Cellular parameters predict favourable response treatment with vedolizumab?

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To exploit CyTOF technology and carry out an in depth investigation of the phenotypical and functional heterogeneity of the innate and adaptive immune cell compartments and the stromal cell compartments present in rectum biopsies of patients with CD...

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

Summary

ID

NL-OMON42625

Source
ToetsingOnline

Brief title
Cellular parameters aas treatment predictor?

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease and cell characteristics

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: subsidieaanvraag loopt.,Takeda

Intervention

Keyword: cellular parameters, Crohn's disease, vedolizumab

Outcome measures

Primary outcome

1. Determine if the immune and/or stromal cell status prior to the application

of vedolizumab correlates with response to treatment.

2. Determine which changes in cellular parameters correspond to favourable

response to treatment with vedolizumab.

Secondary outcome

Use this information to design an optimized patient inclusion protocol for the

use of vedolizumab for treatment of Crohn*s disease.

Study description

Background summary

Disruption of intestinal homeostasis lies at the heart of a variety of intestinal disorders in man including Crohn*s disease, a chronic inflammatory disorder of the gastrointestinal tract that can affect both the distal ileum and colon. While the actual disease trigger is unknown, there is strong evidence that a combination of genetic and environmental factors lead to impaired barrier function in the intestine, allowing translocation of bacterial products and/or commensals into the mucosal tissue which leads to immune activation and inflammation. In the absence of appropriate regulatory mechanisms this can lead to chronic inflammation affecting the intestinal mucosa. Consequently, many studies have focussed on the role of the mucosal immune system in CD. The prominent role of the immune system is evidenced by the strong involvement of a variety of cytokines, including macrophage derived IL12, IL6, IL23 and TNF* which impacts on adaptive Th1 and Th17 T cell subsets, leading to the secretion of the pro-inflammatory cytokines IFN*, IL17 and IL21. Despite significant improvements in the management of CD, remission is often difficult to maintain. Consequently, there is significant morbidity in many patients. In addition, due to unknown causes the incidence of childhood CD is rising. Novel therapeutic approaches are therefore highly desirable and need to

be explored.
Fistulisation in Crohn*s disease (CD) is a major problem which can result in considerable morbidity. Around 35% of the CD patients have at least one fistula episode. Of these, 54% is perianal and 9% is rectovaginal [1]. Patients with perianal fistulas can present with symptoms such as constant anal pain or pain after defecation, (painful) swelling around the anus, continuous (malodourous) discharge of pus and/or blood from the external opening with skin irritation around the anus, fever and even incontinence [2]. Patients with colonic and active rectal disease have more frequently perianal fistulas compared to patients with isolated ileal or ileocolonic disease [1,3-8]. Male gender, age at diagnosis of CD and smoking are risk factors for the development of perianal fistulas although data are conflicting [1,3,5,7-12]. While a range of potent drugs and advanced surgical techniques are available nowadays, the treatment of perianal fistulising CD remains challenging.
The Accent II trial and subgroup analysis of the CHARM study have demonstrated the efficacy of anti-TNF* with varying degrees of success in achieving closure of the fistula benefitting up to one half of patients [13,14]. Previous studies have suggested that combined surgical drainage and anti-TNF* can result in closure of the fistula in 40*70% of patients [15-18]. Recently Sandborn et al. [19] reported the results of the first induction and maintenance trials of vedolizumab, an *4*7-integrin specific antibody. This antibody inhibits the interaction between immune cells and the intestinal vasculature resulting in a decreased migration of systemic leukocytes to the inflamed intestinal tissues. Although the number of patients with fistulas at baseline in this trial was quite low (165/1115; 14.8%) and the number of patients available for evaluation at week 52 even lower (n = 57), vedolizumab every 8 weeks resulted in a significant higher closure rate (41.2%) compared to placebo (11.1%) ($p = 0.03$) [19]. Due to the highly variable clinical outcome, however, there is a strong need to determine biomarkers that correlate with response to treatment.
Next to a prominent role for the adaptive immune system, recent studies have indicated a crucial role for innate lymphoid cells (ILCs) in inflammatory bowel diseases as well. ILC have been found in mucosal tissues and are functionally specialized cells characterized by the expression of lineage-defining transcription factors: cytotoxic Eomes+ cells (cNK), IFN*-producing T-bet+ cells (ILC1), IL-5-producing GATA-3+ cells (ILC2) and IL-22-producing ROR*t+ cells (ILC3) [20]. Each subset displays highly distinct functions that appear to parallel those of T-helper cells subsets with pro- (ILC1) or anti-inflammatory properties (ILC3). Strikingly, these cells display plasticity as evidence has been presented that in response to cytokines ILC3 cells can differentiate into ILC1 cells and vice versa, implying that they will modulate immune responses depending on the local cytokine milieu. Moreover, in our recent studies we defined four subsets of innate lymphocytes (CD45+CD7+CD3-CD14-CD19-) in the human intestinal epithelium, distinguished by the presence or absence of CD56 and IL-7R* (CD127) [21]. Of these four subsets, the CD56+CD127- subset bears strong resemblance to the recently described innate-like lymphoid cells (ILC) type 1 in the epithelium. To investigate the full diversity of intestinal lymphocytes and their functions, we have most

