PRACTICAL study: Pharmaco-enhancement in Rheumatoid Arthritis with Cobicistat to dose Tofacitinib In Clinic Adequately Low. A within-subject sequential study.

Published: 18-12-2018
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The aim of this study is to investigate the use of cobicistat to reduce the required dose and dose frequency of tofacitinib in the treatment of RA.

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

Summary

ID

NL-OMON48994

Source
ToetsingOnline

Brief title
PRACTICAL

Condition

- Autoimmune disorders
- Joint disorders

Synonym
chronic inflammation of the joints, psoriatic arthritis, Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Subsidie van VGZ: betaalbaar beter project

Intervention

Keyword: Dose reduction, Psoriatic Arthritis, Rheumatoid Arthritis, Tofacitinib

Outcome measures

Primary outcome

To investigate the bioequivalence of tofacitinib 5mg and cobicistat 150 mg QD (intervention) compared to tofacitinib 5mg BID alone (control) with regard to the relevant steady state pharmacokinetic parameters (average concentration at steady state (Cavg,ss)/Area Under the Curve (AUC0-24), as defined by a 90% confidence interval of the geometric mean ratio falling entirely between 75% and 125%.

Secondary outcome

* To construct a mechanistic population pharmacokinetic model describing the quantitative effect of cobicistat on tofacitinib pharmacokinetics;
* To describe the relevant pharmacokinetic parameters (Cavg,ss, AUC0-24, Cmax,ss, tmax,ss, Ctrough and t1/2) after administration of tofacitinib 5mg and cobicistat 150 mg QD compared to tofacitinib 5mg BID alone;
* To evaluate the safety and tolerability of tofacitinib 5mg and cobicistat 150 mg QD compared to tofacitinib 5mg BID alone;
* To provide a suitable dosing scheme of tofacitinib and cobicistat for a future clinical non-inferiority study, based on the developed pharmacokinetic model, in case tofacitinib 5mg and cobicistat 150 mg QD is not equivalent to

tofacitinib 5mg BID alone in this study;

* To evaluate the efficacy of both regimes by DAS28-CRP;

* To establish which regimen is preferred by patients based on medication QD or

BID.

Study description

Background summary

Tofacitinib is a relatively new drug for treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA), which appears to have at least similar efficacy and safety as currently available biological disease modifying anti-rheumatic drugs (bDMARD), though it has directly been compared to adalimumab only. As the yearly costs per patient of tofacitinib treatment at the 5mg BID dose are significant (approximately ¤12,000 per patient per year), interventions that might reduce this cost are of interest in order to keep health care costs in control.
Because tofacitinib is mainly metabolized by CYP3A4, the manufacturer recommends halving the dose of tofacitinib from 5mg BID to 5mg QD in patients using concomitant medication which strongly inhibits CYP3A4 in order to maintain a similar drug concentration and safety. This creates the opportunity to halve the required dose (and thus cost) of tofacitinib, by deliberately adding a CYP3A4 inhibitor to tofacitinib treatment. One such CYP3A4 inhibitor is cobicistat, which is already registered as a pharmacokinetic enhancer (or booster) in the EU and used for this purpose in human immunodeficiency virus (HIV) treatment without significant adverse events.
Besides the obvious benefit of lower costs, halving the dose may also improve medication adherence as only one dose per day is required (versus BID without a booster) and medication adherence is negatively associated with dosing frequency. Furthermore, CYP3A4 inhibition will lead to more predictable pharmacokinetics of tofacitinib as natural variation in CYP3A4 activity is reduced. This has the potential for an improved safety/efficacy ratio.

Study objective

The aim of this study is to investigate the use of cobicistat to reduce the required dose and dose frequency of tofacitinib in the treatment of RA.

Study design

We will perform an open-label, within-subject sequential trial of tofacitinib

where patients meeting eligibility criteria receiving tofacitinib 5mg BID will switch to the combination of tofacitinib 5mg combined with cobicistat 150mg QD during 2 -6 weeks.

Intervention

Reference treatment
All patients are using the conventional dose of tofacitinib which is tofacitinib 5mg BID orally.

Intervention treatment
For 2-6 weeks, patients will switch to tofacitinib 5mg orally together with 150mg cobicistat orally QD.

Study burden and risks

The risks associated with this study are limited. It is plausible and in accorcance with the SPC that the dosage of tofacitinib can be reduced when its metabolization is inhibited by cobicistat. Possible risks are adverse effects related cobicistat treatment and possible interactions with other medications. The burden for patients participating in this study is mainly time-investment associated with the study visits and the number of blood samples.

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

* Rheumatoid arthritis (either 2010 ACR RA and/or 1987 RA criteria and/or clinical diagnosis of the treating rheumatologist, fulfilled at any time point between start of the disease and inclusion) or Psoriatic arthritis (either Classification Criteria for Psoriatic Arthritis (CASPAR) and/or diagnosed with peripheral SpA of the psoriatic arthritis subtype by a rheumatologist)
* Patients using tofacitinib for * 2 weeks in the standard dose of 5mg BID.
* Patient informed consent, *18 years old and mentally competent
* Ability to measure the outcome of the study in this patient (e.g. patient availability; willing and being able to undergo repeated serum samples)
* Ability to read and communicate well in Dutch

Exclusion criteria

* Concomitant use of inducers or potent inhibitors of CYP3A4 or moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19, or medication sensitive to changes in metabolism as a result of cobicistat co-treatment, as assessed with the KNMP *G-standaard* unless an alternative is listed in Table 1.
* Known contra-indications for treatment with cobicistat in line with the summary of product characteristics

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):	16-09-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tybost
Generic name:	Cobicistat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	18-12-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	07-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	04-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	06-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	09-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26019
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-000766-11-NL
CCMO	NL65634.091.18
Other	NL7766
OMON	NL-OMON26019

Study results

Date completed:	09-03-2021
Actual enrolment:	30

Summary results

Trial is onging in other countries