PREVAS: prevention of ankylosing spondylitis.

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29047

Source
Nationaal Trial Register

Brief title
PREVAS

Health condition

ankylosing spondylitis, inflammatory back pain, morning stiffness, chronic (low) back pain, arthiritis, buttock pain, dactylitis, enthestitis, psoriasis, non-gonococcal urethritis or cercvicitis

Sponsors and support

Primary sponsor: investigator drive study supported by Wyeth
Source(s) of monetary or material Support: investigator drive study supported by Wyeth

Intervention

Outcome measures

Primary outcome

Inflammation of the SI- joints on MRI after 16 weeks and after 6 months.

Secondary outcome

1. Disease acitivity after 16 weeks and 6 months (questionnaires, physical examination and labaratory findings);

2. Radioactive progression after 3 years;

3. Development of A.S.

Study description

Background summary

Background of the study:

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.

Objective of the study:

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 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).

The secondary 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.

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 inflammatory lesions of the SI joint and/or spine on MRI and no definite sacroiliitis on X-ray, the patients will randomly and double blind be assigned to etanercept or placebo treatment.

However, if a patient has no inflammatory lesions on MRI of the SI-joint or spine, the MRI will be repeated after 16 weeks. In case of inflammation, the patient will be included in the trial and randomized as described before.

Study population:

Patients will be recruited from the patient population of the rheumatology outpatient clinic of the VU medical center and the Jan van Breemen Institute. Patients who fulfill the inclusion criteria will be included in this study after giving their informed consent.

In this study patients are included with early symptoms who have a high chance to develop ankylosing spondylitis (AS) without having AS. From the SpA population with different subgroups of SpA-patients, the patients with predominantly axial symptoms are most likely to develop AS. Therefore patients with inflammatory back pain and 2 or more other (SpA) features will be asked to participate in this study when they have no definite sacroiliitis on X-ray but do have inflammatory signs on MRI of the spine/SI-joint.

Moreover, we do have an opportunity to diminish the clinical symptoms of patients who would otherwise not fulfill the current treatment criteria for TNF-blocking agents and would never have the benefit of these drugs.

Intervention (if applicable):

Subjects will be randomly assigned in a 1:1 ratio to one of the two treatment groups:

1. Group 1 (n=40); 16 weeks etanercept twice weekly 25 mg subcutaneous;

2. Group 2 (n=40); 16 injections with placebo twice weekly subcutaneous.

Primary study parameters/outcome of the study:

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

Secundary study parameters/outcome of the study (if applicable):

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

2. 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.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):

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.

Study objective

N/A

Study design

1. Visit 1 (week 0) = Baseline;

2. Visit 2 (week 2), Visit 3 (week4), Visit 4 (week 8), Visit 5 (week 12) = Efficacy visits;

3. Visit 6 (week 16), Visit 7 (6 months) = Efficacy visits and MRI visit;

4. Visit 8 (year 1), Visit 10 (year 3) = Efficacy visit and X-ray visit;

5. Visit 9 (year 2) = Efficacy visit.

Intervention

Double blinded, placebo controlled study with 80 patient, divided in a 1:1 ratio over 2 groups:

1. Group 1 (n=40); 16 weeks etanercept, 2 x a week 25 mg subcutaneous;

2. Group 2 (n=40); 16 injections with placebo 2 x a week subcutaneous.

Contacts

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Eligibility criteria

Inclusion criteria

Patients to be included must meet the following criteria:

1. Age between 18-45 years, both male and female;

2. Inflammatory back pain for at least 3 months, but less than two years;

3. Presence of 2 or more SpA-features or;

4. Presence of 1 or more SpA-feature with HLA-B27 positivity or two family members with definite AS (1e or 2e degree family-member);

5. No definite sacroiliitis on the X-ray (sacroiliitis grade 1 is sustained);

6. Active inflammatory lesions on MRI of the sacroiliac-joint and/or vertebral column;

7. Have the capacity to understand and sign an informed consent form, are capable of reading and understanding subject assessment forms, and are willing and able to adhere to the study visit schedule and other protocol requirements;

8. The screening laboratory test results must meet the following criteria:

A. Hemoglobin for males 9.0 g/dL (5.6 mmol/L) or more and females 8.5 g/dL (5.3 mmol/L) or

more;

B. Serum transaminase levels must be within 3 times the upper limit of normal range for the laboratory;
serum creatinine 1.4 mg/dL (123.8 mol/L) or less.

9. NSAIDs it must be on a stable dose for at least 2 weeks prior to the first administration of study agent. If they currently are not using NSAIDs, they must not have received NSAIDs for at least 2 weeks prior to the first administration of the study drug.

Exclusion criteria

Specific medical exclusion criteria:

1. Definite AS (modified New York criteria (9));

2. Previous treatment with TNF-blockers.

General medical exclusion criteria:

1. Women who are pregnant, nursing, or planning pregnancy within 2 months after the last; infusion (this includes fathers who plan on fathering a child within 2 months after the last infusion);

2. Documented seropositive for human immunodeficiency virus (HIV);

3. Documented positive for hepatitis B surface antigen or hepatitis C;

4. History of alcohol or substance abuse within the preceding 6 months that, in the opinion of the investigator, may increase the risks associated with study participation or study agent administration, or may interfere with interpretation of results;

5. Known history of serious infections (e.g., herpes zoster, cytomegalovirus, pneumocystis carinii, aspergillosis, histoplasmosis, coccidioidomycosis or mycobacteria other than TB) within 6 months prior to screening;

6. History of lymphoproliferative disease, including lymphoma or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location (e.g., nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic area), or splenomegaly;

7. Any current known malignancy or history of malignancy within the previous 5 years, with the exception of basal cell or squamous cell carcinoma of the skin that has been fully excised with no evidence of recurrence;

8. Any current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease;

9. History of known demyelinating diseases such as multiple sclerosis or optic neuritis;

10. Being unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access;

11. Use of any investigational drug within 30 days prior to screening or within 5 half-lives of the investigational agent, whichever is longer;

12. Presence of a transplanted solid organ (excluding a corneal transplant);

13. Having a concomitant diagnosis or history of congestive heart failure;

14. Having a history of latent or active TBC prior to screening;

15. Having signs or symptoms suggestive of active TBC upon medical history and/or physical examination;

16. Having had a recent close contact with a person with active TBC. If there has been such contact, a patient will be referred to a physician specializing in TBC to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TBC prior to or simultaneously with the first administration of study agent;

17. Having contraindications for making an MRI such as electronically, magnetically, and mechanically activated implants, cardiac pacemakers, ferromagnetic or electronically operated stapedial implants, hemostatic clips (CNS) or metallic splinters in the orbit.

Exclusions are in line with warnings and contra-indications in the SmPC.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-08-2009
Enrollment:	80
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL1835
NTR-old	NTR1945
Other	METC VU MC : 09-206
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results

N/A