LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) The European NAFLD Registry

Published: 12-12-2018
Last updated: 19-08-2024

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

Summary

ID

NL-OMON48831

Source
ToetsingOnline

Brief title
LITMUS

Condition

- Hepatic and hepatobiliary disorders

Synonym
NAFLD, non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: EU;bedrijven

Intervention

Keyword: biomarkers, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), registry

Outcome measures

Primary outcome

• Cross-sectional correlation of clinical phenotype data with blood-based biomarkers (genetic, epigenetic, transcriptomic, metabolomics, proteomic and metagenomic) and/or imaging biomarkers to develop and validate optimum biomarker approaches for the diagnosis and risk stratification of NAFLD.

Secondary outcome

• Longitudinal correlation of clinical phenotype data with blood-based biomarkers (genetic, epigenetic, transcriptomic, metabolomics, proteomic and metagenomic) and/or imaging biomarkers to develop and validate optimum biomarker approaches for the diagnosis, risk stratification and monitoring of NAFLD.

• Study of dietary habits and lifestyle factors (sedentary behaviour/exercise levels) in patients with NAFLD;

• Study of symptom burden in patients with NAFLD to develop and validate a new disease-specific Patient Reported Outcome Measure (PROM) for NAFLD.

• Study the underlying pathogenic processes contributing to disease progression in NAFLD:

o Conduct of candidate gene and genome-wide disease association studies (GWAS) to identify genetic variants influencing disease severity in NAFLD;

o Analysis of circulating miRNA, mRNA and DNA methylation (mDNA) profiles in

the liver and/or blood of patients with NAFLD;

o Study of the blood lipid/metabolic/proteomic profiles of patients with NAFLD;

o Study of the intestinal bacterial flora of patients with NAFLD;

Study description

Background summary

Internationally, there is a dramatic increase in the number of patients presenting with liver disease, with as many as 1 in 10 of the population having some form of liver disorder. Recent estimates have suggested a doubling of liver disease mortality over the next decade. Liver disease is also associated with considerable morbidity, ranging from impaired quality of life through to the classical complications of advanced liver disease including liver failure, variceal bleeding, ascites, encephalopathy and hepatocellular carcinoma. These conditions, all the result of progressive liver fibrosis, are the complications that dominate the wards of Liver Units throughout the country. One of the major reasons for the increase in mortality from liver disease is the well-publicised "obesity epidemic" pre-disposing to non-alcoholic fatty liver disease (NAFLD)1. Non-alcoholic fatty liver disease (NAFLD) represents a spectrum from isolated hepatic fat accumulation (steatosis, NAFL); through hepatic fat accumulation plus inflammation (non-alcoholic steatohepatitis, NASH); and ultimately progressing to fibrosis/cirrhosis and potentially hepatocellular carcinoma in the absence of excessive alcohol consumption2.
NAFLD is strongly associated with the Metabolic Syndrome (MetS) including obesity, type 2 diabetes mellitus (T2DM) and dyslipidaemia2, 3. With the advent of increasingly sedentary lifestyles and changing dietary patterns, NAFLD prevalence has increased dramatically in concert with the rapidly progressing epidemics of both adult and childhood obesity and T2DM. Although estimates vary, one large European study found NAFLD in 94% of obese patients (BMI >30 kg/m2), 67% of overweight patients (BMI >25 kg/m2), and 25% of normal weight patients3. The overall prevalence of NAFLD in T2DM ranges from 40-70%3. NAFLD has therefore become one of the top concerns for practising hepato-gastroenterologists and endocrinologists due to its potential to progress to advanced liver disease and metabolic complications2, 4. NASH is projected to be the principal aetiology for liver transplantation within the decade. Importantly, there is a growing body of clinical and epidemiological evidence suggesting that NAFLD leads to not only liver-related mortality but also worsening insulin resistance and increased risk of ischaemic heart disease and stroke2, 5. However, in planning health strategies related to obesity and T2DM, MetS-related NAFLD and its clinical impact has often been forgotten.
NAFLD is characterized by substantial inter-patient variability in terms of

severity and rate of progression: although a large proportion of the population is at risk, only a minority experience associated morbidity2, 6. Epidemiological evidence indicates that patients with NASH are at significantly greater risk than those with NAFL. However, what determines the progression to NASH and beyond is not clear and these groups can only be differentiated by liver biopsy, a procedure that is not well suited to widespread use given the size of the population at risk of NAFLD4, 5. Key challenges are to understand the biological and environmental factors that drive inter-patient variability within the NAFLD spectrum and to use this understanding to develop robust methods for diagnosis, risk stratification (e.g. NAFL vs. NASH) and therapy so that effective medical care may be targeted to those at greatest risk7. Current evidence suggests that pathogenesis is driven by a combination of genetic/epigenetic factors8, 9 interacting with the intestinal microbiome and nutritional factors2. However, many of the specific factors are unidentified or uncharacterised and the nature of these interactions is not yet understood. The transition from NAFL to NASH and the stage of fibrosis are important discriminators between a relatively benign prognosis and an increased risk of morbidity/mortality2, 10. Liver biopsy remains the established but imperfect *gold standard* investigation being invasive, resource intensive, prone to sampling error and carrying a small but significant risk of complications11. Such invasive tests are not practical outside specialist practice, and are particularly unsuitable with such a large *at risk* population. A lack of tractable non-invasive biomarkers has impeded the diagnosis, risk stratification and monitoring of patients6. It has also hampered drug development and the conduct of clinical trials, which still depend on histological effect as an endpoint. The overarching aim of LITMUS is to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage. Success will help target care to those at greatest risk, facilitate drug development and ultimately give patients access to approved medicines. To support drug development optimally, LITMUS will align its data generation and processes to comply with the European Medicines Agency (EMA)/US Food and Drug Administration (FDA) accord for Qualification of Biomarkers & Clinical Outcome Assessments. Our ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to/regression from NAFL through NASH to fibrosis and cirrhosis; to provide a clear path for regulatory biomarker qualification as surrogate endpoints for therapeutic trials or as diagnostics; to assist drug development and to enable cost-effective diagnosis and management of NAFLD.

