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

Published: 13-09-2018
Last updated: 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).

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25125

Source
Nationaal Trial Register

Brief title
TOF-RCDII

Health condition

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

Sponsors and support

Primary sponsor: Amsterdam UMC, location VU University Medical Center
Source(s) of monetary or material Support: Amsterdam UMC, location VU University Medical Center

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

Secondary efficacy endpoints:
- Histological response, as defined by: improvement from baseline in histology scores for celiac disease, as defined by Marsh classification.
- Clinical response: changes from baseline in clinical symptoms, as assesed by:
Bristol Stool Forming Scale (BSFS), gastrointestinal symptom rating scale (GSRS), which includes the celiac disease GSRS (CeD)-GSRS, Celiac Disease Patient Reported Outcome (CeD-PRO), Celiac Disease Symptom Diary (CDSD).

Exploratory endpoints:
- Safety of tofacitinib for patients with RCDII
- Quality-of-life: as evaluated with EQ-5D-5L questionnaire.
- Immunological changes, by tracking of immune subsets in duodenal biopsies and blood after tofacitinib treatment (single-cell CyTOF) and tracking histological changes in the small intestine after tofacitinib treatment (IHC; Vectra, imaging CyTOF). - In vitro tofacitinib assay: to evaluate predictability of tofacitinib responsiveness with an in vitro assay (FACS) vs. in vivo immunological response. - Pharmacokinetics analysis: to assess tofacitinib concentrations in blood after oral intake (HPLC-MS/MS assay).

Study description

Background summary

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.

Study objective

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).

Study design

12 weeks

Intervention

Tofacitinib 10mg BID

Contacts

Public
Amsterdam UMC, location VU University Medical Center
Gerd Bouma

020-4443522
Scientific
Amsterdam UMC, location VU University Medical Center
Gerd Bouma

020-4443522

Eligibility criteria

Inclusion criteria

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.

Exclusion criteria

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.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-01-2019
Enrollment:	5
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	13-09-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52502
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

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

Study results

Summary results
NA