A clinical outcomes study to evaluate the effects of IL-6 receptor blockade with tocilizumab (TCZ) in comparison with etanercept (ETA) on the rate of cardiovascular events in patients with moderate to severe rheumatoid arthritis (RA).

Published: 05-07-2011
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Primary ObjectiveThe primary objective of this study is to compare prospectively in patients treated with TCZ or etanercept (ETA), the time to first occurrence of any component of a composite of major adverse cardiovascular events (MACE) consisting...

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

Summary

ID

NL-OMON39743

Source
ToetsingOnline

Brief title
ENTRACTE

Condition

- Myocardial disorders
- Autoimmune disorders

Synonym

inflammation of the synovium in joints, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Roche

Intervention

Keyword: cardiovascular events, etanercept (ETA), rheumatoid arthritis (RA), tocilizumab (TCZ)

Outcome measures

Primary outcome

This event-driven study will continue until 131 adjudicated endpoint events

have been confirmed. The end of data collection for the study will occur when

the last patient, last visit (LPLV) occurs. The LPLV is either the date of the

last patient visit, or the date at which the last data point from the last

patient, which is required for statistical analysis, is received, whichever is

the later date.

Secondary outcome

NA

Study description

Background summary

Cardiovascular disease is a leading cause of death in patients with rheumatoid arthritis (RA), with heart attacks and strokes occurring more often and at an earlier age in patients with RA than those who do not have RA.
Effective RA treatment may reduce the risk of having a heart attack or stroke.
Tocilizumab and etanercept are two medications that are already approved for the treatment of patients with RA.

In earlier clinical studies of tocilizumab, patients initially experienced an increase in cholesterol that stabilized over time.
It is not known if long-term treatment with tocilizumab affects the occurrence of cardiovascular-related illnesses. This will be the first controlled study of a medication for RA that will look at the effect of treatment of disease and cholesterol levels on the risk of cardiovascular illness.
The ENTRACTE Study will compare the effects of tocilizumab with etanercept on the occurrence of cardiovascular illnesses, including heart attacks, strokes, and death related to cardiovascular disease.
The study will last for at least 5 years and approximately 2800 patients worldwide will take part.
If you take part in the ENTRACTE Study, you will be given either tocilizumab or etanercept.

Study objective

Primary Objective
The primary objective of this study is to compare prospectively in patients treated with TCZ or etanercept (ETA), the time to first occurrence of any component of a composite of major adverse cardiovascular events (MACE) consisting of:

Cardiovascular death
Non-fatal myocardial infarction
Non-fatal stroke of all classifications (ischemic, hemorrhagic, or undetermined origin)

The criteria and complete definition for CV events is taken from the guidance entitled, *Standardized Definitions for End Point Events in Cardiovascular Trials* (October 20, 2010) issued by The Standardized Data Collection for Cardiovascular Trials Initiative Working Group. All endpoint events will be adjudicated by an independent cardiovascular events adjudication committee (CV-EAC).

Secondary Objective
The secondary objective of this study is to investigate the effects of TCZ compared to ETA on:
The time to first occurrence of an expanded composite endpoint, defined as the cardiovascular composite of the primary endpoint with the additional of non-elective coronary revascularization procedures and hospitalization for unstable angina.
Each of the individual components of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke of all classifications (including stroke of ischemic, hemorrhagic, and undetermined origin).

Exploratory Objectives
The exploratory objectives of this study are:

To assess the potential impact of lipid levels and CRP on cardiovascular risk as well as the potential contribution of concomitant lipid lowering agents in modifying risk.
To assess the incidence of heart failure requiring hospitalization in patients treated with TCZ as compared with ETA.

Study design

This is a 2-arm, randomized, open-label, parallel-group, multi-center trial in patients with a diagnosis of moderate to severe rheumatoid arthritis.

Patients will be stratified by the following criteria:
Previous exposure to an anti-TNF therapy
History of CV event as defined in the study primary objectives or the presence of clinical atherosclerotic disease defined by at least one of the following:
Clinical CHD
Symptomatic carotid artery disease
Peripheral arterial disease
Abdominal aortic aneurysm.

