T-cell receptor and B-cell receptor repertoire analysis in patients with immune-mediated liver disease

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Objective: Primary objectives: To screen TCR/BCR repertoires in patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and IgG4-associated cholangitis (IAC).Secondary objectives: To determine the influence of disease...

Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON34876

Source
ToetsingOnline

Brief title
RAIL

Condition

- Hepatic and hepatobiliary disorders

Synonym
Auto-immune liver disease, immune-mediated liver 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: B-cell receptor, immune, liver, T-cell receptor

Outcome measures

Primary outcome

The TCR and BCR-repertoire is the main endpoint of the study.

Secondary outcome

To assess the influence of disease activity and treatment on the TCR and BCR

repertoire.

Study description

Background summary

Background: Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and IgG4-associated cholangitis (IAC) are disabling diseases of the biliary tract. Their etiology is incompletely understood, but it is generally accepted that deregulation of the immune system contributes to these conditions. Treatment options are focussed on the inhibition of the progressive destruction of the biliary tract and the consequences of chronic cholestasis including fibrosis, cirrhosis, and the risk of hepatobiliary malignancy, by decreasing bile toxicity, by improving secretory function of hepatocytes and cholangiocytes, and by reducing local damage caused by chronic inflammatory activity. However, these strategies often lead to incomplete responses. Novel therapies are, therefore, needed to more effectively protect these patients against biliary fibrosis, cirrhosis, malignancy and the need for liver transplantation.

T cells and B cells with their unique receptors, respectively the T-cell receptor (TCR) and B-cell receptor (BCR), are major components in the normal adaptive immune response. However, they are also implicated in the pathogenesis of systemic auto-immune diseases such as rheumatoid arthritis (RA), spondylarthropathies (SpA) and systemic lupus erythematosus (SLE). In small-scale analyses of T cell repertoires of patients with primary biliary cirrhosis clonal expansion was reported, but these results should be verified as patient numbers were limited.

When B- and T-cells become activated, they undergo clonal expansion, producing

multiple cells with identical TCRs or BCRs on the cell surface. Previously it has been hypothesized that clonally expanded T-cells or B-cells or so-called disease specific clones are present and possibly causative in auto-immune diseases. Specific targeting of such clones may eradicate antigen-driven immune responses, providing a novel therapeutic strategy to control these diseases.
To identify and quantify specific clones, a microarray based technique was developed in the Department of Clinical Immunology and Reumatology that is able to screen the complete TCR and BCR repertoire for dominant clones or for quantitative changes in this repertoire.

Study objective

Objective: Primary objectives: To screen TCR/BCR repertoires in patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and IgG4-associated cholangitis (IAC).
Secondary objectives: To determine the influence of disease activity and treatment on the repertoire.

Study design

Study design: Explorative study. The work will include patient recruitment and collection of blood samples. Lymphocyte DNA will be isolated from tissue by laser capture microdissection if liver biopsy specimens are available. The TCR and BCR repertoire will be analysed for specific clones using a novel microarray sequencing technology that was validated for repertoire screening in rheumatoid arthritis patients.

Study burden and risks

Burden:
Patients will visit the Investigator a total of 5 times during 10 years.

Risks:
The risks associated with participation in this study are those associated with the performance of a vena punction. These risks include hematoma, protracted bleeding and flebitis.

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

- Patients diagnosed with the diagnosis of PBC, PSC or IAC (study groups), or AIH or hepatitis C (disease controls)
- The diagnosis must be confirmed using the appropriate criteria (see: EASL Clinical Practice Guidelines, J Hepatol 2009;51:237).
- Patients need to be 18 years of age or older

Exclusion criteria

Inability to provide informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2010
Enrollment:	50
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	NL31142.018.09