A randomised, double-blind, placebo controlled, multicentre, exploratory, pilot, phase II trial of 150 mg ataicept given subcutaneously in combination with rituximab in subjects with rheumatoid arthritis.

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Primary objective:* To assess the safety and tolerability of combined treatment with atacicept and rituximab insubjects with active rheumatoid arthritis receiving re-treatment with rituximab.Secondary objectives:* To evaluate the effect of combined...

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

Summary

ID

NL-OMON32036

Source
ToetsingOnline

Brief title
AUGUST 3

Condition

- Autoimmune disorders

Synonym
rheumatism

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Merck Serono International S.A.;an affiliate of Merck KGaA

Intervention

Keyword: atacicept, placebo, rheumatoid arthritis, rituximab

Outcome measures

Primary outcome

Primary endpoints:

* Nature, incidence and severity of adverse events (AEs); in particular,

proportion of

subjects with treatment-emergent infection-related AEs and proportion of

subjects with

serious infections.

* Proportion of subjects who develop IgG <3 g/L.

* Changes and abnormalities in vital signs and routine safety laboratory

parameters.

* Changes over time in vaccine immunisation status, assessed through

anti-tetanus

toxoid, anti-pneumococcus and anti-diphtheria toxoid antibody titres.

Secondary outcome

Secondary endpoints:

* B cell subsets, T cell subsets and natural killer (NK) cells measured by flow cytometry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IgG, IgM, IgA, rheumatoid factors (RFs) * IgM-RF, IgG-RF and IgA-RF, anti-cyclic citrullinated peptide antibodies (ACPA or anti-CCP antibodies) and disease-related cytokines.

* Levels of free BLyS and free APRIL.

* PK profiles of free atacicept, atacicept·BLyS complex, composite atacicept (free atacicept + atacicept·BLyS complex) and *total atacicept* (free atacicept + atacicept·BLyS complex + atacicept·APRIL complex).

PK profile of rituximab.

* ACR core measures, and morning stiffness, enabling calculation of ACR and DAS28 composite scores.

* Time to loss of response.

* Incidence of antibodies to atacicept, both binding and neutralising.

* Incidence of antibodies to rituximab.

* Gene expression profiles and/or genetic variations that would predict drug response and/or that would explain the drug*s mechanism of action.

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. Decreasing the B cell population could give a positive effect on the inflamation, which could result in a decrease of the inflamation activity, pain, swelling and destruction of the joints. Atacicept recombinant fusion protein functions as an antagonist to B-Lymphocyte Stimulator (BLys) and A Proliferation Inducing Ligand (APRIL), these take care of the growing of the B-cells in the bone marrow.

Study objective

Primary objective:
* To assess the safety and tolerability of combined treatment with atacicept and rituximab in
subjects with active rheumatoid arthritis receiving re-treatment with rituximab.
Secondary objectives:
* To evaluate the effect of combined treatment with atacicept and rituximab on levels of
peripheral blood B cell populations over time.
* To gain further information on the effect of combined treatment with atacicept and
rituximab on biomarkers reflecting their mechanism of action (MoA) and disease activity.
* To characterise the pharmacokinetic (PK) profiles of atacicept and rituximab when given
in combination.
* To identify potential associations between gene polymorphisms and drug response, at a
genome scale and with a focus on BLyS, APRIL, BAFF-R, TACI, BCMA and HLADRB1.
* To investigate the preliminary efficacy of combined treatment with atacicept and rituximab
compared to rituximab alone in the treatment of signs and symptoms in a population of
subjects with active RA receiving re-treatment with rituximab

Study design

This is a randomised, placebo controlled, double-blind trial in subjects with moderate to severe
active RA who have previously received rituximab and who are candidates for a new course of
rituximab treatment. Candidates for re-treatment are subjects who have previously responded
to rituximab and have significant residual disease activity or have

deteriorated clinically after initial response. Response to a previous course of treatment should be evaluated after an observation period of at least 16 weeks from the initiation of treatment. The previous course of rituximab treatment should have been given at least 24 weeks before SD1. Residual active disease and clinical deterioration after initial response are defined by disease activity with a minimum of 8 swollen joints (66-joint count) and 8 tender joints (68-joint count).

