Studie naar het werkingsmechanisme van ustekinumab in artritis psoriatica: de impact op cellulaire en moleculaire mechanismes in synoviale inflammatie en tissue-remodelling.

Gepubliceerd: 26-01-2015 Laatst bijgewerkt: 22-04-2024

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...

Ethische beoordeling	Goedgekeurd WMO
Status	Werving gestopt
Type aandoening	Auto-immuunziekten
Onderzoekstype	Observationeel onderzoek, met invasieve metingen

Samenvatting

ID

NL-OMON47065

Bron
ToetsingOnline

Verkorte titel
MoA-Ustekinumab

Aandoening

- Auto-immuunziekten
- Gewrichtsaandoeningen

Synoniemen aandoening
artritis psoriatica, psoriasis arthropatica

Betreft onderzoek met
Mensen

Ondersteuning

Primaire sponsor: Academisch Medisch Centrum
Overige ondersteuning: collectebussen,Janssen-Cilag

Onderzoeksproduct en/of interventie

Trefwoord: Artritis psoriatica, Synoviale biopten, Ustekinumab therapie, Werkingsmechanisme

Uitkomstmaten

Primaire uitkomstmaten

Veranderingen in synoviale, cellulaire en moleculaire pathways zoals beschreven

in de objectives, tussen baseline en week 12/24.

Secundaire uitkomstmaten

- veranderingen van cullulaire en moleculaire pathways relateren aan genetische

biomarkers relevant in de anti-IL12/23 respons

- correlatie tussen synoviale kenmerken tussen baseline en de klinische respons

op week 12/24

- vergelijking van de moleculaire veranderingen van het synovium geinduceerd

door anti-IL12/23 therapie met de veranderingen geinduceerd door anti-TNF

therapie (in historische samples, in een vergelijkbare patienten populatie en

studieopzet)

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksopzet

Non-interventional, open-label, phase IV studie, waarin patienten die ustekinumab gaan krijgen via de polikliniek voor 24 weken klinisch worden gemonitord en waarbij op 3 tijdspunten (week 0,12 en 24) een mini-artroscopie wordt verricht voor het verkrijgen van synoviale biopten.
Effectiviteit/mechanism of action wordt gemeten middels verschillende parameters, uitgebreid toegelicht in sectie *efficacy and effectiveness

assessments*.
Veiligheid wordt gemonitord door het evalueren en rapporteren van Adverse events en routine lab tijdens de visites.

Inschatting van belasting en risico

Laag risico. Het betreft bloedafnames en mini-artroscopien met een klein risico op bijwerkingen.

Contactpersonen

Publiek

Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Wetenschappelijk

Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Locaties

Landen waar het onderzoek wordt uitgevoerd

Netherlands

Deelname eisen

Leeftijd
Volwassenen (18-64 jaar)
65 jaar en ouder

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Artritis psoriatica volgens de CASPAR criteria
- Actieve ziekte, gedefinieerd als minimaal 3 gezwollen en pijnlijke gewrichten
- Minimaal 1 gezwollen knie of enkel ivm de mini-artroscopie
- Krijgt ustekinumab voorgeschreven voor deze indicatie van eigen behandelend arts

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- eerder gebruik van anti-IL17/ustekinumab of multipele anti-TNF therapien
- contra indicaties voor een artroscopie zoals gewrichtsprothese en anti-stolling therapie waar geen overbrugging bij is toegestaan

Onderzoeksopzet

Opzet

Fase onderzoek:	4
Type:	Observationeel onderzoek, met invasieve metingen
Blindering:	Open / niet geblindeerd
Controle:	Geen controle groep
Doel:	Behandeling / therapie

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	08-12-2015
Aantal proefpersonen:	16
Type:	Werkelijke startdatum

In onderzoek gebruikte producten en hulpmiddelen

Soort:	Geneesmiddel
Merknaam:	stelara

Generieke naam:	ustekinumab
Registratie:	Geregistreerd voor de te bestuderen indicatie/dosering

Ethische beoordeling

Goedgekeurd WMO Datum:	26-01-2015
Soort:	Eerste indiening
Toetsingscommissie:	METC Amsterdam UMC
Goedgekeurd WMO Datum:	29-01-2015
Soort:	Eerste indiening
Toetsingscommissie:	METC Amsterdam UMC
Goedgekeurd WMO Datum:	18-01-2016
Soort:	Amendement
Toetsingscommissie:	METC Amsterdam UMC
Goedgekeurd WMO Datum:	12-07-2016
Soort:	Amendement
Toetsingscommissie:	METC Amsterdam UMC
Goedgekeurd WMO Datum:	13-03-2018
Soort:	Amendement
Toetsingscommissie:	METC Amsterdam UMC

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
EudraCT	EUCTR2014-003148-11-NL
CCMO	NL50218.018.14