Adoptive Transfer of T cell Receptor-engineered T cells to treat hepAtocellular Carcinoma recurrence after liver Transplantation: a preclinical feasibility study

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To isolate and validate TCRs that exclusively recognize liver antigens presented by specific (*recipient*) HLA-molecules (LSARH) on the surface of tumor cells.

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

Summary

ID

NL-OMON47991

Source
ToetsingOnline

Brief title
ATTRACT

Condition

- Hepatic and hepatobiliary disorders
- Autoimmune disorders
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Liver Cancer; Primary Liver Cell Carcinoma

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

Intervention

Keyword: Adoptive T-cell therapy, Hepatocellular carcinoma, Immunotherapy, Liver transplantation

Outcome measures

Primary outcome

(a series of) TCR(s) that have a high affinity and show exclusive recognition

of liver antigens when presented by HLA molecules of liver transplant

recipients, and that can safely be used in a future clinical trial of adoptive

T cell therapy for HCC recurrence after LTx.

Secondary outcome

N/A.

Study description

Background summary

An increasing indication for liver transplantation (LTx) is hepatocellular carcinoma (HCC). Despite LTx, HCC often recurs, after which prognosis is dismal. From an immunological point of view the post-transplant setting is of a particular interest since donor and recipient of the transplant liver have a different Human Leukocyte Antigen (HLA)-background. The objective of this pilot study is to isolate T cell receptors (TCR) that are highly specific for liver antigen presented by recipient HLA expressed on residual tumor cells of recipients of liver transplants.

Adoptive transfer of T cells gene-engineered with antigen-specific receptors has proven its feasibility and therapeutic potential in the treatment of cancer. Recently, T cells gene-engineered to express a HBV-specific TCR have been described treating recurrent HBV-related HCC after liver transplantation. However, in HBV-low endemic regions (e.g. Western society) targeting HBV

antigens to treat HCC will only have limited impact.

We hypothesize that gene-engineered TCRs recognizing liver-specific antigen in the context of recipient HLA (LSARH) have a unique safety profile and are suited for adoptive T cell therapy for all patients with HCC recurrence after LTx, independent of the cause of the liver disease

Study objective

To isolate and validate TCRs that exclusively recognize liver antigens presented by specific (*recipient*) HLA-molecules (LSARH) on the surface of tumor cells.

Study design

Expression of pre-selected non-secretory liver-specific antigens will be validated ex vivo in healthy liver and HCC tissues. In silico predicted HLA epitopes of the validated antigens will be tested in vitro for HLA binding and immunogenicity to select peptides being most potent in inducing T cell responses.

A cohort study in autoimmune hepatitis (AIH) patients (N=35) will be conducted as these are highly likeable to have enhanced frequencies of circulating LSARH-specific T cells. Peripheral blood mononuclear cells (PBMCs) from AIH patients will be co-cultivated with the highest ranked peptides and T cell supporting cytokines to enrich for LSARH-specific T cells. T cells harboring peptide-HLA cognate TCRs and responding to peptide stimulation will be sorted and TCRs will be sequenced. Obtained TCR genes will be cloned into viral expression vectors to express TCR in lymphocytes by viral transduction. TCRs will be tested in vitro for liver/tumour specificity and lack of cross-reactivity.

Study burden and risks

Intervention: invasive measurement of 80mL of blood collected at the out-patient clinic during regular check-ups. No benefit and negligible risk for the patients are expected. Hopefully, the results of this study will benefit HCC patients after liver transplantation in the future.

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 autoimmune hepatitis
- Age: 18 years or older
- Written informed-consent

Exclusion criteria

- Patients with current use of immune suppressive agents/medication, not other specified
- Patients with an immunocompromised medical condition, not other specified
- Patients who refuse to participate in the study (refusing blood donation)
- Patients that for medical reasons are judged unfit to donate blood by the treating physicians

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2019
Enrollment:	35
Type:	Anticipated

Ethics review

Approved WMO

Date:	28-10-2019
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	NL70521.078.19