An explorative Study to Examine the Role of IL-23-Responsive Immune Cell Subsets in Post-Operative Recurrence in Patients with Crohn*s Disease

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Primary Objectives: To unravel the immunological characteristics of postoperative recurrent CD and study the immunological changes in the IL-23 pathway following treatment with biological agents.Secondary Objectives:To study clinical, endoscopic and...

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

Summary

ID

NL-OMON53563

Source
ToetsingOnline

Brief title
DIVE-23

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Crohn's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Eigen onderzoeksfondsen van prof dr D'Haens

Intervention

Keyword: Crohn's Disease, IL-23, Postoperative recurrence

Outcome measures

Primary outcome

Immunological changes in postoperative CD at baseline endoscopy and after 12-16

weeks of routine care treatment with a biological agent.

Secondary outcome

-Clinical, endoscopic and histological response to different targeted

treatments given for postoperative CD.

-Change from baseline in IL-23 pathway cytokines and mediators.

-Differences in transcriptional signatures (single cell RNA sequencing) in

ileal tissue.

-Change in IL-23R+ cells, IL 23+ cells, FcγR+ cells, IL-23+ FcγR+ cells, and

ILCs using single-cell RNA sequencing.

Study description

Background summary

Inflammatory Bowel Diseases (IBDs), including ulcerative colitis and Crohn*s disease (CD), constitute a group of debilitating chronic diseases that profoundly impact patient quality of life and incurs large costs in terms of treatment and lost productivity. Incidence of IBD is rising worldwide, and there is a pressing clinical need for development of new therapies. Discovery and development of effective therapies to treat IBDs depend first on

a better understanding of the underlying mechanisms, including how proinflammatory cells proliferate unchecked.

It has been established that the cytokine interleukin (IL)-23 plays a pivotal role in IBD pathophysiology and antibodies targeting IL-23 are currently in late stage development for the treatment of both CD and ulcerative colitis (UC). IL-23 is part of the IL-12 family of cytokines. The p40 subunit is shared among IL-23 and IL-12; the p19 subunit is unique to IL-23. Thus far, the efficacy of selective anti-IL-23 blockade (via anti-p19 antibodies) appears 5-10% better for clinical and endoscopic outcomes than targeting both IL-23 and IL-12 using anti-p40 antibodies. Understanding the effects of IL-23 (and IL-12) in IBDs requires identification of the most relevant immune cells that respond to these cytokines.

One cell type strongly controlled by the IL-23 pathway are presumably the innate lymphoid cells (ILCs). ILCs consist of 5 subsets: ILC1, ILC2, ILC3, NK cells, and Lymphoid tissue inducer cells. These are relatively rare cells that are strategically located in tissues to regulate innate immunity and tissue homeostasis. Of these subsets, ILC3s are dominant in healthy intestinal tissue. These cells are capable of producing IL-22 which maintain intestinal epithelial homeostasis. The composition of ILCs in diseased tissues of CD patients undergoing surgery is dramatically altered compared to normal tissue, which is partly due to extensive plasticity of ILCs. ILC3s are capable of shifting into high interferon (IFN)gamma-producing ILC1 in response to IL-12 produced by intestinal macrophages. It is possible that IL-23 facilitates the IL-12-induced shift to ILC1 which are contributing to the disease-causing chronic inflammation, but this has yet to be investigated. Nonetheless, it is very likely that this mechanism also plays a pivotal role in CD recurrence following resectional surgery. Postoperative recurrence is observed in >80% of CD patients undergoing resection. Other IL-23-responsive cell types including Th17, mucosal-associated invariant T (MAIT) cells, and TCR-gammadelta-cells are also present in the intestine but whereas Th17 cells are involved in IBDs in experimental animal models, it is yet unknown whether these cells are involved in pathology of CD.

Study objective

Primary Objectives:
To unravel the immunological characteristics of postoperative recurrent CD and study the immunological changes in the IL-23 pathway following treatment with biological agents.

Secondary Objectives:
To study clinical, endoscopic and histological response to different treatments given for postoperative CD.

