The therapeutical efficacy of senolytic drugs in the treatment of non-alcoholic fatty liver disease with fibrosis - the truth study

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This study has been transitioned to CTIS with ID 2024-517593-21-00 check the CTIS register for the current data. To examine the effect of oral dasatinib plus quercetin on liver fibrosis as assessed by histology in individuals with biopsy-proven...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53809

Source
ToetsingOnline

Brief title
Truth

Condition

- Other condition

Synonym
Hepatic Steatosis, Non-Alcoholic Fatty Liver Disease

Health condition

NAFLD met leverfibrose

Research involving

Human

Sponsors and support

Primary sponsor: vasculaire geneeskunde
Source(s) of monetary or material Support: ZONMW

Intervention

Keyword: Dasatinib, NAFLD, Quercetine, senescence

Outcome measures

Primary outcome

The primary objective is to examine the effect of dasatinib plus quercetin on liver fibrosis as histologically assessed in individuals with biopsy-proven NAFLD with fibrosis by performing a double*blind randomized controlled proof*of* principle study. The primary endpoint is the binary outcome improvement of fibrosis with at least 1-point without worsening of fibrosis and NAFLD score based on histology after 21 weeks (yes/no).

Secondary outcome

1. To examine the effect of dasatinib plus quercetin on liver related histological parameters and high dimensional data by addressing the:

- mean number of senescent cells baseline vs end of treatment (week 21).
- percentage of patients with reversal of NAFLD and no worsening of fibrosis (week 21).
- differences in hepatic gene expression (determined by RNA seq) baseline vs end of treatment (week 21).
- differences in NAFLD activity score (NAS) baseline to end of treatment (week

21).

- activity component of NAFLD using the steatosis-activity-fibrosis (SAF) score baseline vs end of treatment (week 21).

- Differences in EPOS 7-tier staging system score baseline to end of treatment (week 21)

2. To examine the effect of dasatinib plus quercetin on biomarkers of NAFLD by addressing the:

- Fibrosis-4 score (Fib-4 score) and NAFLD Fibrosis Score (NFS) baseline vs end of treatment (week 21).

- circulating liver enzymes and synthesis function (e.g., ALT, AST, and γGT, albumin, INR) baseline vs end of treatment (week 21).

- liver stiffness and liver steatosis (with controlled attenuation parameter) using Fibroscan baseline vs end of treatment (week 21).

3. To examine the effect of dasatinib plus quercetin on glucose metabolism-related parmaters by addressing the:

- glycosylated haemoglobin type A1c (HbA1c), fasting plasma glucose (FPG), fasting insulin and glucagon baseline vs end of treatment (week 21).

- Homeostatic model assessment of insulin resistance (HOMA-IR) baseline vs end of treatment (week 21).

- Glucose day curve (Freestyle libre)

4. To examine the effect of dasatinib plus quercetin on patient reported outcome including by addressing:

- RAND-36 and EQ-5D-5L: physical and mental component summary scores and scores on the individual sub-domains: Physical functioning, daily functioning, bodily pain, general health, vitality, social functioning, and role emotional and mental health, baseline vs end of treatment (week 21).

5. To examine the safety of dasatinib plus quercetin as assessed by:

- Number of treatment-emergent adverse events during the trial, during the trial.
- Number of treatment-emergent myelosuppression, during the trial.
- Number of treatment emergent infections, during the trial.
- Number of patients discontinuing treatment due to gastrointestinal adverse events, during the trial.

6. To examine the effect of dasatinib plus quercetin on:

- Pulse, blood pressure, blood pressure and ECG, baseline vs end of treatment (week 21).
- Physical examination, baseline vs end of treatment (week 21).
- Haematology (haemoglobin, thrombocytes, erythrocytes, leucocytes, differential count), during the trial.
- Biochemistry (creatinine, creatinine phosphokinase, urea, bilirubin (total),

alkaline phosphatase, ferritin, sodium, potassium, calcium), during the trial.

