
Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Investigator initiated study

Intervention

Keyword: Immuno-monitoring, KLH Challenge, Methotrexate, Rheumatoid arthritis

Outcome measures

Primary outcome

• Pharmacodynamic endpoints:

o In vivo immune challenge (KLH):

* Anti-KLH IgG and IgM in serum.

* Skin biopsy: IHC staining of immune cells and RNA sequencing.

* Skin blood perfusion with LSCI, erythema with multispectral imaging (Antera 3D) after intradermal KLH re-challenge.

o Ex vivo immunomonitoring:

* Production of cytokines after PHA stimulation, including but not limited to IFNγ, IL1b, IL2, IL6, IL8, IL17.

* Inflammatory gene expression after PHA stimulation.

* KLH-specific T cell response.

o Flow cytometry

* Characterization of monocytes, and T and B cell subsets by flow cytometry

• Pharmacokinetic endpoints:

o MTX-PG concentrations in erythrocytes and PBMCs over time.

o Non-compartmental analysis of the PMBC and erythrocytes concentration-time

data: AUC0-8m, Cmax (dose-normalized), Tmax.

• Clinical endpoints:

o DAS44 <= 2.4 and/or ΔDAS44 >0.6 at 3 months

o DAS44 <= 2.4 at 6 months

o DAS44 <1.6 at 3 and 6 months

o Boolean remission 2.0 at 3 and 6 months (14)

o Individual components DAS44

o Evaluator global assessment of disease activity (VAS 0-100mm)

o Treatment response as assessed by the investigator.

o Adverse events (AEs)

o Concomitant medication

Baseline for PD measurements is defined as the last value prior to dosing on

Day 1.

Secondary outcome

N.a.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic and systemic autoinflammatory disease that causes synovial inflammation and leads to joint damage. To prevent irreversible joint damage and improve long term outcome, it*s important to start effective treatment early after diagnosis. The first line of treatment for RA is conventional disease-modifying antirheumatic drugs (DMARDs), of which methotrexate (MTX) is the preferred drug to start, often combined with

short-term glucocorticoids. If symptoms are not effectively controlled within 3-6 months, treatment is escalated to other conventional DMARDs in mono- or combination therapy (e.g. hydroxychloroquine, sulfasalazine or leflunomide), biological DMARDs (e.g. TNF blockers) or more specific targeted synthetic DMARDs (e.g. JAK inhibitors) (1).

While for most RA patients MTX is effective and results in a reduction of the disease activity score (DAS), for more than one third of the RA patients MTX therapy does not give the desired effect. Although several demographic, clinical, biochemical and genetic predictors for MTX response have been studied (2-5), identifying a reliable biomarker to predict treatment response that can be used in clinical practice remains a challenge. While for other immunomodulatory drugs the monitoring of plasma drug concentration is often used, for MTX treatment this type of pharmacokinetic monitoring is less informative. MTX has a relatively short half-life (~6 hours) and is undetectable in serum after 18 hours, while patients are usually dosed once a week to achieve clinical effect (6). However its main metabolites MTX 1-3 polyglutamates can be quantified in blood cells such as erythrocytes and polymorphonuclear blood cells (PBMC*s) (7). It would be more informative to monitor the effects of MTX on the immune system, rather than measuring circulating drug concentrations alone. Monitoring the patient*s immune status at the cellular level, and how it is affected by MTX treatment, could provide a better understanding of the MTX response and may enhance the adequate use of MTX in RA patients.
Since B and T cells play a critical role in the pathogenesis of RA (8) two different immune challenges, ex vivo and in vivo, will be used to study the immune-competence of B and T cells during MTX therapy.

For the in vivo immune challenge, the keyhole limpet hemocyanin (KLH) will be used as a stimulus. KLH is a neo-antigen that has been safely used in many clinical trials (9-12). When injected intramuscular, KLH elicits a T cell-dependent immune response that can be studied by quantifying the KLH-specific antibody response. Moreover, an extra adaptive immune response will be evoked via a prime-boost regimen in which KLH is administered intradermally, 2 to 4 weeks after the intramuscular (i.m.) KLH immunization. This intradermal KLH challenge induces a delayed-type IV hypersensitivity (DTH) reaction at the injection site. The immune response following this injection can be quantified by monitoring the local skin response.