Study design

This is an open-label, multi-center trial studying CD patients with postoperative recurrence, diagnosed at ileocolonoscopy. Recurrence of CD is defined by presence of ulcerations (endoscopic Rutgeerts* score >i2a) in the neoterminal ileum.
We will take 8 biopsies at the baseline endoscopy (4 more than routine practice) and 8 biopsies at the week 12-16 endoscopy. All biopsies will be taken in areas of inflammation, in the proximity of (but not in the middle of) ulcers. The number of biopsies taken is based on earlier experience on the number of biopsies that is needed for reliable single cell read-out. Six biopsies taken in the neoterminal ileum (edge of ulcerations) from the ileum will be analyzed to identify immune cell populations of interest including rare cells such as ILC and IL-23R positive immune cells, and two biopsies will be used for Hematoxylin and eosin (H&E) staining and spatial transcriptomics. Patients will be treated by their attending gastroenterologist and choice of treatment will be determined by previous biologic agent exposure (as in routine practice). Biological treatments that will be prescribed, are at the moment of inclusion used in common IBD practice, which creates a heterogeneous group of patients.

Intervention

The intervention consists of the administration of a biological (guselkumab, adalimumab or ustekinumab) that would also be given in routine practice. The only exception to routine practice is the number of biopsies that will be taken during endoscopy. Guselkumab has not been registered for Crohn's disease to date (currently only for psoriasis), but will be registered for CD next year.

Study burden and risks

Patients will treated according to routine practice. It*s acceptable to expect an effect from the started biological treatment. However, as in routine practice, it*s possible that patients will not response to the therapy. Participants will not have direct benefit from the data we collect by taking biopsies and withdraw blood. However, with the data which we will retrieve from this study we can explore the role of IL-23-responsive immune cell subsets in CD-affected ileal resection tissue and post-operative recurrence.

Participants will undergo surgical resection and ileocolonoscopy as part of their follow-up. Biopsy collections is part of routine clinical care and is not associated with additional burden for the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Age >/= 18 years;
• Male or non-pregnant, non-lactating females;
• Females of child bearing potential must use appropriate contraception during the trial;
• Patients with postoperative recurrence at routine endoscopy 6-24 months following resection, defined by presence of ulcerations (endoscopic Rutgeerts* score >i2a) in the neoterminal ileum;
• Negative tuberculosis (TB) screening per local protocol (see Section 8.3);
• In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements;
• The subject signs and dates a written informed consent form and any required privacy authorization prior to the initiation of any study procedures.

Exclusion criteria

• Any conditions (eg, history of alcohol or substance abuse, or lack of compliance) which, in the opinion of the investigator, may interfere with the patient*s ability to comply with study procedures;
• Any condition in which one of the potential treatments are contraindicated in the opinion of the investigator (eg, cardiac failure class 3-4 according to the New York Heart Association [NYHA], multiple sclerosis, active infections).
• Received any investigational drug in the past 30 days or 5 half-lives, whichever is longer.
• Currently participating or planning to participate in a study involving an investigational product.
• Current diagnosis of untreated tuberculosis (active or latent), human immunodeficiency virus (HIV) or active/chronic hepatitis B or C infection (HBV, HCV).
• Active or planned pregnancy during the trial.
• Prior diagnosis of dysplasia in the colon (excluding in resected adenomas).
• History of malignancy in the 3 years prior to randomization except for non-melanoma skin cancer.
• Received a biologic treatment between surgery and first endoscopy.
• Positive Clostridium difficile toxin B in faeces. Patients who test positive can be treated per local practice and still enter the trial if no longer than 4 weeks after the screening visit, they test negative for Clostridium difficile toxin B.
• Presence of a stoma without ileocolonic anastomosis or pouch.
• Active perianal abscess or draining fistula
• ALT or AST > 3x the upper limit of normal measured at screening
• Increased risk of bleeding: coagulation disorder, use of anticoagulants and DOACs

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-06-2023
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	19-05-2023
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL82888.018.22