- Fecal microbiota composition (morning stool and bile acids)

Study description

Background summary

Non-Alcoholic Fatty Liver Disease (NAFLD) is estimated to affect approximately 25-30% of the population in Western countries and is now the leading cause of chronic liver disease globally. NAFLD is a progressive liver disease and approximately 30% of individuals progress from simple steatosis to Non-Alcoholic Steatohepatitis (NASH), which can further progress to cirrhosis and hepatocellular carcinoma. In the Netherlands, it is estimated that 2.5 million people have NAFLD. This number is thought to increase by 50% in the next 10 years. This is mainly due the rising prevalence of obesity and type 2 diabetes, and an aging population, which are main drivers of NAFLD. Independent of other cardiometabolic diseases, cardiovascular disease is the leading cause of death in individuals with NAFLD, followed by extrahepatic malignancies and liver-related complications. NAFLD results in sustained healthcare costs and economic losses, and reduced health-related quality of life.

It is now widely accepted that liver fibrosis is a result of liver injury secondary to NAFLD and is a major predictor for liver-related and overall mortality in individuals with NAFLD. The process of fibrosis progression is not completely understood, and it can vary considerably from one individual to another. Several risk factors for fibrosis progression have been identified including age, hypertension, obesity and type 2 diabetes. As of to date, no treatment is available that proved to be successful to target hepatic fibrosis. The only therapeutic options currently available therefore are diet and lifestyle changes and control of concomitant metabolic diseases. Unfortunately, this inevitably leads to polypharmacy, which decreases treatment adherence and increases the risk of adverse events and interactions with other drugs.

Considering the role of senescence in NAFLD-related fibrosis, dasatinib plus quercetin might be an interesting therapeutic intervention to meet the high unmet clinical need for NAFLD. Importantly, dasatinib and quercetin have a strong long-term safety profile. We therefore aim to perform a double*blind randomized controlled proof*of*principle study in which patients with NAFLD-related liver fibrosis will be treated with dasatinib plus quercetin. The treatment will be intermittent (three days per week for three weeks) followed by a four-week medication-free period. This treatment cycle will be repeated

three times.

Study objective

This study has been transitioned to CTIS with ID 2024-517593-21-00 check the CTIS register for the current data.

To examine the effect of oral dasatinib plus quercetin on liver fibrosis as assessed by histology in individuals with biopsy-proven NAFLD with fibrosis by performing a double*blind randomized controlled proof*of*principle study. The primary endpoint is the binary outcome improvement of fibrosis with at least 1-point without worsening of fibrosis and NAFLD score based on histology after 21 weeks (yes/no).

Study design

Double*blind randomized controlled proof*of*principle study in which 30 patients with fibrotic NAFLD will use dasatinib plus quercetin intermittently three days per week for three weeks, followed by a four-week medication-free period. This treatment cycle will be repeated three times and thus a total of 21 weeks.

Intervention

Intermittent oral administration of a combination of Quercetin and Dasatinib or a placebo

Schedule (total of 21 weeks):
3 weeks: 3 days a week a daily dose of 1000 mg Quercetine +100 mg Dasatinib, or placebo.
Followed by a medication free period of 4weeks.
This cycle will be repeated 3 times.

Study burden and risks

With the help of the Nederlandse Leverpatienten Vereniging (NLV, director drs J. Willemse), we estimated that the total study burden is in balance with potential risks and benefits of participation for patients with liver disease in in this study. Nevertheless, the study can be considered extensive and invasive for the participants due to following procedures:

1. Liver biopsy: Study participants will undergo a liver biopsy at the end of the study (or at baseline when no baseline biopsy was performed within six months prior to the start) because a Fibroscan, MRI or ultrasound, although non-invasive, are inferior for the accurate diagnosis and are therefore not used in clinical trials for primary endpoints1 Although a liver biopsy is an

invasive procedure, it remains the gold standard for the diagnosis of NAFLD and is therefore required for the interpretation of the results.

Given the fact that the individuals are recruited via our outpatient NAFLD clinic, oftentimes a biopsy of the liver has already been performed. Therefore, only one additional biopsy is necessary for this trial. Liver biopsies are performed after informed consent, via the AMC intervention radiology department or gastroenterology department for an ultrasound-guided liver biopsy to assess NAFLD/NASH histology. As an experienced hepatologist or interventional radiologist will perform the liver biopsy, the risk of complications will be very low (<0.1%) and comprises mostly bleeding at the biopsy sites (see METC 2017_311, 2019_61 and 2022_236). Bleeding disorders therefore are an exclusion criterion.