Intervention

Patients will be randomized to either TCZ or ETA:
TCZ 8 mg/kg IV with or without non-biologic DMARD given every 4 weeks.
OR
ETA 50 mg weekly, injected subcutaneously (SC) with or without non-biologic DMARD

Once randomized, patients assigned to TCZ study treatment will receive monthly IV infusions from the study staff. Patients randomized to ETA will be allowed to self-administer their weekly SC injections once they are trained by the study staff.

Patients may switch to another RA therapy during the study at the discretion of the investigator. However, patients randomized to ETA are prohibited from switching to commercial TCZ for 3 years after the time of randomization.

All patients who are actively participating in the study are assessed for CV endpoint events monthly for the duration of the study regardless of treatment.

Patients who wish to no longer actively participate in scheduled study visits but wish to remain in the trial will be re-consented for annual phone follow-up for CV events. These patients will no longer receive study drug.

Study burden and risks

The study drug and procedures may have risks, cause discomforts, or be inconvenient. See the patient information for known risks and discomforts for both treatment arms.

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

1. Patients with RA of > 6 months duration at the time of the baseline visit. RA must be diagnosed according to the revised 1987 American College of Rheumatology (ACR; formerly American Rheumatism Association) criteria (Appendix 3)
2. Inadequate response to at least one non-biologic DMARD
3. Have a CRP > 0.3 mg/dL at screening or at the baseline visit
4. Receiving treatment on an outpatient basis
5. Swollen joint count (SJC) * 8 (66 joint count) and tender joint count (TJC) * 8 (68 joint

count) during screening or at the baseline visit.
6. Males and females, age * 50 years
7. Presence of one or more additional Coronary Heart Disease (CHD) risk factor including:
* Cigarette smoking (current)
* Hypertension (BP ><=140/90 mm Hg or on antihypertensive medication)
* Low HDL cholesterol (HDL <50 mg/dL for women; HDL <40 mg/dL for men)
* Family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age)
* Diabetes
* Presence of extra-articular disease associated with RA (e.g., rheumatoid nodules, secondary Sjogren's syndrome, serositis, rheumatoid lung disease/ interstitial lung disease, vasculitis, inflammatory peripheral neuropathy, or scleritis/ episcleritis) ;* History of at least one of the following:
o Myocardial infarction
o Stroke of atherothrombotic origin
o Coronary revascularization procedure
o Hospitalization for unstable angina
* The presence of at least one of the following clinical atherosclerotic diseases that confers high risk for coronary heart disease (CHD) events:
o Clinical CHD
o Symptomatic carotid artery disease
o Peripheral arterial disease
o Abdominal aortic aneurysm;8. At the time of randomization, will have discontinued:
* infliximab, adalimumab, golimumab, or certolizumab for * 4 weeks

Exclusion criteria

1. Major surgery (including joint surgery or coronary revascularization) within eight weeks prior to screening or planned major surgery within one year of baseline
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), Mixed Connective Tissue Disease (MCTD), scleroderma or variants, and polymyositis. Patients with systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis) and secondary Sjögren*s syndrome, and/or nodulosis with RA are permitted (see Inclusion #7). Patients with Felty*s syndrome are not permitted
3. History of or current inflammatory joint disease other than RA (e.g., tophaceous gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease, pseudogout, arthropathy of inflammatory bowel disease)
4. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
5. Current or recent (within the past 3 months) evidence of serious uncontrolled concomitant cardiovascular or cerebrovascular disease (MI, revascularization, ischemic stroke, transient ischemic attack, or acute coronary syndrome)
6. Current or previous (within the past 2 years) evidence of serious uncontrolled concomitant pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including

uncontrolled diabetes mellitus) or gastrointestinal disease.

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):	18-04-2012
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enbrel
Generic name:	Etanercept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	RoActemra
Generic name:	Tocilizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-07-2011
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	31-08-2011
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	17-10-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	09-11-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	16-12-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	30-01-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	15-02-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO	

Date:	11-04-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	23-05-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	21-06-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	18-09-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO	

Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2010-020065-24-NL
ClinicalTrials.gov	NCT01331837
CCMO	NL36154.048.11