Towards the identification of molecular pathways predicting response to vedolizumab (Entyvio®) in Crohn*s disease deploying Systems Medicine: the BullsEye Study XL

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In the present study, we propose to explore whether a Systems Medicine approach can identify biomarkers that predict the clinical outcome in patients with Crohn*s disease in whom vedolizumab is started.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational non invasive

Summary

ID

NL-OMON54895

Source
ToetsingOnline

Brief title
BullsEye XL

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease; inflammatory bowel disesae

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Takeda,Takeda USA;fabrikant van vedolizumab

Intervention

Keyword: Crohn's disease, Systems Medicine, vedolizumab

Outcome measures

Primary outcome

To identify biomarkers predicting response to vedolizumab in patients with CD

Secondary outcome

Clinical response at 20 weeks, after induction therapy with vedolizumab defined as a reduction in the Harvey Bradshaw Index (HBI) score of at least 3 points -To gain insight in pathways, associated with (non)reponse to vedolizumab in patients with CD -Remission at 20 weeks, defined as a HBI < 4 -Sustained clinical benefit at 52 weeks, i.e. persistent clinical improvement under vedolizumab treatment during follow-up without need for new courses of corticosteroids or any other systemic drug (azathioprine, methotrexate, anti-TNF or investigational drugs), or surgery -Molecular handprint defining response to therapy -Calprotectin < 100 mg/mL at 1 year -CRP< 5 mg/mL at 1 year -HBI at 1 year -Change in IBDQ and EQ5D

Study description

Background summary

The introduction of monoclonal antibodies (ani-TNFs) has revolutionized the treatment of the disease. Unfortunately, the success of these agents is

hampered by loss of response in a significant proportion of patients. Since 2015, vedoliumab, an integrin α4β7 antagonist, has been registered for the treatment of inflammatory bowel disease. This drug is well tolerated by patients and has a very favorable safety profile. Response rates range from 31% for patients with Crohn's disease to 47% for ulcerative colitis at week six in the original studies. Cumulative rates after one year for clinical remission, mucosal healing, and deep remission are 58.4%, 38.9%, and 28.3%, respectively. Unfortunately, a large group of patients do not respond to vedolizumab. Since the use of vedolizumab is associated with significant financial expenditures, toolsare needed to help predict who will and who will not respond on the drug. Systems Medicine is an approach, which exploits a multitude of *OMICS* layers (transcriptome, genome, proteome, metabolome and epigenome of individual cells in addition to the fecal microbiome and metabolome) and ultimately integrates these data layers with sophisticated computational approaches to an underlying network of nodes leading to disease. Previously, our group successfully applied an element of this approach to reveal an important initial insight as to how altered plasmacytoid dendritic cells function contributes to pathology in scleroderma. In addition, using this approach we were recently able to identify the molecular pathways that identify rheumatoid arthritis patients that could stop anti-TNF therapy successfully

Study objective

In the present study, we propose to explore whether a Systems Medicine approach can identify biomarkers that predict the clinical outcome in patients with Crohn*s disease in whom vedolizumab is started.

Study design

Treatment: Vedolizumab 300 mg according to standard treatment regimen
Safety precautions: Routine screening prior to starting vedolizumab:
-Feces on bacterial pathogens using PCR and clostridium toxin, X-Thorax, Mantoux, Quantiferon test
Research procedures: Prior to initiation of vedolizumab treatment (base line assays): All patients undergo routine colonoscopy to objectify disease activity as part of routine care. Eight additional biopsies will be collected during this procedure and stored at -80C. Stool and blood samples will be taken for Systems Medicine and the two faecal samples will be frozen for microbiome analysis. Clinical disease activity will be determined by the HBI. Blood count, CRP and faecal protectin will be determined in the context of routine care. Patients will be asked to complete three questionnaires: the EuroQOL five dimensions questionnaire (EQ5D), PRO-3 and the Inflammatory Bowel Disease Questionnaire (IBDQ).
Follow up: At week 6, 40 mL of blood will be drawn from the infusion before the vedolizumab is administered, and trough levels will be determined.
Fecal samples will again be requested for microbiome determination at weeks 20

and 52 after the start of treatment. 40 mL of blood will be drawn for the study. Patients will be asked to complete three questionnaires: the EuroQOL five dimensions questionnaire (EQ5D), the Inflammatory Bowel Disease Questionnaire (IBDQ) and the PRO-3. Clinical disease activity will be determined by the HBI.
After 1 year or in the event of a clinical flare-up, a further colonoscopy will be repeated to assess disease activity. Eight additional biopsies will be taken again.

Study burden and risks

Minimal burden, no risks Extra: Questionnaires and collecting stoolsamples
Minimal risk associated with obtaining extra biopsies during routine colonoscopies

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

- Confirmed and active Crohn*s disease defined as follows
o HBI > 4 and at least 2 of the following
* CRP > 10
* calprotectine > 150
* Endoscopic active disease
* Active disease on MRI-enterography
- Age > 18 year
- Anti-TNF naive or exposed (infliximab and/or adalimumab)

Exclusion criteria

- No consent to participate in the study
- Active perianal disease
- Prior vedolizumab or ustekinumab therapy
- Recent use of antibiotics (within 4 weeks of baseline)
- Hospitalised patients or patients in need of surgery

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-12-2021
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	07-07-2021
Application type:	First submission
Review commission:	METC NedMec

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: 25264
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
Other	NL6439
CCMO	NL74279.041.20
OMON	NL-OMON25264