Immunological profiles in Inflammatory Bowel Disease

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Primary Objective: 1. Determine if assessment of mucosal and serological immunological characteristics in combination with clinical indicators of disease behaviour and response to therapy can identify immune-based phenotypes with implications for…

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

Summary

ID

NL-OMON44555

Source
ToetsingOnline

Brief title
Immunological profiles in IBD

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
IBD, Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: Rijnstate Ziekenhuis
Source(s) of monetary or material Support: Ziekenhuis Rijnstate

Intervention

Keyword: Crohn's Disease, Gutmucosa, Immunology, Ulcerative Colitis

Outcome measures

Primary outcome

The description of the different mucosal T-cell and serological biomarker immunological profiles at baseline and follow up in newly diagnosed IBD patients

Secondary outcome

The correlation between these different immunologic profiles and clinical indicators of disease activity, disease course and response to the received therapy.

To assess clinical disease activity in case of Crohn*s disease (CD) the Harvey-Bradshaw severity Index and in case of Ulcerative Colitis (UC) the simple clinical activity index will be used.
To assess endoscopic activity in case of CD the simple endoscopic score Crohn*s disease (SES-CD) and in case of UC the MAYO score will be used.

Study description

Background summary

Inflammatory Bowel Diseases (IBD) is a heterogeneous group of diseases regarding clinical presentation and treatment response. Incidence is increasing and disease burden is high due to the young age at onset and the chronic nature of the disease. Pathogenesis is complex and multifactorial based on interactions between genetic and environmental factors, gut microbiota and the immune system, leading to intestinal inflammation.

Alterations in T-cell subsets and homing of lymphocytes to gut mucosa were shown to play an important role in the pathogenesis of IBD1, causing inflammation primarily in the intestine but also in extra-intestinal tissues. The therapeutic arsenal is directed to suppress this immune mediated inflammatory reaction.
We previously reported different T-cell maturation profiles in the ileum/colon mucosa of newly diagnosed IBD patients which consist of mainly naïve T cells (Tn cells) and central memory T cells (Tcm cells) versus mainly effector memory T cells (Tem cells). Higher frequencies of Tn cells in patients with Crohn*s Disease (CD) were associated with a more extended and penetrating disease, reflecting a more aggressive initial presentation.2 Furthermore we recently identified several serum markers associated with disease activity and disease course (s-TNF R1, s-TNFR2, sIL2R, MMP1) in newly diagnosed Crohn*s disease patients.3

Migration of Tn * and Tcm cells to the gut is thought to be facilitated by tertiary lymphoid organs (TLOs) containing high endothelial venules (HEVs). The migration of T cells through HEVs is guided by different vascular addressins, such as MAdCAM-1 and peripheral lymph node addressin (PNAd). Differences in HEVs density and TLOs between newly diagnosed IBD patient with active disease has been recently described.4 Increased density of colonic extrafollicular HEVs in the early phase of disease was associated with more Tn- and Tcm cells in the inflamed gut mucosa, which could be responsible for maintaining a continuous inflammatory process.

These differences in the early phase of IBD seem to be mechanistically associated with different migration patterns of T cells into the gut mucosa and might explain the differences in response to therapy with biologicals. Karlsson et.al. (2014)5 showed a decrease in Tn and effector memory T cells re-expressing CD45RA in the gut mucosa with effective treatment (corticosteroids or biologicals), whereas memory T cells remained unchanged. The formation and development of TLOs in other different chronic immune mediated disorders (e.g. rheumatoid arthritis) and malignancies has been found to play an important role in local immunological dysregulation and showed predictive value for disease course (longer duration) and response to therapy. In patients with rheumatoid arthritis, TLOs were associated with inferior response to anti-TNF treatment and resolution of TLOs was shown to be a good marker of therapeutic response.6

The roles of CTLA-4 and PD-1 in inhibiting immune responses have recently gained attention. CTLA-4 is thought to regulate T-cell proliferation early in the immune response, primarily in lymph nodes. PD-1 suppresses T cells later in the immune response, primarily in peripheral tissues. Inhibition of CTLA-4 (ipilimumab) and PD-1 (nivolumab) can restore antitumor immune responses leading to long-term benefit in a substantial proportion of treated patients.7 Blockade of CTLA-4 activates a large repertoire of T cells, not only tumour-specific T cells. Patients treated with ipilimumab and nivolumab often

develop immune-related events such as enterocolitis which is the most frequent immune-related adverse event suggesting a role for CTLA-4 and PD-1 in the pathogenesis of IBD. 8

