A phase II study of ARA 290 as therapeutic strategy in rheumatoid arthritis

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

Summary

ID

NL-OMON36765

Source
ToetsingOnline

Brief title
ARARA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ARAIM pharmaceuticals (verstrekking

medicatie, geen financiele ondersteuning),De onderzoeksmedicatie zal verstrekt worden door ARAIM pharmaceuticals.

Intervention

Keyword: rheumatoid arthritis, treatment

Outcome measures

Primary outcome

Efficacy parameters:

- Circulating inflammatory markers (CRP, if this is elevated possibly TNF,

IL-1, IL-6, IL10)

- Health assessment questionnaire disability index (HAQ)

- Patient's assessment of pain on a visual analogue scale (0mm=no pain, 100mm=

worst pain possible).

- Functional health and well being (Short Form-36 questionnaire)

- Symptoms of depression (Beck Depression Inventory-II questionnaire)

- Disease activity, measured with the Disease Activity Score, a composite index

calculated with the number of painfull joints (of 53 joints) and the number of

swollen joints (of 44 joints), Erythrocyte Sedimentation Rate and patient's

assessment of general health on a visual analogue scale (0mm= best possible,

100mm= worst possible).

Secondary outcome

Safety and tolerability parameters:

•General safety measurements

•12-lead ECG

•Blood Hematology

•Blood Biochemistry

•Adverse Event monitoring

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1% of the general population. Patients present with symmetric joint swelling and systemic inflammation. The inflammatory response in RA is associated with over-production and over-expression of tumor necrosis factor (TNF). Uncontrolled active RA leads to joint destruction, disability, and co-morbidities such as cardiovascular disease. RA is associated with increased mortality and reduced life expectancy. Cardiovascular disease is one of the most common causes of death in RA patients, with a 50% increased risk of cardiovascular related death compared to the general population. Active inflammation is one of the predictors of cardiovascular morbidity and mortality in RA patients.

Drug management of RA has undergone dramatic changes in the past 3 decades, with an expansion of the amount of different available drugs. The use of DMARDs like methotrexate (MTX), sulfasalazine and leflunomide has now been well established. In addition to these, several biological agents, targeting TNF, the interleukin-1 or 6 receptor, B lymhocytes or T-cell co-stimulation have been developed for the treatment of RA. However, with the available drugs and strategies, up to 20% do not achieve low disease activity and many patients remain partial responders. Remission is only achieved in 22-49%, depending on the definition.

Erythropoietin (EPO) is a well-known stimulator of erythrocyte production and widely used in the treatment of anemia caused by kidney disease, cancer, or chronic inflammation. Over the past decade, it has become evident that erythropoietin, besides its positive effect on hematopoiesis, possesses many other biological activities that can generally be summarized as counteracting the actions of proinflammatory cytokines and their deleterious effects in tissue injury.
Cross-talk between the circulating hematopoietic and the local tissue protective pools of EPO is avoided by the presence of EPO receptor isoforms that differ greatly in their affinity for EPO. The tissue protective receptor exhibits a lower affinity for EPO (2-20 nM) and therefore does not respond to EPO at concentrations present within the circulation, but rather only to high levels of locally produced EPO. Secondly, in hematopoiesis, the homodimer is expressed continuously by a population of red cell precursors that require

constant circulating EPO to enable survival. In contrast, the tissue protective receptor typically is not expressed until after the occurrence of injury or significant metabolic stress and only requires a brief exposure to EPO to trigger sustained biological activity.
When employed at the high doses required for adequate tissue protection, EPO unfortunately possesses use-limiting side effects, particularly in converting the vasculature into a prothrombotic state, which leads to an increased risk of life-threatening thromboses, as has been observed particularly in injured patients or those with cancer.
Therefore a number of nonerythropoietic tissue protective cytokines (TPCs) have been developed that interact exclusively with the tissue protective receptor, but lack an effect on the hematopoietic receptor. These compounds have been shown to exhibit tissue protective effects but not to induce endothelial cell activation or thrombocyte activation.
ARA 290 is an 11-amino acid, linear peptide that is being developed as a tissue protective peptide. ARA 290 mimics the tissue protective pharmacology of erythropoietin but is devoid of its haematopoietic effects.
In preclinical models, ARA 290 has been shown to exhibit general anti-inflammatory activities. In RA patients, clinical trials investigating the use of recombinant human erythropoietin to correct anemia, showed that disease activity was reduced after treatment. These observations suggest that activation of the tissue protective erythropoietin receptor may reduce disease activity in patients with active RA. To that end we now propose to perform a clinical study of ARA 290 in patients with active RA.

