# Identification of microbiota-specific mucosal immune responses driving primary sclerosing cholangitis (PSC) and concomitant inflammatory bowel disease (IBD).

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON42112

**Source**
ToetsingOnline

**Brief title**
Understanding PSC-IBD

### Condition

- Gastrointestinal inflammatory conditions
- Hepatic and hepatobiliary disorders

**Synonym**
inflammatory bowel disease with bile duct and/or liver disease

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam
**Source(s) of monetary or material Support:** Ministerie van OC&W, NWO (4-jarig beurs voor PhD salaris)

## Intervention

**Keyword:** Inflammatory bowel disease, Microbiota-specific immune responses, Mucosal T-cells, Primary sclerosing cholangitis

## Outcome measures

### Primary outcome

The primary aim is to characterize mucosal immune responses in concomitant PSC

and IBD

### Secondary outcome

-Number and phenotype of immune cells (neutrophils, monocytes, mucosal T-cells)

in peripheral blood, intestinal tissue and liver tissue;

-Base-line levels of cytokines of mucosal T-cells from peripheral blood and

intestinal biopsies;

-The immunological response of mucosal T-cells from peripheral blood and

intestinal tissue upon re-stimulation with superantigens or microbial peptides;

-Extent of microbial translocation in peripheral blood (measured with 16S rDNA

translocation assay);

-Serological parameters (i.e. anti-flagellin antibodies);

# Study description

### Background summary

Patients suffering from primary sclerosing cholangitis (PSC) with concomitant

inflammatory bowel disease (IBD) may develop progressive liver disease while also having chronic intestinal inflammatory lesions of variable severity and extent. The prognosis is grave, with reported median survival times from diagnosis until liver transplantation or PSC-related death varying from 13 to 21 years within 12 years after diagnosis. In addition, patients carry a high risk for developing malignancies, in particular colon and bile duct cancer.

The disease etiopathogenesis and in particular the immunological mechanisms that underlie PSC-IBD are ill defined. Previously, it has been shown that livers of PSC-IBD patients contain T-cells with a typical *intestinal* phenotype. Moreover, PSC liver cells aberrantly express chemo-attractants that are normally expressed in the intestine. In a clinical study treatment of patients with the antibiotic vancomycin appeared effective in reducing liver damage. On the basis of these data PSC-IBD may be driven by the microbiota specific mucosal immune system. We hypothesize that in PSC intestinal microbiota specific mucosal T-cells are aberrantly present and activated in the liver.

Recently, we found that the surface markers CD62L and CD38 allow identification of intestinal mucosal T-cells within the pool of CD4+ circulating T-cells. Staining of peripheral blood from celiac disease patients who underwent a gluten challenge revealed that virtually all gluten-specific T-cells had a CD62LnegCD38+ phenotype. Thus, by selecting for CD62LnegCD38+ expression that comprises 5-10 % of the cells within the total CD4+ T-cell pool we are able to highly enrich for effector T-cells with specificity for mucosal antigens

**Study objective**

The primary aim is to characterize mucosal immune responses in concomitant PSC and IBD. Secondary objectives are (1) to identify phenotype and function of the mucosal immune responses in peripheral blood, liver and intestinal biopsies of patients with PSC-IBD in comparison with patients with a number of other liver disorders, IBD patients without PSC and normal controls; (2) to assess bacterial translocation in PSC-IBD and its correlation to phenotype, severity and disease course; (3) to dissect differences in mucosal immune responses between children and adults with concomitant PSC and IBD. By combining the above data in a longitudinal study we will be able to dissect the phenotype and function of circulating anti-microbial T cells in peripheral blood of PSC-IBD patients and assess correlation with severity of disease and microbial translocation.

**Study design**

The presented study is a single-center observational study with a four year inclusion period. Patients will be asked to participate by their treating physician during a regular visit to the out-patient clinic. If patients are

eligible and give informed consent, patients will be seen every 6 months by their treating physician. After inclusion, patients will participate in the study until the end of the 4-year study period.

**Study burden and risks**

Our study population will partly consist of pediatric patients, as pediatric PSC-IBD seems to represent a specific group of PSC-IBD patients with a distinct disease phenotype and clinical presentation compared with adults.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

## Inclusion criteria

-Diagnosis of PSC according to generally accepted criteria (EASL diagnostic guidelines): presence of elevated serum markers of cholestasis (ALP, GGT) not otherwise explained, when MRCP or ERCP show characteristic bile duct changes with multifocal strictures and segmental dilatations, and causes of secondary sclerosing cholangitis and other cholestatic disorders are excluded;
-IBD (CD, UC or indeterminate colitis) confirmed by clinical evaluation in combination with endoscopic and histological investigations;
-Informed consent by patients or, when applicable, parents.

## Exclusion criteria

-Diagnosis of immunodeficiency syndromes;
-Secondary causes of sclerosing cholangitis;
-Evidence of decompensated liver disease such as previous variceal bleeding, ascites, or hepatic encephalopathy;
-Anticipated need for liver transplantation within one year; after liver transplantation these patients will be eligible again.
-Findings highly suggestive of liver disease of an alternative or concomitant etiology, such as alcoholic liver disease, hepatitis B or C, haemochromatosis, Wilson*s disease, a1-antitrypsin deficiency, non-alcoholic steatohepatitis, primary biliary cirrhosis;
-Pregnant or lactating patients;
-Active illicit drug or alcohol abuse;
-Suspicion of ascending cholangitis or acute (septic) cholangitis or one of these events in the previous 6 months;
-Any infection necessitating antibiotics use >14 days in the previous 6 months.

# Study design

## Design

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| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Basic science

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 08-06-2015 |
| Enrollment: | 250 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 11-05-2015 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

## 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 | NL51104.078.15 |