IMPROVED: Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease;A randomized clinical trial in patients with recent-onset arthritis to compare the efficacy of DMARD combination therapy including prednisone with combination therapy including adalimumab, a TNF-blocking agent.

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

Summary

ID

NL-OMON30362

Source
ToetsingOnline

Brief title
IMPROVED

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatoid arthritis - rheumatic disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Abbott,Abbott Laboratories Ltd.

Intervention

Keyword: clinical remission, DMARD combination therapy, rheumatoid arthritis, undifferentiated arthritis

Outcome measures

Primary outcome

1. The percentage of patients achieving remission after 4 months and after 1

year of combination therapy, defined as a DAS < 1.6

After 4 months: with the combination therapy methotrexate and prednisone

After 1 year: after randomization into the combination therapy with either

prednisone or adalimumab.

2. Functional capacity, measured by the health assessment questionaire (HAQ)

after 1 year

3. Radiological joint damage: absolute and progression from baseline, measured

by the modified Sharp/van der Heijde score.

Secondary outcome

- MACTAR questionnaire

- Short Form 36 questionnaire

- EuroQol questionnaire

- Time Trade Off technique

- costs

- ACR painful and swollen joint count

- Patient measures, via visual analog scale (VAS)

pain, morning stiffness, disease activity, general health

- laboratory measurements: chemical (kidney and liver function), hematological

(leucocytes, thrombocytes, hemoglobine), parameters of inflammation (C-reactive

protein, erythrocyte sedimentation rate), bone markers, genetic factors

Study description

Background summary

During the last decades a dramatic change has taken place in the way rheumatoid arthritis (RA) patients are treated. Disease modifying antirheumatic drugs (DMARDs) are prescribed earlier in the disease course and often in combinations with or without prednisone or a tumor necrosis factor (TNF)-blocking agent. Frequent assessments, for instance using the Disease Activity Score (DAS), can be used to adjust the medication in order to achieve optimal suppression of the disease process, regardless of the therapeutic strategy used. For patients with recently established RA, these changes have resulted in earlier suppression of disease activity, earlier improvement in functional ability and less radiological joint damage, without more side effects. Moreover, with these novel insights in treatment strategies clinical remission appears to be a goal within the reach of many patients.

In order to start treatment as early as possible, it has been argued to start treatment even before the diagnosis of RA is made. Undifferentiated arthritis (UA), defined as an inflammatory arthritis in which no definitive diagnosis can be made, has been shown to progress to RA within 1 year in 6 to 55 % of cases, dependent on the UA criteria used, with similar clinical and radiological outcome as patients that presented with RA. Recently, the PROMPT-study showed that treatment of UA patients with MTX monotherapy for one year postponed the progression to RA and retarded radiographic progression during treatment. After discontinuation of MTX, however, disease activity increased and patients still progressed to RA, defined by fulfilling the criteria of the American College of Rheumatology (ACR). It appears that if a window of opportunity exists in UA, in which by temporary treatment the course of the disease can be fundamentally altered, MTX monotherapy is not the treatment to rely on. Since combination therapy is the superior therapy in established RA, initial combination therapy aiming at clinical remission may also be the best choice for patients with recent-onset UA.
Current knowledge suggests that combination therapies including prednisone or a TNF-blocking agent with MTX as the anchor drug are most effective in suppressing disease activity, reducing radiological damage and functional disability and can even induce clinical remission in recent-onset RA. Even short-term use of combination therapy can lead to long-term benefits. However, there is still no systematic approach to the treatment of patients with recent-onset arthritis. A head-to-head comparison of DMARD combination therapy including prednisone and DMARD combination therapy including a TNF-blocking agent could provide insight into which treatment is superior in efficacy and cost-effectiveness with the most acceptable toxicity profile.
Therefore, we designed a randomized clinical trial to compare two combination therapies, including prednisone or a TNF-blocking agent, in recent-onset arthritis (UA and RA) patients aiming at clinical remission: the IMPROVED-study: Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease. After the same initial treatment with MTX and a tapered high dose of prednisone, the two different treatment strategies will allow a comparison of efficacy, safety and cost effectiveness of early treatment with a combination of MTX, SSZ, HCQ and low dose prednisone (MSHP), versus treatment with a combination of MTX with the TNF-blocking agent adalimumab.

Study objective

The objectives of this study are:
* To determine the percentage of patients with recent-onset RA and UA who achieve and maintain clinical remission on treatment with a combination of methotrexate 25 mg/week and extended prednisone pulse (tapered high dose) after 4 months.
* To determine whether, if clinical remission is not achieved, methotrexate+prednisone combination therapy should be extended with sulphasalazine and hydroxychloroquine or switched to methotrexate+adalimumab

combination therapy.

Study design

This protocol describes a multicentre, randomized, single-blinded one-year follow-up clinical trial comparing two combination therapies in patients with recent-onset arthritis (UA and RA) aiming at clinical remission.

In an initial open parallel prospective desing all patients will receive an initial combination therapy with MTX and tapered high dose prednisone. Patients who do not achieve clinical remission after 4 months, defined as a disease activity score (DAS) of <1.6, will subsequently be randomized into two treatment arms.

