An open label exploratory analysis of blood, stool and the histological and immunological changes of the colonic mucosa during treatment with tofacitinib for moderate to severe ulcerative colitis

Gepubliceerd: 18-09-2017 Laatst bijgewerkt: 15-05-2024

This is an exploratory study to assess changes in blood, stool and colonic inflammation after 8 weeks of treatment with tofacitinib (XELJANZ) 10 mg BID in patients with moderate to severely active UC

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

Samenvatting

ID

NL-OMON25297

Bron
NTR

Verkorte titel
Tofa-histo

Aandoening

Ulcerative colitis

Colitis ulcerosa

Ondersteuning

Primaire sponsor: University Center Amsterdam (AMC)
Overige ondersteuning: Investigator Initiated

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To investigate the efficacy of twice daily doses of tofacitinib (10 mg bid) to decrease histological inflammation after 8 weeks of treatment in patients with moderate to severely active ulcerative colitis measured by:
Median change in inflammatory infiltrates at week 8 in 2 colon biopsies as assessed by the Robarts Histopathology Index [Mosli, Gut, 2015] and the Geboes index [Geboes, Gut, 2000], by an independent GI pathologist.

Toelichting onderzoek

Achtergrond van het onderzoek

Biomarker analysis of blood, stool and histological and immunological information of the effects of tofacitinib in ulcerative colitis (UC) is lacking. This is an exploratory study to assess changes in blood, stool and colonic inflammation after 8 weeks of treatment with tofacitinib (XELJANZ) 10 mg BID in patients with moderate to severely active UC. Insight in the histological and immunopathological changes in the colonic mucosa is essential to understand the mode of action of this drug, as patients with residual microscopic inflammation are more likely to relapse. This study will assess the histologic severity, immune cell infiltration, gene expression of inflammatory cytokines and changes in the microbiome in active UC in an open label 8-week study with 2x10 mg tofacitinib per day. Besides severity of inflammation, we will investigate immunological changes in both peripheral blood and mucosa and in stool microbiome after eight weeks of treatment. Analysis of all collected parameters may allow to establish a predictive biomarker profile for response to tofacitinib.

The primary endpoint of this study is to investigate the efficacy of twice daily doses of tofacitinib (10 mg bid) to decrease histological inflammation after 8 weeks of treatment in patients with moderate to severely active ulcerative colitis measured by:

Median change in inflammatory infiltrates at week 8 in 2 colon biopsies as assessed by the Robarts Histopathology Index [Mosli, Gut, 2015] and the Geboes index [Geboes, Gut, 2000], by an independent GI pathologist.

Doel van het onderzoek

This is an exploratory study to assess changes in blood, stool and colonic inflammation after 8 weeks of treatment with tofacitinib (XELJANZ) 10 mg BID in patients with moderate to severely active UC

Onderzoeksopzet

Baseline, week2,4, and week 8. Follow-up at week 12

Onderzoeksproduct en/of interventie

Tofacitinib 10 mg twice a day

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Subject must be at least 18 years of age.

2. Males and females with a documented diagnosis of UC ≥ 4 months prior to entry into the study. A biopsy report supporting the diagnosis must be available in the source documents.

3. Subjects with moderately to severely active UC as defined by a total Mayo score of ≥6, with a rectal bleeding score of ≥ 1 and an endoscopic (sigmoidoscopy) subscore of ≥ 2 on the Mayo score determined within 7 days of starting the study treatment (tofacitinib).

4. Subjects must have failed or be intolerant (discontinued the medication due to an adverse event as determined by the investigator) of at least one of the following treatments for UC:

- Oral corticosteroids

- Azathioprine or 6-mercaptopurine (6-MP).

- Anti-TNF therapy: infliximab, adalimumab or golimumab.

5. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by negative QuantiFERON-TB Gold (QFT-G) test and a chest radiograph, taken at or within the 3 months prior to a given screening visit, without changes suggestive of active TB infection as determined by a qualified radiologist.

6. If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test nor a PPD test is needed, but a chest radiograph must still be obtained if not performed within 3 months prior to a given Screening visit. Documentation of adequate treatment for TB will be obtained prior to first dose of study drug.

- A subject who is currently being treated for active TB infection is to be excluded.

- A subject who is currently being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection in the locale, documentation of an adequate treatment regimen, and with prior approval by the sponsor (AMC) .

7. Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 4 weeks after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

8. Women of childbearing potential must have a negative pregnancy test prior to study enrollment.

9. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, daily diary, and other study procedures.

10. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn’s disease.

2. Subjects without previous treatment for UC (ie, treatment-naïve).

3. Subjects displaying clinical signs of fulminant colitis or toxic megacolon.

4. Subjects with evidence of colonic adenomas or dysplasia. However, subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed and the subjects are free of polyps at baseline.

5. Subjects at risk for colorectal cancer must have a Colonoscopy. Colonoscopy report and pathology report (if biopsies are obtained) must be available in the source document:

• If the subject is >50 years of age, a colonoscopy within 10 years of the screening visit is required to exclude adenomatous polyps. Subjects whose adenomas have been completely excised at baseline will be eligible.

• If the subject has extensive colitis for >8 years or disease limited to left side of colon (ie, distal to splenic flexure) for >10 years, regardless of age, a colonoscopy within 1 year of the screening visit is required to survey for dysplasia. Subjects with dysplasia or cancer identified on biopsies will be excluded.

6. Subjects who have had surgery for UC or in the opinion of the Investigator, are likely to require surgery for UC during the study period.

7. Subjects who have positive stool examinations for enteric pathogens, pathogenic ova or parasites, or Clostridium difficile toxin at screening.

8. Subjects with clinically significant infections currently or within 6 months of baseline (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), a history of any infection requiring antimicrobial therapy within 2 weeks of baseline, or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study.

9. Subjects with a history of more than one episode of herpes zoster, a history of disseminated herpes zoster or disseminated herpes simplex.

10. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses (Subjects with negative HBV surface antigen but positive HBV core antibody must have further testing for HBV surface antibody and if negative for HBV surface antibody, will be excluded from study enrollment).

11. Subjects who have been vaccinated with live or attenuated vaccine within 6 weeks of baseline or scheduled to receive these vaccines during study period or within 6 weeks after last dose of study medication.

12. Subjects with history of any lymphoproliferative disorder (such as EBV-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.

13. Subjects with malignancies or a history of malignancies, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.

14. Subjects with a history of bowel surgery within 6 months prior to baseline.

15. Subjects with significant trauma or major surgery within 4 weeks of screening visit.

16. Subjects likely to require any type of surgery during the study period.

17. Subjects with the following laboratory values at screening:

• Hemoglobin levels <9.0 g/dL or hematocrit <30%.

• An absolute white blood cell (WBC) count of <3.0 x 109/L (<3000/mm3) or absolute neutrophil count of <1.2 x 109/L (<1200/mm3), or an absolute lymphocyte count of <0.5 x 109/L (<500/mm3).

• Thrombocytopenia, as defined by a platelet count <100 x 109/L (<100,000/mm3).

• Subjects with estimated GFR <50 ml/min based on Cockcroft-Gault calculation.

• Subjects with total bilirubin, AST or ALT more than 1.5 times the upper limit of normal.

18. Subjects with evidence of or suspected liver disease ie, liver injury due to methotrexate or primary sclerosing cholangitis.

19. Subjects with current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic (including uncontrolled hypercholesterolemia), endocrine, pulmonary, cardiac, neurological disease.

20. Subjects with any condition possibly affecting oral drug absorption (eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass). Procedures such as gastric banding that simply divide the stomach into separate chambers are NOT exclusionary.

21. Women who are pregnant or lactating, or planning to become pregnant during the study period.

22. History of alcohol or drug abuse with less than 6 months of abstinence prior to baseline.

23. Donation of blood in excess of 500 mL within 8 weeks prior to baseline.

24. Subjects with a first-degree relative with a hereditary immunodeficiency.

25. Subjects who have previously participated in any study of CP-690,550.

26. Subjects who have received any investigational drug or device within 3 months prior to baseline.

27. Subjects who, in the opinion of the investigator, will be uncooperative or unable to comply with study procedures.

28. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of a psychiatrist , would make the subject inappropriate for entry into this study.

29. Subjects who are investigational site staff members or relatives of those site staff members.

30. Chronic treatment for ulcerative colitis with antibiotics. All antibiotics should be discontinued 4 weeks prior to baseline.

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 gestopt
(Verwachte) startdatum:	15-10-2017
Aantal proefpersonen:	40
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	18-09-2017
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 47601

Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6520
NTR-old	NTR6708
CCMO	NL57944.018.16
OMON	NL-OMON47601

Resultaten