Mechanism of action study of Ustekinumab treatment in psoriatic arthritis:
Impact on cellular and molecular pathways of synovial inflammation and tissue remodeling

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ObjectivePlease describe:• the specific goal to be reached by the study• the hypothesis to be answered by the studyThe overall aim of the study is to determine which downstream cellular and molecular pathways involved in PsA pathogenesis are...

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

Summary

ID

NL-OMON47065

Source
ToetsingOnline

Brief title
MoA-Ustekinumab

Condition

- Autoimmune disorders
- Joint disorders

Synonym
psoriatic arthritis, psoriatic arthropathy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: collectebussen,Janssen-Cilag

Intervention

Keyword: Mechanism of action, Psoriatic arthritis, Synovial biopsies, Ustekinumab therapy

Outcome measures

Primary outcome

- changes in the synovial cellular and molecular pathways as indicated in the

objectives between baseline and week 12/24.

Secondary outcome

- Stratification of these cellular and molecular changes according to the

genetic biomarkers of relevance for ustekinumab treatment response

- Correlation between the synovial features at baseline and the clinical

response at week 12/24.

- Comparison between the synovial features at baseline and the clinical

response at week 12/24.

- Comparison of the synovial molecular changes induced by ustekinumab therapy

with the changes induced by anti-TNF (historical samples in a similar patient

population and study setting)

Study description

Background summary

Psoriatic arthritis is an inflammatory arthritis and can presents with arthritis, axial disease, psoriatic skin and nail lesions, dactylitis and enthesitis. The prevalence of active psoriatic lesions in PsA patients is reported between 6-48%. Current treatment consists primarily of disease-modifying anti-rheumatic drugs, despite lack of large evidence for clinical benefit and as a second line treatment TNF-inhibitors with a well proven efficacy in psoriatic arthritis. TNF blockade has a major impact on signs and symptoms of PsA but:
1. only 50% of the patients respond well and tolerate the treatment
2. TNF blockade does not induce long-lasting remission as almost all patients relapse within a few week after interruption of the treatment
3. TNF blockade does not halt the structural damage
There is thus a high unmet medical need for alternatives for TNF blockade in this disease.

Based on the role of IL-17/IL23 in various inflammatory and autoimmune models various biological drug against IL17 and IL23 are currently in clinical development. Ustekinumab, a monoclonal antibody against p40, has proven efficacy and safety in plaque psoriasis and is approved and reimbursed for this indication. An early phase II study by Gottlieb et al (lancet 2009) indicated clinical benefit of this drug in PsA. More recently, the large phase III Psummit I and Psummit II trials confirmed the efficacy and safety of ustekinumab in PsA (McInnes et al, Lancet 2013). Ustekinumab significantly improved psoriatic arthritis symptoms including skin lesions and ACR20 response (50 v.s. 12 in placebo) and was well tolerated. 1 year results show that the treated patients maintained a better clinical improvement compared with placebo and the treatment had a good safety profile. Based on these data, ustekinumab is the first non-TNFi biological to be approved for treatment of PsA and is expected to be soon reimbursed in many European countries, including the Netherlands.

Besides the obvious clinical issues which need to be further addressed in phase III and/or phase IV trials, these observations raise the question which down-stream cellular and molecular pathways involved in PsA pathogenesis are affected by p40 blockade. This includes the inflammatory pathways and, specifically, the quantitative and qualitative impact of the treatment on the IL-17 producing cells and the overall cytokine milieu. An additional point of interest, however, is the stromal remodelling and osteoproliferation leading to new bone formation, as this process does not seem to be significantly modulated by other treatments (in particular TNF blockers) and thus represents an important unmet medical need in SpA/PsA management. Recent studies have yielded new insights on the potential mechanisms of structural remodelling in SpA, focusing mainly on BMP and Wnt signalling. Additionally, we have recently identified a unique stromal cell signature in SpA synovitis and have related this to the presence of a specific remodelling cell population in the target

tissues (Yeremenko et al, Arthritis Rheum 2012). Whether this cell population is directly involved in ankylosis or is a surrogate marker for this process is currently under investigation. Of relevance for the present proposal, the stromal cell signature is not significantly modulated by TNF blockade.

This MoA study aims to provide insights in the depth and width of the immunomodulation by IL-23/12 p40 blockade by assessing the impact on molecular pathways of disease, including but not restricted to cytokine production, in the primary target tissue. These data are relevant to support clinical efficacy as well as safety data. Moreover, it will teach us whether IL-23/12 p40 blockade has any impact on important pathways of structural remodeling in PsA. If the case, this may point to a unique feature of IL-23/12 p40 blockade over established treatments which warrants further long-term imaging studies on new bone formation. Finally, an unbiased gene expression analysis will allow us to determine the specific molecular profiles of IL-23/12 p40 blockade versus TNF blockade and may thereby help to identify novel biomarkers for tailored therapy.

Study objective

Objective
Please describe:
• the specific goal to be reached by the study
• the hypothesis to be answered by the study

The overall aim of the study is to determine which downstream cellular and molecular pathways involved in PsA pathogenesis are modulated by IL23/12 P40 blockade. As we have ample evidence that relevant disease-specific pathways are found in the primary target tissues, in particular in synovial tissue obtained from peripheral joints, but not in peripheral blood, we will strongly focus on this compartment by obtaining paired biopsies before and after treatment.

The primary objective is to assess the effect of IL23/12 P40 blockade on:
- the global synovial histology and inflammatory infiltration
- the number and type of IL-17 producing cells in PsA synovitis
- the synovial stromal cell signature
- the pan-genomic synovial gene expression profile

The secondary objective is to compare which molecular disease pathways are affected by IL23/12 P40 blockade and not by TNF blockade and thereby identify molecular biomarkers which may help to determine which patients may benefit from this treatment in comparison with anti-TNF treatment.

Study design

Non-interventional, open-label, phase IV study in which patients receiving

ustekinumab treatment from their own treating physician will be monitored for 24 weeks, including synovial biopsies and paired peripheral blood withdrawal at week 0,12 and 24. Effectiveness/mechanism of action will be measured by determination of different parameters as described in section *efficacy and effectiveness assessments*. Safety will be monitored by adverse events reporting and routine hematology and chemistry variables at visits including bloodwithdrawal.

The study will primarily be conducted in the Academic Medical Center/University of Amsterdam (Prof. Baeten).

Study burden and risks

low risk

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Psoriatic artrhritis according to the CASPAR criteria
Active disease defined as SJC/TJC of 3 or more
Presence of knee and/or ankle arthritis in order to get synovial tissue biopsies
Is going to receive ustekinumab treatment for his/her psoriatic artrhitis

Exclusion criteria

- Previous use of ustekinumab, il17blocking therapy or multiple TNF blocking therapy use
- Contra-indication for needle arthroscopy such as joint replacement surgery and anti-coagulation use (that can not be temporarily stopped)

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-12-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	stelara
Generic name:	ustekinumab

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-003148-11-NL
CCMO	NL50218.018.14