1. Extended medication, adding hydroxychloroquine and sulphasalazine while methotrexate and low dose prednisone are continued.

2. Switching to adalimumab and discontinuation of prednisone, while methotrexate is continued.

Intervention

1) The initial combination therapy includes methotrexate building up to 25 mg/day and prednisone pulse therapy starting with 60 mg/day and tapering to 7,5 mg/day in 7 weeks. Subsequently, methotrexate will be continued in a dose of 25 mg/day and prednisone in a dose of 7,5 mg/day for 4 months.

2) After 4 months, patients who did not achieve remission according to a DAS < 1.6 will be randomized into two different treatment groups:

A) Extended combination therapy with:
methotrexate 25 mg/day
prednisone 7,5 mg/day
sulfasalazine 2000 mg/day
hydroxychloroquine 400 mg/day

B) Switching therapy to:
methotrexaat 25 mg/dag
adalimumab injection subcutaneously 40 mg every other week

Study burden and risks

The burden for the patients associated with participation include systematic physical joint examination, questionnaires, blood samples and X-rays of hands and feet every four months for 1 year. At start and after 1 year a DEXA scan

and extra blood samples. At start screening for tuberculosis and hepatitis B, consisting of lung X-ray, skin test and serology.

Possible risks to the patient are mainly associated with the toxicity of the drugs used in both treatment arms:
- increased risk for tuberculosis or reactivation of hepatitis B infection
- increased risk for virus, bacteria and other infections
- skin injection reaction with erythema, itching
- allergic reactions including headache, nausea, dizziness, palpitations and breathing problems
- possible increased risk for lymphoma
- central nervous system symtoms like tintling, muscle ache or stiffness

More general adverse events:
- gastrointestinal: nausea, vomiting, stomache ache
- huid: rash, stomatitis
- bloed: decrease in leucocytes
- liver function disturbances
- kidney function disturbances
- visus disturbances
- hypertension and hyperglycemia

Combination therapies as the ones used in this study, did not show more toxicity than the single drugs in prior studies, with a comparable or higher efficacy. Moreover, next to a direct expected beneficial effect for the patients included,
this study will provide important scientific information for the amelioration of treatment strategies for patients with recent-onset rheumatoid arthritis in the future.

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. minimum age of 18 years
2. at least one swollen joint
3. at least one other painful joint
4. symptom duration shorter than 2 years
5. diagnosis rheumatoid arthritis according to the ACR classification criteria or
6. diagnosis undifferentiated arthritis, suspected for rheumatoid arthritis by the rheumatologist, as no classification criteria exist.
7. patients naive for treatment with corticosteroids or disease modifying anti-rheumatic drugs (DMARDs).

Exclusion criteria

1. previous therapy with DMARDs or with corticosteroids (exception: one dose of parenteral corticosteroids within the last 6 months, but not within the last 2 months, or an oral dose of prednisone of =<10 mg/day for =< 2 weeks within the same period allowed).
2. pregnancy or wish to become pregnant during the study, or childbearing potential without adequate contraception
3. concomitant treatment with another experimental drug
4. history or presence of malignancy within the last five years
5. bone marrow hypoplasia
6. elevated hepatic enzyme levels (ASAT, ALAT > 3 times normal value)
7. serum creatinine level > 150 umol/l or estimated creatinine clearance of < 75%
8. uncontrolled diabetes mellitus (according to the rheumatologist)
9. uncontrolled hypertension or moderate to severe heart failure (NYHA class III/IV)
10. alcohol or drug abuse
11. history of infected joint prothesis within the previous 3 months
12. serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months

13. chronic infectious disease such as chronic renal infection, chronic chest infection with bronchiectasis or sinusitis
14. history of active tuberculosis requiring treatment within previous 3 years, or signs and symptoms of latent infection with tuberculosis, based on medical history, physical examination, tuberculin (PPD) skin test or chest radiograph (see 9.3.1).
15. history of other granulomatous infections as histoplasmosis or coccidiomycosis
16. evidence of active cytomegalovirus, active pneumocystis carinii, active aspergillosis, or drug resistant atypical mycobacterium infection
17. history of opportunistic infections such as herpes zoster within previous 2 months.
18. history of active hepatitis B infection or evidence of a latent infection (see 9.3.1).
19. documented HIV infection, AIDS related complex (ARC) or AIDS.
20. history of lymphoproliferative disease including lymphoma or signs suggestive of possible lymphoproliferative disease.
21. Multiple sclerosis or neurological symptoms suspect for demyelinising disease.
22. Hypersensitivity to human immunoglobuline or other constituents of adalimumab

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2007
Enrollment:	535
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira

Generic name:	Adalimumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plaquenil
Generic name:	Hydroxychloroquine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisone
Generic name:	Prednisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Salazopyrine
Generic name:	Sulphasalazine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-12-2006
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-08-2009
Application type:	Amendment
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
EudraCT	EUCTR2006-006186-16-NL
CCMO	NL15233.058.06
Other	volgt

Study results

Date completed:	19-10-2015
Actual enrolment:	610