Screening will be performed within 28 days before Study Day 1 (SD1), defined as the first day of treatment with rituximab (Cohort 1) or atacicept/placebo (Cohort 2). Following provision of written Informed Consent and confirmation of eligibility for the trial, subjects in Cohort 1 will receive two doses of rituximab 2 weeks apart, followed by 28 days without treatment then subjects will be randomised to receive atacicept or placebo in a 2:1 ratio. Following provision of written Informed Consent and confirmation of eligibility for the trial, subjects will be randomised to receive atacicept or placebo in a 2:1 ratio (Cohort 2).

Subjects will receive atacicept 150 mg or placebo subcutaneously (SC) once weekly for 25 weeks. There will be two different cohorts, which will differ in terms of the start time of atacicept/placebo treatment in relation to rituximab treatment. Atacicept/placebo will commence 4 weeks after the last infusion of rituximab in Cohort 1, and 9 days before the first infusion of rituximab in Cohort 2.

Cohort 1

Twenty-seven subjects will receive rituximab at a standard dosing regimen at SD1 and SD15.

At SD43 (four weeks after the last infusion of rituximab), subjects will be randomised to receive atacicept 150 mg or placebo (2:1) given SC once weekly for 25 weeks and will begin atacicept/placebo treatment.

Trial assessments for Cohort 1 will take place before rituximab administration on SD1 and on SD 15 and at Weeks 7, 9, 12, 16, 20, 26 and 32. Post treatment follow-up assessments will take place at Weeks 40, 48, 56 and 64.

Cohort 2

Twenty-seven subjects will be randomised at SD1 to receive atacicept 150 mg or placebo (2:1)
SC once weekly for 25 weeks; these subjects will begin atacicept/placebo treatment at SD1.
Subjects will receive rituximab at a standard dosing regimen at SD10 and SD24, rituximab
infusions will be given 2 days after the Weeks 2 (SD8) and 4 (SD22) atacicept/placebo doses
to avoid dosing of atacicept and rituximab on the same day.
Trial assessments for Cohort 2 will take place before dose administration on SD1, on SD10
and SD24 and at Weeks 8, 12, 16, 20 and 26. Post treatment follow-up assessments will take place at Weeks 34, 42, 50, 58 and 66.
Subjects who withdraw prematurely from the trial should undergo the assessments planned for
Week 32 (for subjects in Cohort 1) or Week 26 (for subjects in Cohort 2) at the time of
withdrawal, and should then have a Follow-up visit for safety 12 weeks after the last dose of
trial medication: this will involve the assessments planned for Week 48 (for subjects in Cohort
1) or Week 42 (for subjects in Cohort 2).
Subjects will be followed up for approximately 60 weeks after the last dose of rituximab.
Subjects who discontinue treatment and receive only rituximab or only atacicept/placebo will
be followed up for at least 12 weeks after the last dose.

Intervention

In cohort 1, 27 patients will receive rituximab on study day 1 and on study day 15.
On study day 43 (four weeks after last rituximab infusion) the patients will be randomized to receive either atacicept or placebo (2:1). This will be administered once a week sub cutanous for 25 weeks.

In cohort 2, 27 patients will be randomized on study day 1 to receive atacicept or placebo (2:1). This will be administered sub cutanous once a week for 25 weeks. Rituximab infusion will be on study day 10 and on study day 24.

Study burden and risks

From the patient information:

Approximately 54 trial subjects will be enrolled in this trial, which will be conducted in several countries in the European Union. If you are accepted into

this trial, you will be participating for a total duration of 65 to 70 weeks (approximately 16 months), which consist of the following:

- Screening period of 1 to 4 weeks before treatment
- Treatment period of 25 to 31 weeks (approximately 6-7 months)
- Follow-up period of between 32 and 40 weeks (approximately 8-10 months) after completing treatment

Side effects, discomforts and inconveniences
As with any treatment, adverse effects are possible. Please review the information regarding adverse effects and potential risks and ask your study doctor if you have any questions or concerns.
Atacicept has been well tolerated when tested in healthy male volunteers and in patients with rheumatoid arthritis, systemic lupus erythematosus and B-cell cancers. The main adverse effects reported included viral respiratory tract infections (colds and flu), fatigue, shortness of breath, reduced appetite, nausea, and diarrhoea, but a causal relationship between atacicept and these symptoms and illnesses has not been established. There have been short-lived reactions at the injection site (bruising, redness and swelling).
Rituximab can lower your body*s ability to fight infections. Taking rituximab can make you more prone to getting infections or make any infection you have worse. Potential risks associated with treatment with rituximab include serious infection (including fatalities), reactivation of hepatitis B, infusion reactions, anaphylactic and other hypersensitivity reactions and the worsening of pre-existing heart conditions.
The combination of rituximab and atacicept may result in excessive suppression of the immune system, leading to an increased risk of infection.

