A controlled, randomised, double-blind, multicenter study, comparing methotrexate vs placebo in steroid-refractory ulcerative colitis

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This multicenter, prospective, controlled, randomized, double-blind study aims at provingthat the success level measured by steroid-free remission in patients with steroiddependentulcerative colitis (UC) is higher with methotrexate than with placebo...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON32416

Source
ToetsingOnline

Brief title
Meteor study

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohns Disease, M. Crohn

Research involving
Human

Sponsors and support

Primary sponsor: Besancon University Hospital

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: steroid dependent, steroid refractair, Ulcerative Colitis

Outcome measures

Primary outcome

Success at the 16th and the 24th week of treatment is the main criteria.

The success is measured by:

- Remission according to a Mayo Disease Activity Index <= 2 with no items >1,

and

- complete stop of prednisone or prednisolone for 7 days or more.

and

- no other immunosuppressive or colectomy between inclusion and the 24th week

Secondary outcome

- Success on the 16th week measured according to 6.1

- Success on the 24th week measured according to 6.1

- Clinical remission on each visit

- Steroid cumulative dose in both groups at 16th and 24th weeks.

- CRP measurements on each visit

- Side effects in both groups

Study description

Background summary

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that slightly reduces life

expectancy, strongly reduces its quality and can lead to serious complications such as acute
colitis, dysplasia and colon cancer. About 40'000 patients are affected in France Among
them, 15% suffer from a chronic active form that often leads to an extended steroid
therapy, and its known side effects. Azathioprine has already proven its efficacy in this
indication but brings a lasting remission without steroid in only 41% of the patients (1-4).
What are the medications available for the patients who failed in maintaining a remission
with azathioprine ? Cyclosporin is designed for severe or steroid-resistant forms. (5). The
results of two recent studies have showed that infliximab is more efficacious than placebo in
active UC (6, 7). Infliximab is expensive, its efficacy in steroid-dependent UC has not been
specifically tested yet, and its tolerance on the long term remains uncertain. Methotrexate
proved its efficacy in Crohn's disease with an intramuscular dose of 25mg/week (8). In UC a
controlled trial has been negative with an oral dose of 12.5mg/week (9). Another study
compared mercaptopurine, methotrexate (15mg/week) and 5-aminosalicylate in 72 steroiddependent
patients with CD or UC (10). The remission rates obtained were 58% after 30
weeks with methotrexate (not significantly different from 5-ASA) and 14% after 106 weeks
(not significantly different from 5-ASA). Few data are available on the efficacy of
methotrexate in UC, at a dose which is active in Crohn's disease (25mg intramuscular/week). Several uncontrolled series have been published, including 91 patients
whose remission failed under azathioprine.
The results from these studies suggest that methotrexate is active with a 20 to 25 mg intramuscular dose
per week. Methotrexate is largely used, outside from the field of oncology, with more than
20 years experience in inflammatory diseases (rheumatoid polyarthritis, psoriasis).
Methotrexate is cheap and its patent has fallen in the public domain. Only institutional
research will be able to finance a study in this new indication.
This is a prospective, controlled, randomized, double-blind study of methotrexate with an
intramuscular dose of 25mg/week vs placebo in patients with steroid-dependent

UC.

Study objective

This multicenter, prospective, controlled, randomized, double-blind study aims at proving
that the success level measured by steroid-free remission in patients with steroiddependent
ulcerative colitis (UC) is higher with methotrexate than with placebo.

Study design

A CONTROLLED, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY.

Intervention

Methotrexate and placebo. Regimen will be 1 intramuscular injection
every week, always on the same weekday.
A 5mg tablet of folic acid (will be prescribed every week, 24 hours to 48 hours after the
methotrexate (or the placebo) injection in order to reduce the side effects

Study burden and risks

The side effects of methotrexate are well known. \Some patients do not tolerate this drug because of digestive problems (nausea, vomiting), rarely hepatitis or pneumonia, mouth ulcers, stomatitis. A decrease of white cell number can be observed therefore a monitoring by blood draws is necessary (every 2 weeks for the first month, then
every month during the rest of the study). The methotrexate can cause foetus malformations if the father or the mother is under such treatment. Consequently it is mandatory to avoid pregnancy during the methotrexate treatment and during 3 months after its termination.

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

INCLUSION CRITERIA
Patients, male or female, will be eligible if they meet the following criteria:
* Between 18 and 75 years of age.
* UC diagnosed according to the Lennard-Jones criteria (Appendix 1) with endoscopic colorectal lesions, whatever their extension may be.
* A Mayo Disease Activity Index <= 4, with no item >1 for the clinical part of the score and from 0 to 2 for the endoscopic part at the time of inclusion.
* Steroid-dependence defined by at least 1 unsuccessful attempt to stop systemic steroid therapy during the last 12 weeks. Steroid therapy might have been completely stopped if it has been restarted within the last 30 days.
* To be receiving a treatment of prednisone at a dose between 10 and 40mg, stable for at least 2 weeks at the time of inclusion.
* Under an adequate contraception for male or female subjects of childbearing potential: mechanic methods of contraception (condom, female condom, diaphragm, spermicidal gel) and oral contraception started at least 15 days before inclusion. This contraception will be continued throughout the study duration and at least 3 months after study termination.

Exclusion criteria

EXCLUSION CRITERIA
* Indication to a colectomy.
* Alcoholism (more than 21 glasses per week for male subjects and 14 glasses per

week for female subjects). 1 glass corresponds to 3 cl of strong alcohol, 10 cl glass of wine or a half pint of beer.
* Pregnant or breast-feeding female subjects.
* No efficacious contraception.
* NSAIDS or cotrimoxazole intake upon inclusion, or probenecide intake within 1 month prior to inclusion.
* Anti-TNFα treatment within 2 months prior to inclusion.
* Azathioprine, mercaptopurine, cyclosporin or thalidomide within 1 month prior to inclusion.
* Modification of mesalazine or olsalazine dosage within 1 month prior to inclusion.
* Chronic (broncho) pneumopathy.
* Renal failure (creatininaemia > upper limit of normal laboratory values limit).
* Liver disease apart from primary sclerosing cholangitis.
* Unexplained rise higher than twice the normal level for transaminases, alkaline phosphatases and/or bilirubin.
* Folate level < normal level.
* Infection by HIV, HBV (except in case of positive antibodies anti-HBs), HCV with serologies not older than 3 months.
* Past history of malignant condition (including leukaemia, lymphoma and myelodysplasia) except for baso-cellular cutaneous cancers.
* Obesity (BMI>30).
* Diabetes mellitus.
* Known hypersensitivity to methotrexate.
* Non-compliant subject.
* Participation in another therapeutic study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-08-2008
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-06-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-11-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-03-2009
Application type:	Amendment
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	EUCTR2006-003607-40-NL
ClinicalTrials.gov	NCT00498589
CCMO	NL23095.058.08