Tacrolimus versus mycophenolate for AutoImmune hepatitis patients with incompLete response On first line therapy: a Randomized trial

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The aim of this study is to compare the effectiveness of TAC with MMF as a second line treatment for AIH. Proportion of patients with CR after 12 months of treatment will be the primary outcome parameter to determine effectivity.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON49891

Source
ToetsingOnline

Brief title
TAILOR

Condition

- Hepatic and hepatobiliary disorders
- Autoimmune disorders

Synonym
Autoimmune hepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW,Chiesi Farmaceutici,Chiesi Pharmaceuticals

Intervention

Keyword: Autoimmune hepatitis, Liver disease, Mycophenolate mofetil, Tacrolimus

Outcome measures

Primary outcome

Difference in proportion of patients with CR at 12 months (normalization of

ALT, AST and IgG) between the TAC and MMF treatment group.

Secondary outcome

Secondary parameters:

- Safety and tolerability of TAC and MMF treatments

- Difference in proportion of patients with CR at 6 months (normalization of

ALT, AST and IgG) between the TAC and MMF treatment group.

- Difference in ALT, AST and IgG at 6 and 12 months versus baseline

- Difference in fibrogenesis and fibrosis parameters between groups and before

and after treatment

- Difference in quality of life between groups and before and after treatment

Study description

Background summary

The combination of azathioprine and prednisone is the first-line treatment for autoimmune hepatitis (AIH), a chronic inflammatory disease of the liver. Complete biochemical remission (CR) is the first treatment goal in autoimmune hepatitis. CR is determined by AST and ALT and IgG within the reference range.

CR is not reached in a substantial proportion of AIH patients: after one year 50%, after three years around 20% did not achieve CR. Without CR ongoing hepatitis leads to progression towards fibrosis and eventually (decompensated) cirrhosis. Not achieving CR is the most important risk factor for the need for liver transplantation or liver related death, independent of age and presence of cirrhosis. Tacrolimus (TAC) and mycophenolate mofetil (MMF) are frequently used to prevent rejection in kidney and liver transplant patients. In AIH patients with insufficient response or intolerance to first-line therapy in retrospective cohort studies with MMF 0-57% and with TAC 20-95% CR was reached.

Study objective

The aim of this study is to compare the effectiveness of TAC with MMF as a second line treatment for AIH. Proportion of patients with CR after 12 months of treatment will be the primary outcome parameter to determine effectivity.

Study design

Randomized open-label two arm study. Patients will be randomized between treatment with TAC or MMF.

Intervention

In the TAC group baseline treatment will be replaced by tacrolimus. In the MMF group baseline treatment will be replaced by MMF. The current dose of prednisolone, or at least 5 mg daily, will be continued in both arms. After achieving CR prednisolone will be tapered according to protocol.

Study burden and risks

The burden of this study consists of:
- 5 visits to the outpatient clinic in a 12 month period
- Extra blood samples will be taken
- 3 fibroscans will be performed
- 3 times patients will be asked to fill in questionnaires regarding quality of life

Most importantly, patients could reach complete biochemical remission. Complete biochemical remission is an important treatment goal in autoimmune hepatitis to prevent further progression to (decompensated) cirrhosis, liver transplantation or liver related death. Additionally, patients could possibly benefit from second-line treatment by experiencing a decrease of symptoms.

Risks of the study consist of side-effects of TAC or MMF. As TAC and MMF are widely used in transplant patients side effects are well known and dose related. In case of severe side effects the dose can be lowered or study

medication can be discontinued.
Besides side effects, increased immunosuppression could lead to infections. Several precautions will be taken during the study to minimise the risk. Patients will be screened for latent infections before the study and other immunosuppressive medication is stopped.

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

• Patient is older than 18 years old
• Probable or definite auto immune hepatitis according to the original or simplified IAIHG criteria (>10 points pre-treatment on the original criteria or >6 points on the simplified criteria)(2, 3)
• Incomplete responder on at least a half year of first-line treatment, with at

least last 6 months azathioprine / 6-MP) / 6-TG and prednisolone or budesonide, and ALT 1.5 - 10x ULN for at least 2 months
• Patient is capable of understanding the purpose and risks of the study, has been fully informed and has given written informed consent to participate in the study

Exclusion criteria

• Presence of decompensated liver disease, defined as ascites, coagulopathy (INR >1.5), encephalopathy, variceal bleed, hepatopulmonal syndrome, hepatorenal syndrome or HCC in the past 6 months
• Signs of other liver diseases as NAFLD, Wilson disease, hemochromatosis, alcoholic liver disease or hepatitis B/C/D
• Clinical diagnosis of overlap / variant syndrome with PBC or PSC
• Liver transplantation in the medical history or currently on the waiting list for liver transplantation
• Incompliance with therapy during the last 12 months
• Active infections during inclusion including latent tuberculosis and HIV co-infection
• Allergic or hypersensitive to tacrolimus or MMF
• An estimated glomerular filtration rate (eGFR) of <60 mL/min
• Pregnancy or intention to become pregnant in the next 12 months
• Use of TAC or MMF in the past
• Malignancy in the medical history in the past five years, with no history or current use of chemotherapy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-01-2022
Enrollment:	86
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cellcept
Generic name:	Mycophenolate mofetil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tacrolimus
Generic name:	Tacrolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-08-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	13-12-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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
EudraCT	EUCTR2021-003420-33-NL
CCMO	NL78216.058.21