recently applied high-parameter mass cytometry (cytometry by time-of-flight; CyTOF). To this end, we designed a CyTOF panel with 32 monoclonal antibodies recognizing lineage markers, activation markers, and chemokine and cytokine receptors. This panel was used to define and compare the phenotypic diversity of innate and adaptive lymphocytes in intestinal biopsies and blood samples from non-diseased individuals and from patients with inflammatory intestinal diseases (i.e. celiac disease and fistulizing Crohn*s disease). By combining bio-informatics tools that allow unsupervised hierarchical clustering (SPADE) [22] and nonlinear dimensionality reduction (viSNE) [23], we were able to visualize innate and adaptive lymphocytes at single-cell resolution in a single map that took into account all phenotypic markers concurrently.
In our initial analysis we observed highly distinctive tissue and disease-specific expression profiles both within the adaptive and innate lymphocyte compartments. For example, a distinct central memory T cell subset was found to be exclusively present in small intestinal biopsy material of patients with celiac disease while an ILC3 population was exclusively identified in rectum biopsy material of CD patients in remission. Moreover, in a pilot study (7 patients), we analyzed material from the fistula (obtained from the surgeon during examination under anesthesia). Results of the immune system composition demonstrate that there is a dominant myeloid cell population (average 66.7%) present in the fistulas of five patients while in the fistulas of the two other patients lower percentages of myeloid cells were found (30%) while a higher percentage of T cells was observed, indicative of inter-patient variability that could correlate with response to treatment with vedolizumab as this would block the migration of pro-inflammatory T cells to the fistula. More general, the analysis revealed heterogeneity within the mucosal immune system which is far greater than previously appreciated. Therefore, CyTOF technology offers unprecedented depth in the analysis of cellular heterogeneity of both the innate and adaptive lymphocyte compartment present in intestinal biopsies. This offers a unique opportunity to determine if cellular parameters can be identified that correlate with and predict response to treatment, an important step towards personalized and (cost-) effective treatment strategies.

Next to the involvement of the mucosal immune system, there is significant evidence for an important role of the stromal cell compartments, including the epithelium, in the maintenance of intestinal homeostasis. The epithelium not only forms a barrier between the intestinal lumen and the underlying submucosa, but also has important functions in the specific defence against invading pathogens as evidenced by the secretion of antimicrobial peptides, the expression of pattern recognition receptors and the ability to produce and respond to a variety of cytokines. Next to the epithelium, stromal cell populations of mesenchymal origin are found throughout the intestinal mucosa and their phenotype is location dependent. In the small intestinal villi, for example, stromal myofibroblasts form a subepithelial layer just below the basal membrane in the lower part of the villi while towards the tip of the villi fibroblasts occupy this niche, indicating specialized functions. In this niche both myofibroblasts and fibroblasts can establish close contacts with all

immune components in the lamina propria and epithelium as well as with the epithelial cells themselves. There is emerging evidence that these CD45-CD90+ myofibroblasts can play a crucial role in the maintenance and breaking of intestinal homeostasis as they express a variety of pattern recognition receptors, can act as non-professional antigen presenting cells and produce and respond to a variety of cytokines. In fact, the immune modulatory properties of mesenchymal stromal cells are well established. Exploration of the phenotypical and functional heterogeneity in patients with CD is thus highly warranted as this may reveal additional biomarkers relevant to response to treatment. A special CyTOF antibody panel designed for this purpose is currently available.

Study objective

To exploit CyTOF technology and carry out an in depth investigation of the phenotypical and functional heterogeneity of the innate and adaptive immune cell compartments and the stromal cell compartments present in rectum biopsies of patients with CD with perianal fistulas before (week 0) and after treatment with vedolizumab (week 24) and to correlate these data with the clinical outcome of the patients at week 24.

Study design

Pilot study.
Patients with CD with peri-anal fistulas, who will start with vedolizumab treatment, age group 18-75 years old, who undergo endoscopy, will be included for taking biopsies for the current protocol. After treatment of 24 weeks this prcedure is repeated.
The biopsies will be evaluated by CyTOF.

Study burden and risks

Minimal bleeding risk by taking 8 extra biopsies.
In adults there is a limited risk to taking biopsies like in children. Taking biopsies during endoscopy can cause intra-intestinal or intramural haemorrhage, or even perforation. The risk is estimated to be < 1:10000. There is no additional risk in sampling an extra 10 ml of blood.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;1. Male and female patients with CD, aged > 18 years;
2. Perianal disease;
3. Initiating vedolizumab for approved indications (moderately to severely active Crohn*s Disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF* antagonist);
4. Signed informed consent and medical records release by the patient or a legally acceptable representative.

Exclusion criteria

* No informed consent
* Insufficient knowledge of Dutch language and/or inability to
understand the information provided
* active proctitis
* Hypersensitivity to the active substance or to any of the following
excipients: L-histidine; L-histidine monohydrochloride; L-arginine hydrochloride; sucrose and polysorbate 80
* Active severe infections such as tuberculosis, sepsis,

cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML) (see section 4.4. in SmPC).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2015
Enrollment:	10
Type:	Anticipated

Ethics review

Approved WMO

Date:	13-01-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL54290.058.15