Early phase development of antibodies against biologicals in rheumatoid arthritis patients

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON25457

Bron
NTR

Verkorte titel
Early ADA

Aandoening

Rheumatoid arthritis
Anti-drug antibodies
Biologicals
Reumatoide artritis
Antistoffen
Biologicals

Ondersteuning

Primaire sponsor: Academisch Medisch Centrum
Overige ondersteuning: ABIRISK

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Immunization of anti-drug specific B cells against the BP defined by the presence of ADAb within the first 3 months Study parameter: different variables will be evaluated; these techniques are still partly under construction. It involves serological, cellular, immunological and genetic markers.

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

The introduction of biopharmaceuticals (BP) has been a critical step forward in care for RA and 10 BP are now licensed for the treatment of RA. In spite of this progress, failure of response to BP is frequent and in most of the registries, less than 50 % of patients are still on drug at 5 years. These failures may be primary failures or secondary failures. The fact is that the low level of responses becomes insufficient compared to the expectations. One of the main potential causes of these failures of BP therapy response is the development of ADAb in some patients. ADAb may decrease the efficacy of BPs by neutralizing them or modifying their clearance and they may be associated with BP-specific hypersensitivity reactions. The prediction, prevention and cure of anti-drug (AD) immunization are thus major goals in BP development. Humoral response against an antigen begins with a short-term massive antibody production and continues with the development of long term memory immunogenicity. Antibody-secreting plasmablasts can be detected in peripheral blood only for a few days (5 to 10) after antigen encounter. They circulate in transit to the bone marrow where they become long-living memory B cells. Thanks to the process of affinity maturation, memory B cells are much more specific and efficient in recognizing the antigen compared to plasmablasts. As a consequence, at a second encounter with the antigen, the antibody response driven by memory B cells is faster, stronger and more specific. It has been shown that memory B cell generated against an antigen can be clonally related to plasmablasts found in the peripheral blood few days after the encounter with that antigen on the base of their B cell receptor (BCR) sequence. By analyzing the mutations that occurred in the plasmablast BCR sequence compared to the memory B cell BCR sequence, it is also possible to follow the process of affinity maturation. The same has been proven to be true the other way around: plasmablasts generated during a secondary humoral response can be clonally related to memory B cell found before the second encounter with the antigen. In order to develop a (early) predictive tool for immunogenicity, it is necessary to know which are the earliest markers of immunogenicity and how immunogenicity then evolves. By sequencing

the BCRs of anti-drug specific plasmablast and memory B cell that form after the biological infusion, we can identify some peculiar common traits that characterize biologicals immunogenicity. Based on these common immunogenicity trait, we could eventually be able to predict unresponsive patients before starting the treatment or at least, after the first biological infusion. This prospective study will assess the occurrence of early humoral responses and ADAb formation using newly developed assay(s) in RA patients treated with any of the BP treatments, to address the mechanism of early immunogenicity. Patient-related factors that might predispose an individual to an immune response will be taken into account: underlying disease, genetic background, immune status, including immunomodulating therapy and dosing schedule. Thus, novel approaches to characterize anti-drug lymphocytes responses will be tested in patient materials (DNA, RNA, serum, PBMC). The objectives are to understand the early cellular mechanisms causing AD responses that might predispose an individual to an immune response.

Objective of the study:

PRIMARY OBJECTIVE To identify the cellular mechanism behind early antidrug antibody (ADAb) production related to humoral responses within first 3 months of BP treatment. SECONDARY OBJECTIVES - To identify the affinity maturation process in ADAb specific plasmablasts and memory B cell - To identify cellular biomarkers associated with the development of ADAb at any time of treatment

Study design:

Prospective cohort study in patients with rheumatoid arthritis (RA). The total duration of study is 4 years, its include 36 months for inclusion period and 12 months for duration of patient participation STUDY DURATION FOR EACH PATIENT Sampling period(s) will be the same for all BPs 1. M0/W0/D0 (Baseline) 2. W1 ± 1D 3. W2 ± 1D 4. M1/W4 ± 2D 5. M3/W12 ± 2W 6. M6/W26 ± 2W 7. M12/W52 ± 4W - End-of-study : At W48-W56 after all the scheduled study procedures (e.g. blood sampling) and after agreement by the investigator or sub-investigator - Total study participation : 48 to 56 weeks The study will be considered completed for a patient at the time he/she completes all the scheduled study procedures.

