A randomised, double-blind, placebo-controlled, multicentre, Phase II dose-finding study of atacicept given subcutaneously in subjects with rheumatoid arthritis and inadequate response to TNFa antagonist therapy

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The goal of this research trial is to evaluate the efficacy, tolerability and safety of atacicept in patients with active rheumatoid arthritis who have an inadequate response to other treatment(s). In addition, the study will also measure the...

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

Summary

ID

NL-OMON30206

Source
ToetsingOnline

Brief title
A Phase II dose-finding study of atacicept in RA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Serono
Source(s) of monetary or material Support: Serono International; 15 Chemin des Mines; 1202 Geneva; Switzerland.

Intervention

Keyword: anti-B Cell therapy, APRIL, BLys, Rheumatoid Arthritis

Outcome measures

Primary outcome

The proportion of subjects achieving an ACR20 response at Week 26

Secondary outcome

* Proportions of subjects achieving ACR50 and ACR70 responses at Week 26.

* Proportions of subjects achieving ACR20, ACR50 and ACR70 responses at Week 16.

* Changes in ACR scores over time.

* Changes in each ACR core measure from baseline to Week 16 and Week 26.

* Change from baseline to Week 26 in:

o DAS 28 and DAS28 CRP.

o Health Assessment Questionnaire (HAQ) Disability Index (HAQ DI).

o Medical Outcomes Study Short Form General Health Survey (SF-36) subscores.

* Proportion of subjects achieving a DAS 28 of 3.2 or less at Week 26.

* Proportion of subjects achieving a DAS 28 of 2.6 or less at Week 26.

* Proportion of subjects with an improvement in DAS 28 of at least 1.2 from

baseline to Week 26.

* Proportion of subjects with an improvement in the HAQ Disability Index of at

least 0.3 from baseline to Week 26.

Safety Endpoints:

* Nature, incidence and severity of adverse events (AEs) and local injection site reactions.

* Changes in vital signs, ECG, routine laboratory parameters and anti-pneumococcus, anti-diphtheria and anti-tetanus antibodies.

* Formation of antibodies to atacicept.

Other Endpoints:

* Baseline (pre-dose) levels of free BLyS and free APRIL.

* PK profiles of free BLyS and free APRIL (contingent on availability of appropriate assays for post-baseline samples), free atacicept, total atacicept (free atacicept + atacicept*BLyS complex), atacicept*BLyS complex and atacicept*APRIL complex.

* Changes over time in the levels of the following biomarkers: ESR, CRP, IgG, IgM, IgA, rheumatoid factor (RF) IgM, IgG and IgA, anti-cyclic citrullinated peptide (anti-CCP) antibodies and disease-related cytokines (samples for cytokine assessment to be analysed if it is believed that the results may benefit the further development of atacicept).

* Changes over time in B cell subsets, T cells, NK cells and monocytes.

* Pharmacogenetics (samples will be taken from consenting subjects, and analyses will be performed after completion of the trial only if it is believed that these analyses may benefit the further development of atacicept):

o Gene expression profiling at baseline and at Week 26.

o Genotype characterisation.

o Sequencing of BLyS, APRIL, BAFF R, TACI and BCMA genes.

Study description

Background summary

Rheumatoid arthritis is a chronic inflammatory disease of the joints of unknown cause. Certain mechanisms that lead to joint inflammation are becoming better understood and research in rheumatoid arthritis suggests that B cells play an important role in the development of the inflamation activity in the joints.By decreasing the B cel population could give a positive effect on the inflamation, which could result in a decrease of the inflamation activity, pain, swelling and destructios of the joints. Atacicept recombinant fusion protein functions as an antagonist to -B-Lymphocyte Stimulator (BlyS) and A Proliferation Inducing Ligand (APRIL), these takes care for the growing of the B-cels in the bone marrow.

Study objective

The goal of this research trial is to evaluate the efficacy, tolerability and safety of atacicept in patients with active rheumatoid arthritis who have an inadequate response to other treatment(s). In addition, the study will also measure the effects of atacicept on some parameters in the blood, which reflect disease activity. This trial will also look at possible effects of atacicept on disease progression.

