Research with the drug tofacitinib for patients with refractory celiac disease type II

Gepubliceerd: 13-09-2018 Laatst bijgewerkt: 15-05-2024

MAIN OBJECTIVE: To evaluate the efficacy of tofacitinib treatment in patients with RCDII with persistent or recurrent villous atrophy (Marsh III ABC) and aberrant IEL T-cells (≥ 20% as assessed by flow cytometry).

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25125

Bron
Nationaal Trial Register

Verkorte titel
TOF-RCDII

Aandoening

Refractory Celiac Disease type II; RCDII; Refractaire Coeliakie type II

Ondersteuning

Primaire sponsor: Amsterdam UMC, location VU University Medical Center
Overige ondersteuning: Amsterdam UMC, location VU University Medical Center

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Primary efficacy endpoint:
- Immunological response, as defined by:
reduction of ≥ 20% from baseline of aberrant IELs (%) with respect to total IELs in duodenal biopsies at week 12, as assessed by flow cytometry.

Toelichting onderzoek

Achtergrond van het onderzoek

Treatment for patients with refractory celiac disease type II (RCDII) is not optimal, resulting in 5-year survival rates falling below 60%. What¡¯s more, there is a lack of efficacy for most evaluated therapies in RCDII and 50% of patients develop enteropathy-associated T cell lymphoma (EATL) with even lower 5-year survival rates of ¡Ü 20%. This high risk of malignant transformation makes it necessary to develop new treatment strategies for RCDII. Tofacitinib (Pfizer) is a small-molecule drug, inhibiting a broad spectrum of pro-inflammatory cytokines including interleukin (IL)-15, -2 and -21 which are assumed to play a role in RCDII. Aberrant intraepithelial lymphocytes (IEL¡¯s) are the source of this malignancy; our recent data show that proliferation of these cells is induced by IL-15, -2 and -21. Tofacitinib inhibits signalling pathways of these cytokines, hereby blocking proliferation of malignant IEL¡¯s. Therefore, tofacitinib is considered as an attractive drug candidate for treatment of RCDII patients and prevention of EATL development.

Doel van het onderzoek

MAIN OBJECTIVE:

To evaluate the efficacy of tofacitinib treatment in patients with RCDII with persistent or recurrent villous atrophy (Marsh III ABC) and aberrant IEL T-cells (≥ 20% as assessed by flow cytometry).

Onderzoeksopzet

12 weeks

Onderzoeksproduct en/of interventie

Tofacitinib 10mg BID

Contactpersonen

Publiek

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Gerd Bouma

020-4443522

Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Adult patients ≥ 18 years old

2. Given informed consent

3. Diagnosis of RCDII

4. Total adherence to a glutenfree diet for at least 6 consecutive months prior to screening. Subjects must also agree to make no changes to their current GFD for the duration of study participation.

5. Anti-tissue transglutaminase (IgA and IgG) at screening < 2x the diagnostic level for celiac disease (weak positive or negative)

6. In case of female subjects of child-bearing potential: negative serum pregnancy test prior to study enrollment; adequate contraception, up to 4 weeks after final dose.

7. Laboratory values:

a) Total WBC > 0.75 x 10^9/L (i.e. > 750/mm3)

b) Hemoglobin > 5.5 mmol/L (i.e. 8.86 g/dL)

c) Absolute neutrophil count > 1 x 10^9 / L (i.e. > 1000 cells/mm3.)

d) Estimated eGFR > 30mL/min/1.73m2 using the Cockcroft-Gault equation.

e) Platelets > 75 x 109/L (i.e. 75000/mm3)

8. PET/CT-scan without signs of abnormalities suggestive for EATL within 3 months.

9. Willingness and ability to comply with study procedures.

10. Willingness to return for all scheduled follow-up visits.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Diagnosis of RCDI, EATL

2. Presence of any of the following diagnosis:

a) Severe infection prior to screening (e.g. those requiring hospitalization of parenteral antimicrobial therapy or opportunisitc infections. Specific attention for treatment with ketoconazol or fluconazol (as well as other CYP3A4 metabolizers).

b) Active tuberculosis (TBC) (as confirmed in PET-CT-scan; chest radiography)

c) Untreated or inadequately treated latent TB (as confirmed with a positive IGRA test)
i. NB. subjects are permitted to enroll in study after ≥ 4 months treatment with rifampicine.
d) History within 3 years of opportunistic infections typical of those seen in immunocomprised patients, such as systemic candida infection, disseminated herpes zoster.

e) Severe liver insufficiency (Child Pugh Score 10-15)

3. Current diagnosis or history of cancer in the past 5 years, except RCDII, adequately treated squamous cell cancer or basal cell skin cancer.

4. Positive Hep B or Hep C results at the time of screening.

5. Vaccination with live, attenuated vaccines (such as varicella zoster vaccine) within 2 weeks before start of tofacitinib.

6. History of significant immune suppression:

a) BMT therapy less than 6 months prior to baseline

b) Potent systemic immune suppressants (e.g., azathioprine) within the 3 months prior to baseline.

7. Subjects receiving moderate/potent CYP3A inducers or inhibitors in the specified time periods prior to the first dose of study drug:

- Moderate/potent CYP3A inducers, within 28 days of 5 half-lives, whichever is longer, prior to first dose of study drug;

- Moderate/potent CYP3A inhibitors, within 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug.

i. NB.Topical (including skin or mucous membranes) application of antimicriobial and antifungal medications is permitted.

8. Screening 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results.

9. History or presence of clinically significant disease that in the opinion of the investigator would confound the subject¡¯s participation and follow-up in the clinical trial or put the subject at unnecessary risk (e.g. uncontrolled cardiac diseases, uncontrolled/chronic pulmonary, renal, endocrine, hematological, gastrointestinal, immunologic, dermatological, neurological or psychiatric dysfunction).

10. History of drug or alcohol abuse that would interfere with the ability to comply with the study protocol.

11. History of clinically significant hypersensitivity to the study drug or to any of the excipients

12. Females who are pregnant, becoming pregnant or are currently breastfeeding.

13. Participation in any other investigational drug study in the past 30 days/5 half-lives.

14. Any additional reason which would endanger safety of the subject for participation in this study, in the opinion of the investigator.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-01-2019
Aantal proefpersonen:	5
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	13-09-2018
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 52502
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7313
NTR-old	NTR7529
CCMO	NL65853.029.18
OMON	NL-OMON52502

Resultaten

Samenvatting resultaten
NA