Study population:

- Male and female patients of more than 18 years old diagnosed with rheumatoid arthritis according to 2010 ACR/EULAR criteria - Patient for whom the Treating Physician has decided to prescribe a BP in the usual manner in accordance with the terms of the marketing authorization and independently from entry into this study. - Having given written informed consent prior to undertaking any study-related procedures. - Covered by a health insurance

system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research. The rate of immunization against BP is comprised between 15 and 50%. For instance, recent studies found that the rate of ADAb against adalimumab was about 30%, most of this ADAb being present at M12. The rate of immunization differs with the different drugs and is probably lower with etanercept. However we cannot exclude this very low rate of immunization against etanercept might be linked to the absence of current validated assay for detecting it. Thus, in some registries the maintenance of treatment with etanercept is longer than with other anti-TNFs and in others, the treatment duration with etanercept is similar than others anti-TNFs treatment. Moreover, the serum blood level of etanercept may decrease after several months of treatment, as it is the case with other anti-TNFs. In the present study, the goal is to have at least 10 patients ADAb+ at M12 for each of the BPs. Based on an approximate 30% rate of ADAb+ patients at M12 the estimated number of patients to be included in the study is 35 patients per drug. Based on approximate 15% rate of ADAb+ patients at M12 when treated with etanercept, the estimated number of patients to be included in the study is 70 patients for etanercept.

Primary study parameters/outcome of the study:

Primary endpoint: Immunization of anti-drug specific B cells against the BP defined by the presence of ADAb within the first 3 months Study parameter: different variables will be evaluated; these techniques are still partly under construction. It involves serological, cellular, immunological and genetic markers.

Secundary study parameters/outcome of the study

Secondary endpoint: - B cell receptor (BCR) repertoire analysis of anti-drug specific B cells - Fingerprint of anti-drug specific B cell clones and clonal evolution over time - Characterization of anti-drug specific B cell clones (phenotype and receptor characteristic) - Quantification of ADAb at W0, W1, W2, M1, M3, M6 and M12 - Drug levels Study parameter: different variables will be evaluated; these techniques are still partly under construction. It involves serological, cellular, immunological and genetic markers.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Since the BP therapy will be prescribed by the Treating Physician this study is not an intervention trail. Therefore, the pre-screening of patients for administration of BP therapy and safety follow-up will be done according to national guidelines for BP’s. This will be the responsibility of the Treating Physician. The procedures of this study are; 1. gathering clinical data 2. drawing of blood for further analysis Blood drawing has a relatively low risk of

adverse reactions. Due to the fact that this study is accompanied with a small risk of adverse reactions we do not expect serious adverse reactions to occur.

Doel van het onderzoek

The introduction of biopharmaceuticals (BP) has been a critical step forward in care for RA and 10 BP are now licensed for the treatment of RA. In spite of this progress, failure of response to BP is frequent and in most of the registries, less than 50 % of patients are still on drug at 5 years. These failures may be primary failures or secondary failures. The fact is that the low level of responses becomes insufficient compared to the expectations. One of the main potential causes of these failures of BP therapy response is the development of ADAb in some patients. ADAb may decrease the efficacy of BPs by neutralizing them or modifying their clearance and they may be associated with BP-specific hypersensitivity reactions. The prediction, prevention and cure of anti-drug (AD) immunization are thus major goals in BP development.

This prospective study will assess the occurrence of early humoral responses and ADAb formation using newly developed assay(s) in RA patients treated with any of the BP treatments, to address the mechanism of early immunogenicity.

Onderzoeksopzet

o-1-2-4 weeks, 3-6-12 months

Onderzoeksproduct en/of interventie

none

Contactpersonen

Publiek

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Male and female patients of more than 18 years old diagnosed with rheumatoid arthritis according to 2010 ACR/EULAR criteria - Patient for whom the Treating Physician has decided to prescribe a BP in the usual manner in accordance with the terms of the marketing authorization and independently from entry into this study. - Having given written informed consent prior to undertaking any study-related procedures. - Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Received treatment with the same BP before (use of other BP previously is allowed). - Included in another study protocol. - Under any administrative or legal supervision. - Conditions/situations such as: • Patients with conditions/concomitant diseases making them non evaluable for the primary endpoint • Impossibility to meet specific protocol requirements (e.g. blood sampling) • Patient is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol • Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Blindering:	Open / niet geblindeerd

Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	21-04-2016
Aantal proefpersonen:	280
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	20-10-2016
Soort:	Eerste indiening

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
NTR-new	NL6047
NTR-old	NTR6186
Ander register	MEC AMC Amsterdam : METC 2015_325

Resultaten