Study objective

This is an open label proof of principle study, in 14 patients. The objective of the study is to test the efficacy and safety of ARA 290 in patients with active rheumatoid arthritis. To assess the efficacy, disease activity is examined based on joint examination, functional ability, functional health and wellbeing and mood and symptoms of depression based on questionnaires and systemic inflammation based on laboratory investigation. Safety is assessed by registering any adverse events and serious events, patient reported as well as discovered by physical examination and laboratory investigation.

Study design

Patients that are eligible for participation, because they have active rheumatoid arthritis, will be recruted by their rheumatologist and informed by the research physician. After receiving informed consent, the investigation will start.
During the first visit, the patient will be screened to find out if the patient meets all the criteria. If this is the case, randomisation will take place. Patients will be devided into two groups. Each patient will be treated for 4 weeks.

The first groups will visit the hospital once a week to be treated with ARA 290 (iv in 2 minutes, than half an hour observation) and have a physical examination. Blood will be drawn and disease activity will be assessed.
In addition to these visits, the second group will come to the hospital for treatment a second and a third time. The first group receives 4 gifts of RA 290, the second group receives 12. Each group will consist of 6 patients.
At the beginning and at the end of these 4 weeks, functional ability, functional health and well being and mood and symptoms of depression will be evaluated using validated questionnaires (HAQ, SF-36 and BDI-II respectively). The HAQ will be filled out weekly. A month after the last visit, another visit will take place to perform a physical examination, draw blood and assess disease activity and disability.
After this, patients will be contacted by telephone every month (until 6 months after the last treatment) to ask if the disease activity is still low. If this is not the case, patients will be asked to return to the hospital for a last evaluation of disease activity and systemic inflammation.
During the investigation, patients will be asked about side effects regularly.

Intervention

Iv treatment with 2 mg ARA 290 thrice or once a week during 4 weeks.

Study burden and risks

Burden: patients have to come to the hospital for a screening, then for 1 month come to the hospital once or thrice a week, depending on the randomisation, and then for two more visits after treatment.

Risk: Patients continue using their own medication during treatment with ARA 290 so the risk of a further rise of disease activity is not elevated compared to when patients would not participate in the investigation.
There are no known side effects of ARA 290. Patients could experience unknown side effects or have an allergic reaction.

Discomfort: iv treatment and venipunctures could cause bruising.

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 with active rheumatoid arthritis, classified by the ARA criteria (1987) aged 18+

Exclusion criteria

•Current treatment with biological agent or treatment with biological in the 2 months before inculsion.
•Clinically relevant abnormal laboratory results, ECG, vital signs, or physical findings other than conditions related to rheumatoid arthritis (as judged by the investigator)
•Pregnancy or wish to become pregnant during the study, or childbearing potential without adequate contraception
•Participation in an investigational drug trial, current or in the 3 months prior to administration of the initial dose of study drug or more than 4 times per year
•Use of erythropoietin
•Inability to follow the protocol and to comply with the follow up requirements
•Clinically relevant abnormal history of physical and mental health other than conditions related to rheumatoid arthritis, as determined by medical history taking (as judged by the investigator) or any other condition that in the opinion of the investigator would complicate or compromise the well being of the subject.
Current or previous TBC infection

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-07-2011
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	ARA290

Ethics review

Approved WMO Date:	20-12-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-03-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-023469-22-NL
CCMO	NL34245.058.10