Januse kinase Inhibition with Filgotinib to Silence Autoreactive B cells in Rheumatoid Arthritis

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To investigate the effect of filgotinib on phenotype, B cell receptor (BCR) usage and functional parameters of circulating B cells expressing ACPA in patients with ACPA-positive RA that show incomplete response to standard, medium-dose methotrexate...

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

Summary

ID

NL-OMON53878

Source
ToetsingOnline

Brief title
JAKAR

Condition

- Joint disorders

Synonym
Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Gilead Sciences

Intervention

Keyword: ACPA, B cells, Filgotinib, Rheumatoid arthritis

Outcome measures

Primary outcome

The primary endpoint is the change from baseline in the frequency of ACPA-expressing B cells secreting ACPA-IgG in ex-vivo PBMC cultures at the 24 week time-point compared between the two treatment arms.

Secondary outcome

The secondary objectives are designed to define the changes to the auto-reactive B cell compartment induced by filgotinib versus control treatment in relation to the clinical context and to define/elucidate the mode of action of filgotinib with regard to these changes.

Study description

Background summary

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

Study objective

To investigate the effect of filgotinib on phenotype, B cell receptor (BCR) usage and functional parameters of circulating B cells expressing ACPA in patients with ACPA-positive RA that show incomplete response to standard, medium-dose methotrexate (MTX) therapy.

Study design

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

Intervention

Patients will be randomized to treatment with either add-on adalimumab s.c. 40 mg biweekly for 24 weeks or add-on Filgotinib 200 mg p.o. once daily for 24 weeks. *Add-on* means that patients will continue taking methotrexate at a dose of 7.5 - 15 mg once weekly, to which either adalimumab or Filgotinib is added.

Study burden and risks

The burden and risks of participation are related to the number of study site visits and the donation of blood samples. The study consists of five study site visits within a period of 24 weeks (screening visit, baseline visit (start of study medication), visit 2 (baseline + 12 weeks), visit 3 (baseline + 24 weeks)). At all visits participants will be assessed for disease activity and safety parameters (this includes a one-time mandatory screening for latent tuberculosis infection and hepatitis B/C infection prior to the initiation of treatment). 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 3 (= 3 x 20 mL); for assessments of the endpoints: 110 mL of blood at baseline throughout visit 3 (= 3 x 110 mL); total volume for the entire study: 390mL).

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria. Each patient must:
- have a diagnosis of RA and must have fulfilled the revised 2010 EULAR/ACR criteria for classification of RA prior to initiation of first-line treatment.
- have a positive test for the presence of anti-citrullinated protein antibodies (ACPA) in serum with a value of at least 200 U/ml, as determined by routine clinical assay.
- have moderate to highly active disease defined by a disease activity score evaluating 28 joints (DAS28) >= 3.2 or, correspondingly, an sDAI score of > 11.
- have used methotrexate therapy at a maximally tolerated dose once weekly for at least 1 month; concomitant glucocorticoid therapy is allowed if at a stable dose of <= 7.5 mg prednisolon equivalent within 30 days prior to entry in the study.
- have adequate hematologic function (ANC >= 4000 cells/µL, platelet count >= 150000/µL, and haemoglobin >= 10 g/dL (corresponding to 6.2 mmol/L)
- have a serum creatinine clearance of >15 ml/min
- be at least 18 years of age
- if female and of childbearing potential, agree to: comply with effective contraceptive measures, use adequate contraception since the last menses and use adequate contraception during the study
- be willing to undergo pre-treatment screening for latent tuberculosis infection by chest X-ray and Mantoux testing as well as serological screening for chronic viral hepatitis infection. As an alternative for the Mantoux test, a standardized IFN-gamma release assay may be used to assess latent tuberculosis infection.
- be able and willing to give written informed consent prior to entry in the study.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study. Any patient who:
- has ever been treated with rituximab or another B-cell depleting agent
- has been treated with a biological DMARD (except rituximab) or a targeted synthetic DMARD within 3 months prior to entry in the study
- has received intra-articular or systemic glucocorticoid injections within 30 days prior to baseline or requires narcotic analgesics other than those accepted by the investigator for analgesia (e.g. paracetamol, NSAIDs, codeine, tramadol)
* has been tested negative for ACPA
* is in clinical remission as defined by a disease activity score evaluating 28 joints (DAS28) <= 2.6 or, correspondingly, an sDAI <= 3.3
* has evidence of a medical condition which represents a contra-indication for initiation of either a TNF-alpha inhibitor or a Janus kinase inhibitor, as outlined in the most recent SPCs of either adalimumab and/or Filgotinib.
* has liver function abnormality (AST and/or ALT >= 3 x upper limit of normal range)
* has 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
* has past or current history of solid or haematological 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
* is pregnant or a currently nursing woman
* is, female and of childbearing potential, unwilling to use adequate contraceptive measures during the study

Study design

Design

Study phase:	4
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):	06-03-2023
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hyrimoz
Generic name:	Adalimumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Jyseleca
Generic name:	Filgotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-12-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	01-09-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	05-06-2023

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2021-006007-15-NL
CCMO	NL79681.058.21
Other	pending