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A randomised trial of 6 months versus 12 months withdrawal of methotrexate in patients with Juvenile Idiopathic Arthritis (JIA) in clinical remission

Submission date
26/11/2005

Recruitment status
No longer recruiting

Registration date
16/02/2006

Overall study status
Completed

Last Edited
08/04/2010

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.printo.it

Contact information

Type(s)
Scientific

Contact name
Dr Dirk Foell

Contact details
University Hospital Muenster
Department of Pediatrics
Albert-Schweitzer-Str. 33
Muenster
Germany
48149
+49 (0)251 8356584
dfoell@uni-muenster.de

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
2005-001086-34

Study information

Scientific Title

Acronym
MTX-withdrawal-study

Study objectives
Treatment with the disease modifying anti-rheumatic drug (DMARD) methotrexate (MTX) in doses of 10 to 15 mg/m^2 given once weekly has been proven to be safe and effective in JIA. With this regime it is possible to attain relieve of clinical symptoms and normalisation of laboratory parameters in a number of cases. In contrast to the situation in adulthood, clinical remission on and off medication in JIA is possible. Therefore, it has been reported that discontinuation of MTX should be considered after an adequate period of remission.

About 50% of the patients experience a relapse after discontinuation of the immunosuppressive therapy. It is not yet clear if a longer duration of MTX treatment in the status of remission is able to reduce the overall risk of relapses over the course of the disease. Thus, treatment with MTX is continued for a variable time span after documentation of remission and according to the personal beliefs of the attending physicians.

Recently a definition of clinical remission for JIA has been proposed based on clinical examination and laboratory parameters. We also demonstrated that analyses of the phagocyte-specific proteins myeloid related-protein 8 (MRP 8) and MRP 14 provide excellent markers for the disease activity of JIA.

The present study was designed for the follow-up of two groups of patients with JIA, in whom remission was achieved using MTX. In group 1, treatment with MTX will be discontinued as early as six months after documentation of remission on medication. In group 2, treatment with MTX will be discontinued later than 12 months after documentation of remission on medication.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee at the University of Muenster, reference number 0VIIIRot

Study design
Prospective, randomised, clinical multi-centre study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Juvenila Idiopathic Arthritis (JIA)

Interventions
The study is designed as a prospective, randomised clinical trial with follow up documentation of 2 groups of patients.

Group 1:
At three months: first confirmation of remission on medication on the basis of signs of disease activity (no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, no elevation in ESR and/or CRP attributable to JIA; physicians global assessment of disease activity indicates no disease activity). At this point only on a combination of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), low-dose steroids (0.2 mg/kg per day or 10 mg per day whichever is lower), and MTX (max 15 mg /m^2 per week) is allowed, all the other drugs (e.g. biologics, intra-articular joint injections) must have been withdrawn before this date according to the physician decision. During the following three months low dose steroids and NSAIDS must be withdrawn according to the attending physician decision.

Time point zero months treatment with MTX is continued with dose range of 10 to 15 mg/m^2 per week (by oral, subcutaneous, intra-muscular or intravenous admission) after this time point. One NSAID is allowed.
Time point three months documentation of the clinical course after three months in remission.
6 months later confirmation of remission, discontinuation of MTX (and NSAID if applicable).

In further follow up examinations in intervals of three months the clinical course is documented over at least one year.

Group 2:
At time three months: first confirmation of remission on medication on the basis of signs of disease activity (no joints with active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, no elevation in ESR and/or CRP attributable to JIA, physicians global assessment of disease activity indicates no disease activity). At this point only on a combination of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), low-dose steroids (0.2 mg/kg per day or 10 mg per day whichever is lower), and MTX (max 15 mg /m^2 per week) is allowed, all the other drugs (e.g. biologics, intra-articular joint injections) must have been withdrawn before this date according to the physician decision. During the following three months, low dose steroids and NSAIDs must be withdrawn according to the attending physician decision.

Time point zero months treatment with MTX is continued with dose range of 10-15 mg/m^2 per week (by oral, subcutaneous, intra-muscular or intravenous admission) after this time point. One NSAID is allowed.
Time point three months - documentation of the clinical course after three months in remission.
Time point six months - documentation of the clinical course after six months in remission.
Time point nine months - documentation of the clinical course after nine months in remission.
Twelve months later (time point 12) - approval of remission, discontinuation of MTX (and NSAID if applicable).

In further follow up examinations in intervals of three months, the clinical course is documented over at least one year.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Methotrexate (MTX)

Primary outcome measure
Number of relapses

Secondary outcome measures
1. Time to relapse
2. Prediction of relapse by MRP8 or MRP14 serum concentrations

Overall study start date
01/01/2005

Completion date
31/12/2008

Eligibility

Key inclusion criteria
Patients will be included at first confirmation of remission on medication i.e. after clinically documented inactive disease for at least three months (no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, no elevation in Erythrocyte Sedimentation Rate [ESR] and/or C-Reactive Protein [CRP] attributable to JIA, physicians global assessment of disease activity indicates no disease activity).

At three months, patients may be only be on a combination of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), low-dose steroids (0.2 mg/kg per day or 10 mg per day whichever is lower), and MTX (max 15 mg/m^2 per week); all the other drugs (e.g. biologics) must have been withdrawn before this date according to the physicians decision.

Before inclusion into this study (study time point 0 months), patients will be considered to be in clinically documented remission on medication. At this time point, all medications other than NSAIDs and MTX with a dose range of 10 to 15 mg/m^2 per week have to be withdrawn. After

discontinuation of MTX (study time point 6 i.e. after 6 months in group 1; study time point 12 i.e. after 12 months in group 2) treatment with NSAIDs should be stopped.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
300

Key exclusion criteria
Patients should not have received intra-articular corticosteroids up to three months prior to inclusion

Date of first enrolment
01/01/2005

Date of final enrolment
31/12/2008

Locations

Countries of recruitment
Argentina

Brazil

Chile

Croatia

Cuba

Czech Republic

Denmark

Finland

France

Georgia

Germany

Greece

Hungary

India

Israel

Italy

Kuwait

Latvia

Mexico

Montenegro

Netherlands

Poland

Portugal

Romania

Russian Federation

Saudi Arabia

Serbia

Slovakia

Spain

Switzerland

Türkiye

United Kingdom

Study participating centre
University Hospital Muenster
Muenster
Germany
48149

Sponsor information

Organisation
Pediatric Rheumatology International Trials Organisation (PRINTO) (Italy) and Wyeth Pharma

Sponsor details
IRCCS G. Gaslini
Pediatria II Largo Gaslini, 5
Genova
Italy
16147

Sponsor type
Other

Website
http://www.printo.it

Funder(s)

Funder type
Research organisation

Funder Name
Pediatric Rheumatology International Trials Organisation (PRINTO) (EU grant number 2001CVG4-808)

Funder Name
Wyeth Pharma provided funding for patient insurance

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	07/04/2010		Yes	No