Study design

This randomised, double-blind, placebo-controlled, parallel-arm, multicentre, prospective dose-finding trial will enrol at least 288 evaluable subjects with rheumatoid factor-positive active rheumatoid arthritis who have failed treatment with a TNF* antagonist (defined below).
Screening will be performed within 28 days before the first dose. Following provision of written informed consent and confirmation of eligibility for the trial, subjects will be randomised in a 1:1:1:1 ratio to receive one of three dose levels of atacicept or placebo, given by subcutaneous injection.
Subjects will be assessed before dosing on Study Day 1 (SD 1, defined as the day of randomisation and first Investigational Product administration), and then on Days 8 and 22 and at the beginning of Weeks 8, 12, 16, 20 and 26. A final Follow-up visit will take place at Week 38, 13 weeks after the last dose.
In a subset of subjects in selected Western European centres, flow cytometric analyses of B cell subsets, T cells, NK cells and monocytes in peripheral blood

will be performed to characterise atacicept*s effects on these cell populations. Pharmacokinetic sampling will also be performed at additional time points for this subset, which will consist of 24 subjects from each treatment group, including placebo. All subjects in the participating centres will provide consent for these procedures; the subjects who will be part of the subset will be selected by the trial*s central randomisation service.

Intervention

Treatment will consist of a loading period during the first 4 weeks, during which the assigned dose will be administered twice weekly (BIW) followed by a maintenance period over the next 21 weeks, during which the assigned dose will be administered once weekly (QW). Thus:
* Group 1: atacicept 25 mg BIW for 4 weeks, followed by atacicept 25 mg QW for 21 weeks.
* Group 2: atacicept 75 mg BIW for 4 weeks, followed by atacicept 75 mg QW for 21 weeks.
* Group 3: atacicept 150 mg BIW for 4 weeks, followed by atacicept 150 mg QW for 21 weeks.
* Group 4: placebo BIW for 4 weeks, followed by placebo QW for 21 weeks

Study burden and risks

The duration of the study is as follow: screening period of 1 to 4 weeks prior to study medication; treatment period of 25 weeks, follow up period of 13 weeks. In total 10 visits.
The screeening visit can take more then 2 hours, but after this each visit will not take more then 1 hour. During the scrrening visit the demochrafic data, full medical history and rheumatology history, medication history and data regarding opperration pracedures will be collected, a x-ray of the thorax will be performed
Blood samplings and urine analysis will take place on 10 occasions at the following visits: screening, SD1, SD8, SD 22, weeks 8, 12, 16, 20, 26 and at the final follow-up visit. In a subset of subjects in selected Western European centres, flow cytometric analyses of B cell subsets, T cells, NK cells and monocytes in peripheral blood will be performed to characterise atacicept*s effects on these cell populations
Pharmacokinetic sampling will also be performed at additional time points for this subset, which will consist of 24 subjects from each treatment group, including placebo. All subjects in the participating centres will provide consent for these procedures; the subjects who will be part of the subset will be selected by the trial*s central randomisation service.Standard ECG will be performed at screening, SD1, SD8, SD22, weeks 8, 12, 16, 20, 26 and final follow up visit.
Disease activity assessments at screening, SD1, SD8, SD22, weeks 8, 12, 16, 20, 26 and at the final follow up visit

Quality of Life questionnaire (SF-36) on SD1 and week 26.
Physical examination will take place at screening, SD1, final follow- up visit and as required by routine clinical care
Female subjects will have an urine pregnancy test at screening, SD1, SD22, weeks 8, 12, 16, 20, 26 and at the final follow-up visit.
Collection of information on adverse events, local tolerability, concomitant medication and procedures will take place at every visit.
Optional Pharmacogenomics samplings will take place on SD1 and at week 26, for this a seperate patient information and consent form is available.
In order to reduce the risks the standard procedures which will be used for the used assessments, will be done as clean and sterile as possible.
Possible side effects of the study medication are written on page 17,18 and 19 of the protocol. The main adverse effects reported included headaches, respiratory tract infections with cold/flu symptoms, sore throat and gastrointestinal disorders such as nausea, vomiting and diarrhea, but a causal relationship between atacicept and these symptoms and illnesses has not been established. There have been transient reactions at the injection site (redness and swelling).As with other medications, people treated with atacicept may be at risk of developing allergic reactions or anaphylaxis. Symptoms of an allergic reaction generally include overall body itching, hives, skin flushing, or rash. Anaphylaxis is a more serious allergic reaction that may involve dizziness, low blood pressure (loss of consciousness is possible in the case of very low blood pressure), difficulty breathing and swallowing, palpitations, abdominal pain and vomiting.

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

The trial will enrol adult subjects of either sex who have at least a one-year history of rheumatoid factor (RF)-positive rheumatoid arthritis satisfying American College of Rheumatology criteria and who have failed treatment with at least one TNF alpha antagonist (etanercept, infliximab or adalimumab).

Exclusion criteria

Subjects who have received belimumab or abatacept will be excluded, as will those who have received rituximab, etanercept, infliximab, adalimumab or investigational treatments or procedures within specified periods before studyday 1.

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:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	atacicept
Generic name:	TACI-Fc5

Ethics review

Approved WMO Date:	16-11-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2008
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	EUCTR2006-004140-23-NL
CCMO	NL14851.018.06