Genetic risk factors for hepatotoxicity during anti tuberculosis treatment.

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON29714

Source
ToetsingOnline

Brief title
HEPTB

Condition

- Other condition
- Mycobacterial infectious disorders

Synonym
hepatotoxicity, liver side effects

Health condition

leverbijwerkingen van standaard tuberculosebehandeling

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,KNCV Tuberculosefonds te Den Haag

Intervention

Keyword: Drug therapy, Hepatotoxicity, Risk factors, Tuberculosis

Outcome measures

Primary outcome

Association between ATDH and genetic polymorphisms (single nucleotide polymorphisms) in drug metabolising enzymes and regulators of enzyme expression.

Enzymes: N-acetyltransferase 2, glutathione S-transferase, cytochrome P450 2E1.

Receptors: pregnane X-receptor (PXR), multidrug resistance gene 1 (MDR1).

Secondary outcome

Association between ATDH and other risk factors, including age, sex, weight and length, underlying liver disease and HIV-status.

Study description

Background summary

Therapy adherence is crucial for curing patients with active tuberculosis (TB). Incomplete treatment can result in remission of disease and contributes to drug-resistance. Side effects significantly contribute to non-adherence. Standard TB treatment contains isoniazid, rifampicin, pyrazinamide and ethambutol. Anti-TB drug-induced hepatotoxicity (ATDH), one of the most serious side effects, occurs in 2% to 28% of the patients. This rate depends on the investigators* definition of hepatotoxicity as well as the population studied. Previous described risk factors include advanced age, female sex, underlying liver disease (hepatitis B/C), HIV infection, malnutrition and alcohol use. Metabolism is important in the development of ATDH and reactive metabolites are

crucial. Genetic variation in biotransformation of TB drugs, caused by genetic polymorphisms, may result in an increased formation or toxicity of reactive metabolites which increases the risk on ATDH. Several genetic polymorphisms have been associated with ATDH (N-acetyltransferase 2, glutathione S-transferase, cytochrome P450 2E1).
In summary, genetic factors may predispose to the adverse effects of anti-tuberculous drugs. They interact in a complex way and may explain why some individuals develop ATDH. The relative importance of specific genetic polymorphisms is unknown and their interplay has not been evaluated in detail.

Study objective

1. The central hypothesis of this study is that genetic polymorphisms in drug metabolising enzymes and regulators of enzyme expression may predispose to ATDH. We propose to evaluate the presence of genetic polymorphisms among TB patients in different parts of the world. An association between specific polymorphisms and the occurrence of ATDH will be sought.
2. Knowledge on the relevance of specific polymorphisms in the development of ATDH may allow the identification of patients at risk of ATDH. They can possibly be offered adjusted treatment regimens.

Study design

We will conduct a case-control study in three world regions with varying incidences of ATDH and varying risk factor prevalence: the Netherlands and United Kingdom, Indonesia and Tanzania. Cases are TB-patients with liver toxicity during treatment and controls are TB-patients without ATDH.

Study burden and risks

We want to draw 10 ml venous blood of all cases and controls. The risk of venous blood drawing is negligible.

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 treated for tuberculosis (pulmonary or extra-pulmonary) with standard treatment containing at least isoniazid, rifampicin and pyrazinamide.
- Age: above 18 years.

Exclusion criteria

- Patient receives treatment for multi-drug resistant tuberculosis.
- Patient also receives antiretroviral treatment and developed liver function disorders immediately after the start of ART.

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):	01-07-2006
Enrollment:	325
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL12524.091.06