Abatacept to Silence anti-Citrullinated protein Antibody-expressing B cells in Rheumatoid Arthritis

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To investigate the effect of CTLA4-Ig (abatacept) on phenotype, transcriptional profile, B cell receptor usage and functional parameters of circulating B cells expressing anti-citrullinated protein antibodies (ACPA) in patients with early,...

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

Summary

ID

NL-OMON50283

Source
ToetsingOnline

Brief title
ASCARA

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: Bristol-Myers Squibb,IMI (RTCure project)

Intervention

Keyword: Abatacept, ACPA, B cells, Rheumatoid arthritis

Outcome measures

Primary outcome

The primary endpoint is the percentage of ACPA-expressing B cells circulating

in peripheral blood of patients with early, ACPA-positive rheumatoid arthritis

that express the proliferative marker Ki-67 at the 24 week time point in the

two treatment arms.

Outcome measure for the primary endpoint: flow cytometry*based determination of

the percentage of ACPA-expressing B cells that stain positive for Ki-67.

Secondary outcome

The change from baseline in disease activity (expressed as DAS 44) at week 24.

Study description

Background summary

B cells expressing anti citrullinated protein antibodies (ACPA) in patients with rheumatoid arthritis display an activated, proliferative phenotype. Experimental data indicate that ACPA and ACPA-expressing B cells are actively involved in driving the disease process in rheumatoid arthritis . The present study is based on the hypothesis that targeted intervention with CTLA4-Ig (abatacept) as a means to interfere with T cell help for B cells in early, active, ACPA-positive rheumatoid arthritis can reverse the activated, proliferative phenotype of citrullinated antigen-specific B cells.

Study objective

To investigate the effect of CTLA4-Ig (abatacept) on phenotype, transcriptional profile, B cell receptor usage and functional parameters of circulating B cells expressing anti-citrullinated protein antibodies (ACPA) in patients with early, methotrexate-naïve, ACPA-positive rheumatoid arthritis.

Study design

Open-label, randomized, single center, two-arm, investigator-initiated, interventional clinical study.

Intervention

Patients will be randomized to treatment with either methotrexate monotherapy (10 * 25 mg once weekly) or a combination therapy of methotrexate (10 * 25 mg once weekly) and abatacept (125 mg subcutaneously once weekly) for 6 months, followed by methotrexate monotherapy (10 * 25 mg once weekly) in both groups for another 6 months.

Study burden and risks

The burden and risks of participation are related to the number of study site visits, the donation of blood samples, and to a vaccination against tetanus toxoid prior to study start. The study consists of seven study site visits within a period of one year (screening visit, tetanus vaccination visit, baseline visit (start of study medication), visit 2 (baseline + 12 weeks), visit 3 (baseline + 24 weeks), visit 4 (baseline + 36 weeks), visit 5 (baseline + 48 weeks)). At all visits except at the tetanus vaccination visit, participants will be assessed for disease activity and safety parameters (this includes a one-time mandatory screening for latent tuberculosis infection and hepatitis prior to the initiation of treatment with abatacept). At baseline and at all subsequent visits, peripheral blood will be collected to assess the primary, secondary and exploratory endpoints (for routine diagnostics: 20 mL of blood at the screening visit and at baseline throughout visit 5 (= 6 x 20 mL); for assessments of the endpoints: 100 mL of blood at baseline throughout visit 5 (= 5 x 100 mL); total volume for the entire study: 620 mL).

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

- have a diagnosis of rheumatoid arthritis according to the revised 2010 EULAR/ACR criteria for classification of RA
- have a positive test for the presence of anti-citrullinated protein antibodies (ACPA) in serum as determined by routine clinical assay.
- have adequate hematologic function (ANC * 4000 cells/µL, platelet count * 150000/µL, and hemoglobin * 10 g/dL (corresponding to 6.2 mmol/L)
- have serum creatinine concentrations < 1.5 mg/dl and/or a normal creatinine clearance
- be at least 18 years of age
- if a female patient is of childbearing potential, agree to: comply with effective contraceptive measures, use adequate contraception since the last menses, use adequate contraception during the study, have a negative pregnancy test within one week of study entry
- be willing to receive a booster vaccination against tetanus toxoid three to four weeks prior to randomization
- be able and willing to give written informed consent prior to entry in the study

Exclusion criteria

- been previously treated with either abatacept and/or methotrexate or another csDMARD
- been previously treated with a kinase inhibitor
- been previously treated with rituximab or another B-cell depleting agent
- been previously treated with a biological DMARD

- received intra-articular or systemic glucocorticoid injections or has required treatment for acute RA flare (not being part of a regular therapeutic regimen) within four weeks prior to randomization or requires narcotic analgesics other than those accepted by the investigator for analgesia (e.g. paracetamol, codeine, tramadol)
* been tested negative for anti citrullinated protein antibodies
* contraindications for a booster vaccination against tetanus toxoid prior to randomization to the treatment arms; if a patient refuses booster vaccination but has detectable numbers of tetanus toxoid-specific B cells circulating in peripheral blood prior to the baseline visit, the patient can still be allowed to participate in the study at the judgement of the investigator.
* evidence of any other major chronic inflammatory disease (i.e. psoriasis, psoriatic arthritis, spondyloarthritis or inflammatory bowel disease)
* evidence of poorly controlled diabetes, history of clinically significant pulmonary disease including interstitial lung disease or methotrexate-induced lung disease, poorly controlled asthma or a history of severe life-threatening asthma attacks, history of active tuberculosis, history of latent tuberculosis without adequate medical treatment, liver cirrhosis or fibrosis, significant active infection or any underlying diseases that could predispose the subject to infections
* liver function abnormality (total bilirubin * 1.5 x the upper limit of normal range, AST, ALT * 3 x upper limit of normal range)
* concurrent treatment with an experimental drug or who has participated in another clinical trial with an investigational drug within 30 days prior to study entry
* pre-existing sensory or motor polyneuropathy * Grade 2 according to NCI CTC
* past or current history of neoplasms, except for curatively treated non-melanoma skin cancer, adequately treated in situ carcinoma of the cervix or another cancer curatively treated and with no evidence of disease for at least 10 years
* significant cardiac disease, cardiac arrhythmia (Lown Grade * III), uncontrolled hypertension or recent history of myocardial ischemia
* Pregnant or nursing women

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2018
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orencia
Generic name:	Abatacept
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	12-09-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	07-02-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	15-09-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2017-002878-38-NL
CCMO	NL62584.058.17

Study results

Date completed:	06-04-2022
Actual enrolment:	46