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

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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-OMON50386

Source
ToetsingOnline

Brief title
Identification op predictors of response to vedolizumab

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: directe grand van Takeda;leverancier van het geneesmiddel

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

Crohn's disease is an immune-mediated disease that results in chronic inflammation in genetically predisposed individuals exposed to an appropriate environment. The introduction of monoclonal antibodies has revolutionized the treatment of Crohn*s disease (CD). Unfortunately, the utility of these agents have been hampered by loss of response in a significant proportion of patients.

Recently, vedolizumab, an integrin *4*7 antagonist, has been licensed for the treatment of CD and UC. Response rates vary between 31% for CD and 47% for UC at week 6 (1;2). In bio-naive patients response rates may be up to 40% at week 6 and 47% at week 10 (unpublished results from Gemini 2 en 3 studies). However, a considerable proportion of patients do not respond to vedolizumab. Since the use of this treatment modality is associated with substantial financial expenditures, tools to identify patients in whom the drug will be effective are highly warranted.

Although in general criteria for starting immunosuppressive therapy and biologicals (mainly anti-TNFs) have clearly been stated in guidelines and consensus reports, no tools or algorithms are available that reliably guide the clinician selecting patients in whom biological therapy will successfully induce and maintain remission. Several studies have attempted to identify predictors of response to anti-TNF in IBD, mainly in Crohn*s disease (3-6). Although some of parameters, such as increased CRP levels, deep ulcers on endoscopy and short disease duration may identify a subgroup of likely anti-TNF responders, they are often not helpful in daily practice. For vedolizumab no studies on predictors of response are available.

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 (7). 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- induction at 0, 2 and 6 and 10 weeks - every 8 weeks

Safety
Routine screening prior to initiation of biological treatment will include:
-Stool cultures and clostridium toxin
-Chest X-ray, Mantoux, Quantiferon test

Baseline (prior to start of vedolizumab):
All patients will undergo colonoscopy at to objectivate disease activity. Biopsies will be taken and stored at -70 C. Fecal and blood samples (80 mL of blood for Systems Medicine and two fecal samples for microbiome profiling) will be obtained at baseline. Clinical disease activity will be assessed using HBS. Bloodcount, CRP and fecal calprotectine will be assessed. Patients will be requested to fill-out the EuroQOL five dimensions questionnaire (EQ5D) and the Inflammatory Bowel Disease Questionnaire (IBDQ).

Follow-up:
At week 6 and 20 (third and fifth gift of vedolizumab, respectively) and after a year or in case of therapy failure patients will be requested to provide 40 mL of blood, which will be drawn from the infusion prior to the vedolizumab gift At 20 and 52 weeks, patients will be requested to provide a fecal sample for microbiome profiling. Therapeutic drug levels, CRP and fecal calprotectin levels will be determined as part of the routine laboratory screening. EQ5D, PRO-3 and IBDQ will be assessed. Clinical disease activity will be evaluated by the HBS. At 12 months or in case of clinical relapse of disease, the endoscopy with biopsies will be repeated and blood for Systems Medicine will be collected. If patients agree, an additional colonoscopy of only the rectum will be performed at week 20 for extra biopsies.

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

Adult anti-TNF therapy naïve luminalCrohn*s disease patients in whom with vedolizumab therapy is initiated

Exclusion criteria

Hospitalized patients or patients in need of surgery
Active perianal disease
Prior biological use

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):	13-12-2017
Enrollment:	65
Type:	Actual

Ethics review

Approved WMO Date:	28-09-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	01-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-11-2020
Application type:	Amendment
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: 25877
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL60968.041.17
Other	NL6439
OMON	NL-OMON25877