Prevention of the progression of very early symptoms into ankylosing spondylitis

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

Summary

ID

NL-OMON36697

Source
ToetsingOnline

Brief title
PREVAS

Condition

- Joint disorders

Synonym
ankylosing spondylitis, spondyloarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: farmaceutische industrie (Wyeth farmaceuticals) ondersteunt de investigators driven studie

Intervention

Keyword: ankylosing spondylitis, early, prevention, treatment

Outcome measures

Primary outcome

Disease-activity : including questionnaires (BASDAI, BASFI, BASG, pain VAS, ASAS core set, SF-36), measured after 1 and 3 years, physical examination (including BASMI and MASES), measured after 1 and 3 years and laboratory parameters (blood; including acute phase reactants as ESR and CRP and urine), measured after 1 and 3 years.

Secondary outcome

Radiographic changes of the X-SI joint en X-spine (BASRI-score), measured after 1 and 3 years.

Inflammation at MRI SI-joint/spine, after 16 weeks and 6 months.

Study description

Background summary

Ankylosing Spondylitis (AS) belongs to a group of diseases which are referred to as Spondyloarthropathies (SpA), with a prevalence of 1.0% in Caucasians and onset early in life (25-40 years of age). AS as the prototype of an SpA, is a chronic inflammatory disabling rheumatic disease. The diagnosis of AS requires at least one criterion out of three (Inflammatory back pain (IBP), limited spinal motion, decreased chest expansion) and sacroiliitis on X-ray, which is due to chronic inflammation of the sacroiliac (SI) joints and vertebral column. The inflammatory process can result in destruction of the vertebral column leading to serious postural deformities. Extra spinal manifestations of the disease consist of arthritis of the peripheral joints (especially knees, shoulders, and hips) and enthesitis. The diagnosis of AS is based on the modified New York criteria. It requires radiographically proven

sacroiliitis grade 2-4 bilaterally or grade 3-4 unilaterally for a definitive diagnosis. The radiographs are often normal when the first symptoms arise and it usually takes several years before definite radiographic sacroiliitis appears. The mean delay to diagnosis is usually 5-10 years. Therefore is important to diagnose AS in an earlier stage, especially before the onset of irreversible radiographic changes. About 16% of patients with IBP already appear to have radiographic sacroiliitis and almost 30% show inflammation of the SI-joint on MRI. Inflammation on MRI is a prognostic factor for the development of AS; it has a positive predictive value of 60% for the development of radiographic sacroiliitis after 3 years in patients with IBP. Patients with IBP and additional early symptoms of disease, are most likely to progress into AS (about 60% in ten years). This group of patients can be diagnosed with a high probability of at least 90% when IBP and at least two other SpA characteristics are present (especially inflammation on MRI).
Therapy was, until five years ago, symptomatic with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. As a second line approach, the disease modifying antirheumatic drugs (DMARDs) have been used. However, in contrast to RA, the effect of DMARDs in AS is less impressive. A breakthrough in therapy are the tumor necrosis factor alpha (TNF alpha) blockers. Etanercept proved to be effective on almost all clinical features of AS. Furthermore, signs of inflammation as seen on MRI also decreased during anti-TNF therapy. Patients with shorter disease duration showed a better response to the TNF-blockers than patients with longer disease duration.In summary with regard to AS a study to prevent the progression of inflammatory back pain into AS seems to be neededfor the following reasons. The prevalence of AS is estimated about 1%, it starts at a relatively young age and the burden of the disease is high. Moreover, patients with a high risk of developing AS can be identified at a very early stage and effective therapy has become available before irreversible changes occur. All ingredients are available now to start an effort in order to prevent the onset of AS.

Study objective

The general aim of this project is the primary prevention of the development of AS in patients with IBP, additional (SpA) features and inflammation on MRI of the SI joint and/or spine (but still no sacroiliitis on X-ray) by giving them, a short period, anti-TNF therapy. Since the effect of a successful intervention can only be measured after several years, the primary (but short-term) focus is the decrease of the inflammatory abnormalities visible on MRI of the SI-joint and/or spine after 16 weeks of etanercept therapy in comparison to placebo treatment.
The primary objective of this study is the short-term clinical improvement and the long-term delay in clinical deterioration after etanercept therapy in the (preclinical AS) patients and therefore we look at the progression of early symptoms into AS, clinically. This will be done by measuring the ASAS 20% response criteria and by other clinical response criteria such as the BASDAI, BASG, BASFI, acute phase reactants, after 16 weeks, 6 months and after 1, 2 and

3 years.
The secondary objective of this study is to reverse the inflammatory abnormalities visible on MRI in (preclinical AS) patients without sacroiliitis (or grade 1) on X-ray with short-during etanercept therapy. For this purpose MRI scans will be made of the SI-joint and spine after 16 weeks (short term), and after 6 months (long term).
Another secondary focus of this study is the progression into AS both on short and long term, measured by the degree of radiological damage visible on X-ray after one and three years.
The ultimate goals (and secondary objective) of this study are: to prevent or inhibit the radiological progression with etanercept therapy compared with placebo after 3 years and to lower the incidence of AS in this group of high risk individuals

Study design

The study is designed as a randomized, double-blind, placebo-controlled trial. After inclusion patients are randomly assigned to the etanercept- or placebo-arm of the study in a 1:1 ratio. During 16 weeks etanercept (dosage 25 mg) or placebo will be given twice a week as subcutaneous injections.
After inclusion the patients will be screened. If there are no definite sacroiliitis on X-ray, the patients will randomly and double blind be assigned to etanercept or placebo treatment.

Intervention

Subjects will be randomly assigned in a 1:1 ratio to one of the two treatment groups
-Group 1 (n=40); 16 weeks etanercept twice weekly 25 mg subcutaneous.
-Group 2 (n=40); 16 injections with placebo twice weekly subcutaneous

Study burden and risks

The patients might have benefits of this intervention because there is a chance that the disease activity might improve with etanercept even at a very early stage of the disease.

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

Patients to be included must meet the following criteria.
- age * 18 years,
- patient with inflammatory back pain for at least 3 months, with onset < 45 years
- presence of ³2 SpA-features or
- presence of ³1 SpA-feature with HLA-B27 positivity or two family members with definite AS (1e or 2e degree family-member);
- no definite sacroiliitis on the X-ray (sacroiliitis grade 1 is sustained);
- BASDAI score of * 4 (0-10)
- Insufficient response to treatment with NSAID's over a 4-week period

Exclusion criteria

- definite AS (modified New York criteria (9);
- previous treatment with TNF-blockers.
General medical exclusion criteria: for treatnebt with TNF blockers (pregnancy or planning pregnancy, infections, tuberculosis, HIV, Hepatitis B or C, malignincies etc)

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-11-2009
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enbrel®
Generic name:	Etanercept
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-10-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2009
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-015515-40-NL
CCMO	NL28510.029.09