Intracellular signaling pathways in Peripheral Blood Mononuclear Cells in patients with inflammatory bowel disease.

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The current project aims to confirm this defective production of IL-8 and explore the possible underlying defect by examining the functionality of the major signal transduction pathways involved in IL-8 production.

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

Summary

ID

NL-OMON29966

Source
ToetsingOnline

Brief title
Inflammatory bowel disease and intracellular signaling pathways

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn□s disease, ileitis terminalis, inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: inflammatory bowel disease, MAPKs, NFkappaB, PBMC

Outcome measures

Primary outcome

Signal intensity on Western Blots 0, 5, 30 en 60 minutes after stimulation with

TNF-alfa or complement factor 5a.

Secondary outcome

not applicable

Study description

Background summary

Crohn*s disease is a chronic inflammatory disease of the gastrointestinal mucosa that affects approximately 1:1000 persons in the Western world. The molecular etiology of Crohn*s disease remains unclear but involves an overactivity of the adaptive immune response with accumulation of IL-12 producing dendritic cells and CD4+ T cells which are geared towards a Th1 phenotype. One theory is that this overactivity may be the indirect result of a defective mucosal innate immune response. According to this theory mucosal recruitment of neutrophils in response to damage or infection is impaired, resulting an immune response which is overly dependent on other phagocytic cell types such as macrophages and dendritic cells resulting in a chronic granulomatous disease.

It has recently been shown that patients with Crohn*s disease indeed fail to induce production of an important chemokine (IL-8) in response to mucosal damage and infection compared to healthy control patients or patients with ulcerative colitis, an other chronic inflammatory intestinal disease. . This phenotype appears systemic as it was found in the intestinal mucosa, skin and Peripheral Blood Mononuclear Cells (PBMCs). Induction of the IL-8 gene involves activation of mitogen activated protein kinases (MAPKs) and nuclear translocation of the NF-kappaB transcription factor complex and we hypothesize that the function of one of these signaling pathways may be compromised in

patients with Crohn*s disease.

Study objective

The current project aims to confirm this defective production of IL-8 and explore the possible underlying defect by examining the functionality of the major signal transduction pathways involved in IL-8 production.

Study design

We will study the activation of four major signaling pathways in the innate immune response in PBMCs isolated form the blood of the patients included in this study. After isolation PBMCs will be stimulated with TNFalfa or complement factor 5a (C5a). The induction of phosphorylation of relevant kinases will be measured on western blot at two time points relative to unstimulated PBMCs using antibodies specific for the phosphorylated (activated) state of the kinases. We will examine phosphorylation of three different mitogen activated protein kinase (MAPK) pathways and of the NF-kappaB pathway.

Study burden and risks

The burden is limited to periferal sampling of 100 ml blood. This induces no signficant risk.

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

Crohn patients in remission, with (n<=20) and without (n<=20) thiopurine immunesuppression, ulcerative colitis patients in remission (n<=20), rheumatoid arthritis patients on azathioprine (n<=10). Diagnosis made by AMC physisian using standard diagnostic tools. Healthy volunteers recruited among AMC collaborators (n<=20)

Exclusion criteria

Patients suffering from active disease, patient using immunesuppressive therapy other than azathioprine

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-07-2006
Enrollment:	90
Type:	Anticipated

Ethics review

Approved WMO

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	NL12366.018.06