Potential risks
Atacicept is a relatively new medication. To date, approximately 178 subjects (including healthy volunteers and patients with rheumatoid arthritis, systemic lupus erythematosus, and B cell malignancies-[cancers]) have received atacicept at doses up to 1900 mg, which is much higher than you will receive in this study. Atacicept affects the production of immunoglobulins (antibodies) and the immune system, which may lead to increased susceptibility to infection.
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. Prompt medical care is needed since serious allergic reactions may be potentially life threatening. If you think you are having an allergic reaction, you need to notify the study staff immediately.
Study procedures include a chest X ray and regular blood sampling for measurement of safety parameters and biological markers; some minor risks are associated with these procedures.

The standard chest X-ray will involve a small radiation exposure. The radiation exposure is very low and is equal to that you would get from natural sources (like the sun) in less than 2 weeks.
Blood will be drawn at each of the study visits. A number of laboratory tests will be performed (depending upon the visit, tests will differ). These amounts are unlikely to cause you any harm taken over the period of study. For your safety your study doctor may want you to have blood tests more frequently than your scheduled study visits. He/She will let you know if this becomes necessary. The needles used to draw blood may cause local pain, bruising and swelling. Some patients may also experience light-headedness, dizziness and rarely fainting or a local infection.
ECGs and measurements of blood pressure, heart rate and body temperature are safe and are unlikely to cause discomfort.
In some countries, study procedures will include a skin test for tuberculosis (TB). There is a very small risk of severe redness and swelling of the arm in individuals who have had a previous positive PPD test (tuberculin skin test) and who undergo repeat testing. There have been a few cases of this reaction also occurring in individuals who have not been previously tested.
In a pharmaceutical study like this one, every risk or side effect cannot be predicted. Each person*s reaction to a test, drug, or procedure may be different. You may have a side effect or be at risk for symptoms, illnesses and/or complications that could not be predicted by the study doctor or the makers of atacicept.

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 male and female subjects 18 years of age at the time of Informed Consent who have rheumatoid arthritis satisfying American College of Rheumatology criteria and a disease history of at least 12 months. Subjects must have active disease; defined by 8 swollen joints (out of 66), 8 tender joints (out of 68) and CRP 6 mg/L or ESR 28 mm/h. Subjects must have received previous treatment with rituximab and must be candidates for re-treatment
with rituximab: i.e. they must have a documented response after an observation period of at least 16 weeks from initiation of treatment to a previous course of rituximab treatment given at least 24 weeks before SD1 and they must have significant residual active disease after previous rituximab treatment or clinical deterioration after initial response (defined by satisfying the above criteria for active disease).
Female subjects of childbearing potential must be willing to avoid pregnancy by using an adequate method of contraception for four weeks before SD1, during the treatment period and
for 12 months after the last dose of rituximab, and must have a negative urine pregnancy test
at the screening visit and at SD1.

Exclusion criteria

Main exclusion criteria are:
* Neurological disease.
* Inflammatory joint disease other than RA.
* Any contraindication to rituximab as per national label.
* Known presence of human anti-chimeric antibodies (HACA) to rituximab.
* Use of disease-modifying anti-rheumatic drugs (DMARDs; including methotrexate) for less than 3 months or change in dosing regimen within 28 days before SD1, or
methotrexate dose regimen >25 mg/week.
* Participation in any interventional clinical trial within 1 month before SD1 (or within
5 half-lives of the investigated compound before SD1, whichever is longer).
* Prednisone dose regimen >10 mg/day (or equivalent), or change in steroid dosing

regimen within 28 days before SD1.
* Active or latent tuberculosis within the year before screening or major infection requiring hospitalisation or intravenous anti-infectives within 28 days before SD1.
* Serum IgG below 6 g/L.
* Known hypersensitivity to atacicept or to any of the components of the formulated atacicept.
* Known hypersensitivity to rituximab, to any of the components of the formulated rituximab or to murine proteins.
* Breastfeeding or pregnancy.

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):	15-12-2007
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Not Applicable

Generic name:	Atacicept

Ethics review

Approved WMO Date:	04-01-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2011
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	EUCTR2007-003647-75-NL
CCMO	NL20485.018.07