Study objective

1. The primary objective of the European NAFLD Registry observational study is to assemble a cohort of well-characterised patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and to collect associated clinical information, biological samples and imaging data for cross-sectional and longitudinal analyses in order to robustly develop and validate biomarkers for the

diagnosis, risk assessment (prognosis) and monitoring of patients with liver disease.
2. The secondary objectives are to explore the pathophysiology of NAFLD using a range of start-of-the-art scientific techniques and an integrated data-analysis approach:
a. This will characterise key intrinsic factors using a multiple *omics* approach:
i. Genetic differences between patients of varying severity of NAFLD by determining genome-wide single nucleotide polymorphism (SNP) profiles and genetic variation.
ii. Epigenetic variation in liver tissue and circulating cell-free DNA from patients with varying severity of NAFLD by measuring DNA methylation (mDNA) and/or histone acetylation patterns in liver biopsy samples.
iii. Hepatic and circulating mRNA/miRNA expression profiles (transcriptomics) in patients with varying severity of NAFLD.
iv. Circulating metabolomic/lipidomic and proteomic profiles that may reflect underlying disease activity and progression.
v. Faecal bacterial diversity to determine how the above are influenced by the microbiome.
b. Central reading and adjudication of liver biopsies by an international team of expert hepatopathologists using standardised techniques as the *gold standard* measure of disease severity. Digital imaging of liver biopsies to generate a permanent record of histological variation in the LITMUS cohort.
c. These datasets will be computationally integrated and analysed to correlate inter-individual variations with severity of liver injury, serum and hepatic metabolomic/lipidomic/protemic/fibrotic profiles and behavioural (exercise)/dietary factors. This study will thus deliver a substantial and definitive atlas of pathophysiological variation across a spectrum of progressive liver disease and support identification of novel biomarkers for clinical use.
d. To determine whether factors identified in the cross-sectional study predict long-term outcomes and future disease progression.

Study design

The European NAFLD Registry is a prospectively recruited, observational study exploring the pathophysiology of progressive liver disease, disease outcomes and predictive factors in a cohort of patients with NAFLD. The ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to/regression from NAFL through NASH to fibrosis and cirrhosis.
This Master Protocol focuses principally on the recruitment of patients into the European NAFLD Registry, collection of available clinical, imaging and laboratory data from care records generated during routine medical care as well as the collection and use of biological samples for research use. It serves as the basis for a broad international project to discover and validate biomarkers for NAFLD and associated medical conditions (LITMUS). Out-with the current

study, following separate ethical approval and after separate consent, patients who have agreed to join the European NAFLD Registry may also agree to participate in a number of nested sub-studies with bi-directional sharing of data as necessary (see Section 11.2).

Study burden and risks

Registry study, negligible 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

1. Age >=18 years

2. Clinically suspected NAFLD based on any of:
a. Patient with historical liver biopsy providing histological evidence of NAFLD or,
b. Patient undergoing liver biopsy for suspected NAFLD with biochemical and/or radiological findings consistent with NAFLD or,
c. Patient with radiological evidence of cirrhosis (in absence of an alternative aetiology) plus presence of >=2 features indicative of the *metabolic syndrome*:
i. Increased waist circumference by ethnically adjusted criteria (e.g. Europid male/female >=94cm/80cm) or overweight/obese (BMI >=25);
ii. Raised fasting glucose >=100 mg/dL [5.6 mmol/L], HbA1c >=48mmol/mol (6.5%) or previously diagnosed insulin resistance/type 2 diabetes mellitus (or on treatment);
iii. Dyslipidaemia (fasting TG level >=150 mg/dL [1.7 mmol/L]; or fasting HDL <40 mg/dL [1.03 mmol/L] in males and <50 mg/dL [1.29 mmol/L] in females; or on treatment);
iv. Hypertension (systolic BP >=130 or diastolic BP >=85 mmHg, or on treatment).
3. Average alcohol consumption less than 21/14 units/week (males/females) in preceding 6 months and no history of sustained excessive consumption of alcohol in past 5 years.

Exclusion criteria

1. Refusal or inability (lack of capacity) to give informed consent.
2. Average alcohol ingestion greater than approximately 21/14 units/week (males/females) in preceding 6 months or history of sustained excessive consumption of alcohol in past 5 years.
3. History or presence of Type 1 diabetes mellitus.
4. Presence of any other form of chronic liver disease except NAFLD.
5. Recent (within 12 months) or concomitant use of agents known to cause hepatic steatosis (long-term systemic corticosteroids [>10 days], amiodarone, methotrexate, tamoxifen, tetracycline, high dose oestrogens, valproic acid).
6. Any contra-indication to liver biopsy.
7. Recent (within 3 months) change in dose/regimen or introduction of Vitamin E (at a dose >=400 IU/day), betaine, s-adenosyl methionine, ursodeoxycholic acid, silymarin or pentoxifylline.
8. Non-Dutch speaking/unable to access an interpreter. Due to the nature of the study, Dutch language or access to a relevant interpreter is a necessary criterion to ensure lifestyle (diet and exercise) and symptom data are collated.
9. Patients not meeting inclusion criteria or judged by the investigator to be unsuitable for inclusion in the study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2019
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	12-12-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2019
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
CCMO	NL66777.018.18