Tofacitinib: salvage therapy for patients with RCDII - a pilot study

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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	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's T-cell
Study type	Interventional

Summary

ID

NL-OMON52502

Source
ToetsingOnline

Brief title
TOF-RCDII

Condition

- Lymphomas non-Hodgkin's T-cell
- Gastrointestinal inflammatory conditions

Synonym
gluten intolerance, refractory celiac disease type II

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: KWF Kankerbestrijding;Nederlandse Coeliakie Vereniging

Intervention

Keyword: celiac disease, refractory celiac disease, tofacitinib

Outcome measures

Primary outcome

Primary efficacy endpoint:

- Immunological response, as defined by:

reduction from baseline of aberrant IELs (%) with respect to total IELs in duodenal biopsies at week 12, as assessed by flow cytometry. A decrease of at least 20% aberrant IELs will be considered as significant.

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: severity of diarrhea (evaluated by Bristol Stool Forming Scale (BSFS), gastrointestinal symptom rating scale (GSRS), celiac disease symptom diary (CDSD) Celiac Disease Patient Reported Outcome (CeD-PRO).

Safety of tofacitinib for patients with RCDII

Exploratory endpoints:

- Changes in quality-of-life when using tofacitinib, as evaluated by questionnaire EQ-5D-5L.

- Immunological changes:

track changes in immune subsets in duodenal biopsies and blood before and after tofacitinib treatment (single-cell CyTOF). Track 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 (see primare outcome: change in aberrant IELs).

- 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 <= 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

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

Phase II, open label, mono-center, pilot study

Intervention

Tofacitinib 10mg twice daily (BID), orally, for 12 weeks.

Study burden and risks

The main goal of this study is to assess efficacy of tofacitinib for patients with RCDII, a pre-malignant disease for which there is no established treatment. RCDII patients who failed treatment in standard care are potential candidates for this study. We hypothesize that by applying tofacitinib, we achieve better treatment outcomes. There are risks of known side effects, most importantly infections, for patients will be monitored and visit the clinic every other week in a 12-week treatment period. At most visits, blood will be drawn and targeted physical examination will be done. During the 16-week study period, patients need to fill in a 10-second questionnaire each day about their bowel moments; 2x 2-minute questionnaires every day about their health; an extensive 5-minute questionnaire weekly about their health. At a couple of patient visits, patients need to fill in a 5-minute questionnaire about quality-of-life. Overall, this will be a short treatment period with extensive monitoring. To underscore, potential candidates are RCDII patients in which there is lack of efficacy of other treatments

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adult patients >= 18 years old
2. Given informed consent
3. Diagnosis of RCDII
4. Total adherence to a gluten-free diet (GFD) 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 fertile patients: adequate contraception, up to 4 weeks after final dose.
7. Laboratory values:
a) Total WBC > 0.75 x 109/L (i.e. > 750/mm3)
b) Hemoglobin > 5.5 mmol/L (i.e. 8.86 g/dL)
c) Absolute neutrophil count > 1 x 109 / L (i.e. > 1000 cells/mm3.)
d) Estimated eGFR > 30mL/min/1.73m2 using the Cockcroft-Gault equation.
e) Platelets > 50 x 109/L (i.e. 50000/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 opportunistic infections. Specific

attention for treatment with ketoconazol or fluconazole (as well CYP3A4 metabolizers)).
b) Active tuberculosis (TBC)
c) Untreated or inadequately treated latent TBC
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. Positive Hep B or Hep C test results at the time of screening.
4. Vaccination with live, attenuated vaccines (such as varicella zoster vaccine, yellow fever or oral typhoid vaccine) within 2 weeks before start of tofacitinib.
5. History of significant immune suppression:
a) BMT therapy less than 6 months prior to baseline
b) Potent systemic immune suppressants (e.g., azathioprine, within specified time periods per immunosuppressant) prior to baseline.
6. Subjects receiving moderate/potent CYP3A inducers or inhibitors in the specified time periods prior to the first dose of study drug.
7. Screening 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results.
8. 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).
i. Specific attention for risk factors for pulmonary embolism, such as: use of hormonal contraception, heart failure, previous venous thromboembolism, hereditary coagulation disorder, malignancy, patients who get major surgery.
9. History of drug or alcohol abuse that would interfere with the ability to comply with the study protocol.
10. History of clinically significant hypersensitivity to the study drug or to any of the excipients
11. Females who are pregnant, becoming pregnant or are currently breastfeeding.
12. Participation in any other investigational drug study in the past 30 days/5 half-lives.
13. 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-11-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	tofacitinib
Generic name:	tofacitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	20-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25125
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-001678-10-NL
CCMO	NL65853.029.18
OMON	NL-OMON25125

Study results

Date completed: 01-06-2023

Actual enrolment: 4