In the present, diagnosis is based on a combination of internationally accepted clinical, endoscopic, histological and radiological findings. Biomarkers as CRP, ESR, faecal calprotectin and pANCAs can only be used as an adjunct to endoscopic evaluation or in monitoring disease activity. Unless wide differences in disease course between IBD patients, up till now no biomarkers have been identified with predictive value for this course.9,10,11

At present patients are systematically treated using a step up treatment strategy according to the Dutch Guidelines IBD, including steroids, thiopurines and in case of steroid refractory or steroid dependent disease the use of biologicals e.g. anti-TNF. The described immunologic differences between IBD patients at the moment of diagnosis might explain the heterogeneity in response to different medications. These immunological characteristics may enable targeting with more specific medication. Treatment strategy would be more rational and individuals could get more personalised effective treatment without delay.

Study objective

Primary Objective:
1. Determine if assessment of mucosal and serological immunological characteristics in combination with clinical indicators of disease behaviour and response to therapy can identify immune-based phenotypes with implications for prognosis and therapeutic interventions.

Secondary Objective(s):
2. Determine the presence of HEVs/TLOs and T cell subsets in the mucosa of IBD patients at presentation and during follow-up and associate this to clinical phenotypes and treatment response.
3. Analyse the amount of regulatory T cells in combination with PD-1 and CTLA-4 in the mucosa and serum of IBD patients and healthy controls.
4. Determine differences in levels of chemokines and cytokines in serum and mucosa in IBD patients and healthy controls at baseline and during follow-up.

Study design

The study will be a longitudinal, prospective cohort study that will be performed at the Departments of Gastro-enterology and Hepatology, Microbiology and Immunology and Pathology of the Rijnstate Hospital in Arnhem. The patients will undergo diagnostic procedures and treatment according to the standard clinical practice.

Study burden and risks

Ileocolonoscopy with biopsies is a standard examination in patients presenting with chronic (+/- bloody) diarrhoea and in the follow up of patients with IBD. Collection of biopsies during the gastroenterological endoscopy, ie without interventions like polypectomy, is a safe procedure (bleeding, perforation <0,001). In the regular clinical practice, different endoscopists take a variable number of biopsies (4-10) from sites of interest. The intervention in this study comprises taking 4 additional biopsies on top of the regular histological biopsies for immunological examination.
Before ileocolonoscopy, patients normally receive an infusion needle for the administration of sedation (standard care). After ileocolonoscopy this needle will be used to take a venous blood sample. If this is not possible, we take a venous bloodsample during a regular labcontrol. In the follow up period, during regular endoscopies and blood checks the same additional samples will be taken. Therefore, we believe the burden and risks for patients are minimalised.

Contacts

Public
Rijnstate Ziekenhuis

Wagnerlaan 55
Arnhem 6815AD
NL
Scientific
Rijnstate Ziekenhuis

Wagnerlaan 55
Arnhem 6815AD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients with clinical symptoms of chronic diarrhoea, rectal blood loss, abdominal pain or weight loss who underwent ileocolonoscopy. Macroscopic findings during ileocolonoscopy must suggest IBD, such as erythema, mucosal friability, oedema an bleeding, erosions, superficial or deep ulcerations and luminal narrowing.
- Ultimately, the diagnosis of IBD must be based on a combination of clinical, endoscopic, histologic and radiologic internationally accepted criteria.
- Patients must be able and willing to provide written informed consent.
- Patients above the age of 18, both men and women.
AND/OR
- Known IBD patients under treatment during follow up.

Exclusion criteria

- Possible new IBD patients who use immunosuppressive medication 4 weeks prior to inclusion (e.g. corticosteroids and anti-TNF therapy) either for IBD, other autoimmune diseases or after organ transplantation.
- Patients diagnosed with an immune suppressive disease.
- Patients who underwent splenectomy in the past.
- Patients diagnosed with any other autoimmune diseases (e.g. Diabetes Mellitus type I, rheumatoid arthritis, celiac disease, psoriasis, systemic lupus erythematosus).
- Patients diagnosed with cancer including hematologic malignancies (e.g. (non-)Hodgkin lymphoma , leukemia), solid tumors and carcinoma in situ, within 5 years before screening with the following caveats:
- Local basal or squamous cell carcinoma of the skin that has been excised and is considered cured is not exclusionary.
- Chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, or Kaposi sarcoma are exclusionary irrespective of the duration of time before screening.
- Cervical smear indicating the presence of adenocarcinoma I situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of grade>1, is exclusionary, irrespective of the duration of time before screening.
- Follow up IBD-patients who underwent a total colectomy in the past.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-11-2017
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL62103.091.17