In addition, ex vivo cytokine production will be measured after 24 h of phytohemagglutinin (PHA) stimulation in whole blood, to study the immunosuppressive effect of MTX. PHA is a lectin known for its membrane glycoproteins binding, including the T cell receptor (TCR), which leads to the activation of T cells (13). Unravelling the relationship between T cell functionality and MTX dose, and MTX polyglutamate concentration in whole blood and in the target cell, may enable a pharmacodynamic (PD), rather than a pharmacokinetic (PK)-based approach for future therapeutic drug monitoring of

MTX.

In this study, we will investigate the KLH response in RA patients in responders compared to non-responders to MTX therapy, aiming to make the translation from the in healthy volunteers used KLH model to a RA patient population on MTX therapy. Furthermore, the immune status of treatment-naïve RA patients, before and after the start of MTX therapy, will be evaluated aiming to provide a better understanding of the interpatient variability of MTX efficacy and identify biomarkers that can potentially explain the difference between responders and non-responders to MTX therapy. Concomitantly the exposure to MTX will be quantified by measuring MTX polyglutamates in erythrocytes and PBMC*s.

Study objective

• To evaluate the response to an in vivo immune challenge (KLH) in RA patients in responders versus non-responders to MTX therapy.
• To evaluate the immune status of RA patients before and after the start of MTX therapy using an ex vivo immune challenge (PHA stimulation).
• To characterize circulating immune cell subsets in RA patients before and after the start of MTX therapy.
• To monitor MTX pharmacokinetics in RA patients during MTX therapy, by measuring MTX polyglutamates (MTX-PG).
• To explore the relationship between the response to ex vivo and in vivo immune challenges, and the clinical outcome of RA patients on MTX therapy.
• To explore the relationship between the response to ex vivo and in vivo immune challenges and pharmacokinetics (MTX-PG).
• To explore the relationship between pharmacokinetics (MTX-PG), and the clinical outcome of RA patients on MTX therapy.
• To explore the relationship between MTX polyglutamates (MTX-PG) in erythrocytes and PBMCs.

Study design

This is an observational study in 20 treatment-naïve rheumatoid arthritis patients that are starting with weekly MTX and short-term treatment of glucocorticoids as standard of care. After 3 and 6 months, treatment response will be evaluated.

Intervention

Weekly MTX and short-term treatment of glucocorticoids as standard of care.
KLH

Study burden and risks

All rheumatoid arthritis patients will be on methotrexate treatment, which is their standard pharmacological therapy. The dose and regimen of these drugs will not be adjusted for their participation to this study. The main intervention that the study participants will undergo are blood withdrawal for PD measures, KLH immunization and challenge including imaging of the skin and one skin punch biopsy.

Immunization with KLH is not expected to yield any benefit for the participating subjects. In terms of risks, all drugs that are used in the present study are widely used in the Netherlands, and, apart from temporary side effects associated with the administration of the drugs, it is unlikely to expect that the subjects will be at risk of unforeseen events.

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

1. Signed informed consent prior to any study-mandated procedure;
2. Recently diagnosed treatment naïve rheumatoid arthritis patient (male or female) fulfilling to the ACR2010 criteria that are starting methotrexate therapy (with or without corticosteroids).
3. Patient must be between 18 and 75 (inclusive) years old at screening.
4. Has the ability to communicate well with the investigator and willing to comply with the study restrictions.

Exclusion criteria

1. Contra-indication(s) to start methotrexate (e.g. ALT/AST >3x ULN, child wish).
2. The use of any immunosuppressive or immunomodulatory medication other than the patient*s prescribed RA treatment within less than 5 half-lives prior to study participation, if the investigator judges that it may interfere with the study objectives;
3. Any known factor, condition, or disease that might interfere with study conduct or interpretation of the results, in the opinion of the investigator.
4. Unwillingness or inability to comply with the study protocol for any other reason.
5. Participants with known previous exposure to KLH.
6. History of Schistosomiasis (infection with Schistosoma parasite);
7. Have any current and / or recurrent clinically significant skin condition at the treatment area (i.e. atopic dermatitis); including tattoos.
8. Clinically significant bleeding disorders known to interfere with hemostasis after skin biopsy and/or i.m. injection.
9. Disorders in wound healing (peripheral vascular disorders or neuropathy, history of forming keloid scars).
10. Any known significant allergic reactions (urticaria or anaphylaxis) against shellfish.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2024
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	20-12-2024
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL87435.058.24