# Training immune functions through pharmacotherapeutic conditioning in juvenile idiopathic arthritis

Published: 23-05-2018
Last updated: 10-04-2024

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| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Autoimmune disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46548

**Source**
ToetsingOnline

**Brief title**
OPTI-MISS

### Condition

- Autoimmune disorders

**Synonym**
Juvenile idiopathic arthritis / Juvenile Arthritis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universiteit Leiden
**Source(s) of monetary or material Support:** Reumafonds

## Intervention

**Keyword:** Conditioning, Immune system, Juvenile Idiopathic Arthritis, Pharmacotherapeutic effects

## Outcome measures

### Primary outcome

The primary outcome parameter is the difference in percentage of patients who experience MTX intolerance as defined by the Methotrexate Intolerance Severity Score (MISS) with a cut-off score of * 6 between the control and intervention (conditioning) groups.

### Secondary outcome

Secondary outcome measures are achieving low disease activity as measured by the Juvenile Arthritis Disease Activity Score (JADAS < 3), side effects as determined by liver function and gastrointestinal bleeding, laboratory assessments (e.g., cytokine levels and myeloid-related proteins and MTX polyglutamates), and self-report outcomes as assessed by validated scales about pain and burden of disease.

# Study description

### Background summary

A growing body of studies show that treatment outcomes can be influenced by expectations and learned associations, also known as the placebo effect, in both medical and psychological practice. Recently, these placebo effects have been utilized in the context of drug therapy in order to optimize treatment outcomes by using the principle of pharmacotherapeutic conditioning. Pharmacotherapeutic conditioning is based on classical conditioning, where repeated drug administration leads to a learned association. After the association has been made, a learned response can now be induced by a placebo, similar to Pavlov*s famous conditioning experiment where dogs start salivating

upon hearing a bell which indicates food. Medication regimens making use of pharmacotherapeutic conditioning via principles of variable reinforcement (varying doses of medication) have shown to lead to good therapeutic effects, while significantly reducing adverse side effects. Methotrexate (MTX) is a widely prescribed drug for rheumatic diseases in both children and adults, but is frequently hampered by its severe side effects. Especially in children diagnosed with juvenile idiopathic arthritis (JIA) who are treated with MTX as the drug of first choice, side effects are common and new approaches to reduce these burdensome side effects are urgently needed. This study specifically aims to reduce these side effects by administrating MTX through a variable reinforcement schedule.

**Study objective**

This study*s objective is to reduce MTX related side effects with pharmacotherapeutic conditioning, by using variable reinforcement principles in patients with JIA. Pharmacotherapeutic conditioning enables to alternate standard MTX dosing with lower MTX doses, by utilizing learning effects (conditioning). By this, children with JIA will be less affected by MTX related side effects, without compromising for its therapeutic efficacy. A reduction in side effects will be assessed by intolerance percentages as defined by a cutoff score of * 6 on the Methotrexate Intolerance Severity Score (MISS) questionnaire.

**Study design**

A multicenter, clinical, randomized controlled trial will be conducted in patients diagnosed with JIA, closely following current pharmacological treatment recommendations. The study design is divided into 3 periods: 1. A baseline period (6 months) where MTX stable doses are administered according to standard dosing (12,5 - 15 mg/m²/wk). 2. Intervention period (9 months): patients who have followed protocolized treatment and have shown a good MTX response (based on JADAS <3 or based on the paediatric rheumatologist*s opinion, will be randomized to control or intervention group. Both groups will follow different MTX treatment schedules. Group 1 * Control group: Standard MTX dosing schedules as a continuation of baseline period. Group 2 * Conditioning group: Variable reinforcement schedule, where standard MTX dosing is intermittent with subtherapeutic dosing (2,5 - 5 mg/m²/wk, depending on body surface area). Duration of the intervention period is based on a recent revision of clinical (Dutch) guidelines for MTX treatment for JIA. 3. Month 18: End-of-study visit: Treatment effects will be followed up and (early) flare-ups will be monitored.

**Intervention**

The intervention consists of pharmacotherapeutic conditioning (variable

treatment schedule).

**Study burden and risks**

This study closely follows standard treatment for JIA, and assessments will therefore be conducted during regular patient visits to the hospital (at initial screening and subsequently visits every three months up till 18 months) whenever possible, with each appointment lasting approximately half an hour (time invested to complete questionnaires will be 10 to 20 minutes). Blooddraws will take place during regular clinical blooddraws, and do not necessitate for additional puncture, as blooddraws are part of standard of care.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

### Inclusion criteria

- Age between 4 to 17 years (at the time of JIA diagnosis);
- Diagnosed with JIA by their physician as defined by the ILAR-classification;
- Able to speak or understand Dutch;
- Patients (or parents/guardians of the patient under the age of 12) are able to give informed consent;
- Achieve a good MTX response based on the JADAS (Juvenile Arthritis Disease Activity Score) assessing inactive disease scores at 6 months after MTX onset, with a score of 3 or lower or based on the pediatric rheumatologist's opinion.

### Exclusion criteria

- DMARD use at the moment of inclusion; or MTX experience previously
- Alternative route of MTX administration than oral (e.g. subcutaneous)
- Concomitant treatment with an experimental drug or procedure interfering with this study purposes
- Systemic JIA
- Development of uveitis which needs to be treated with a DMARD
- Elevated hepatic enzyme levels (serum aspartate transaminase [AST], serum alanine transaminase [ALT] > 2 times normal value)
- Bone marrow suppression as lymphocyte count <0.9×109/L, granulocyte count <1.5×109/L and/or thrombocyte count <20 × 109/L.39
- Serum creatinine levels > 150 umol/l or estimated creatinine clearance of < 75%
- Biologicals

## Study design

### Design

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|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 132 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Methotrexate |
| Generic name: | Methotrexate |
| Registration: | Yes - NL outside intended use |

## Ethics review

Approved WMO

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| Date: | 23-05-2018 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

Not approved

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|---|---|
| Date: | 20-09-2018 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

## 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 | EUCTR2018-001571-21-NL |
| CCMO | NL63966.058.18 |