2. Safety and tolerability: A possible pitfall is the safety and tolerability of the senolytic drug. However, intermittent dasatinib plus quercetin treatment has an exceptionally good safety profile. Worldwide, hundreds of individuals are enrolled in clinical trials using dasatinib plus quercetin (Table 2, page 25-26) for a variety of conditions, with no severe or serious side effects so far. Dasatinib alone has been approved as prescription drug in the EU for various cancers and for fibrotic diseases (scleroderma, progressive systemic sclerosis), usually at doses of 100 mg/day for life. Of interest, in contrast to other tyrosine kinase inhibitors, dasatinib usage is not associated with an increased risk of hepatotoxicity. Recently, the suggestion that dasatinib is associated with improved glucose metabolism and decreased need for glucose lowering medication was further substantiated. Side-effects of dasatinib include abdominal pain, vomiting, diarrhea, musculoskeletal pain, tiredness, and myelosuppression. Another side effect, which may occur after months of continuous use, include peripheral edema and pleural effusions. Importantly, it has been described that a twice daily dasatinib regimen, as well as a history of cardiac or autoimmune disease, are suspected as predisposing factors. To minimize such risks, these predisposing factors are exclusion criteria in the present RCT. In addition, pleural effusion is driven by a reactive oxygen species (ROS) dependent mechanism. Importantly, these sides effects are reversible. In addition, a recent study showed that the increased endothelial permeability, which drives the side-effects, can be counteracted using antioxidants such as quercetin. Hence, quercetin is not only a senolytic agents by itself, but the combination of dasatinib plus quercetin appears a highly effective and safe drug combination to selectively target age-related diseases via an intermittent treatment strategy.

3. Treatment adherence: In the past decades, extensive research has given important insight into the many complex factors that determine how and why individuals take prescribed drugs. The focus has been on the consumers factors that relate to non-compliance. However, there is also growing awareness that factors beyond consumers' control can affect adherence. It is now widely accepted that communication in its entirety is critical, and it is increasingly

accepted that interventions to improve adherence should focus more broadly on patient context and healthcare system. Patient*centered care and shared decision*making, together with increased attention to barriers that may be targets for interventions is pivotal.

With the input of the NLV (Dutch Liver Patient Society), we created a fundamental basis to make our intermittent treatment strategy attractive and to increase compliance similar to once weekly GLP-1 injections or vitamin D supplementation treatment strategy. In this regard, the NLV was closely involved in the currently acquired ZONMW GGG grant (number 10140262110036) that provided funding to execute this TRUTH trial. The NLV mentioned that regular contact with patients should be implemented in the study to remind the individuals to take their medication to increase adherence. If an individual is found to be non-compliant, the investigator will remind the individual of the importance of following the treatment instructions. Treatment compliance of the trial products will be assessed by asking individuals about missed doses and monitoring of dosing diaries. Information about compliance and missed doses will be descried in the individual*s medical record.

All in all, the proposed trial is important considering the fact that there is currently no registered treatment for NAFLD. Moreover, patients with NAFLD/NASH often have cardiometabolic comorbidity, which can lead to polypharmacy with associated health risks and non-compliance. Senolytics can be orally administrated intermittently, which reduces the risks of adverse effects and drug interactions. In view of the expired patent of dasatinib, targeting senescence might be a safe and innovative way to use generic and safe medication to reverse progressive stages of NAFLD/NASH.

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

- Diagnosis of NAFLD with fibroses score *2 on liver biopsy
- Diagnosis of DM type 2 on stable metformin
- No hepatis B and/or C
- 18-70 years of age
- Subjects should be able to give informed consent

Exclusion criteria

- Compromised immunity - Use of anticoagulants - QTc>450 msec on ECG - Known genetic basis for insulin resistance or glucose intolerance - Ethanol intake > 14 U/week - Pregnancy, females who are breastfeeding - Auto-immune hepatitis - Wilson disease3/ alpha 1-antitripsine deficiency - Hemochromatosis - When subjects use drugs that are dependent on CYP3A4 with narrow therapeutic window and strong inducers or inhibitors of CYP3A4 , the responsible clinician will be consulted to discuss the necessity of dose modification or alternative drug replacement. When this is not optional, subjects will be excluded. - Use of H2-antagonists and/or proton pump inhibitors

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-07-2023
Enrollment:	33
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Sprycel
Generic name:	Dasatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-02-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2024
Application type:	Amendment
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
EU-CTR	CTIS2024-517593-21-00
EudraCT	EUCTR2021-005859-37-NL
ClinicalTrials.gov	NCT05506488
CCMO	NL82729.018.22