The BOKITO-2B Study: Tenofovir DF Bone and Kidney Toxicity.;Incidence and reversibility in HBV-monoinfected patients.

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

Summary

ID

NL-OMON35281

Source
ToetsingOnline

Brief title
BOKITO-2B

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
chronic hepatitis B, viral liver infection with hepatitis B virus

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: bone toxicity, hepatitis B, kidney proximal tubular dysfunction, tenofovir

Outcome measures

Primary outcome

1. The prevalence and incidence of renal insufficiency and kidney proximal tubular dysfunction (KPTD) in chronic hepatitis B patients on tenofovir, entecavir or without treatment.

KPTD is defined as the presence of at least two of the following; a decreased renal threshold phosphate concentration (TmP/GFR < 0.80 mmol/L), any normoglycemic (<10 mmol/L) glycosuria, hyperaminoaciduria, hyper β2-microglobulinuria (normal < 400 µg/L), increased retinol binding protein loss (normal < 0.017 mg RBP/mmol creatinine), hyperuricosuria (normal < 5 mmol/24h).

Renal insufficiency is defined as a confirmed renal clearance of < 80 mL/min, or a confirmed >25% decrease in renal clearance since initiation of TDF.

2. Reversibility of renal insufficiency and KPTD following dose reduction at 24 weeks.

Reversibility is defined as GFR within 10% of baseline GFR/no agreement with

KPTD criteria

Secondary outcome

- The values of plasma TFV, urine TFV and intracellular TFV-DP levels in

studygroup 1 on normal TDF dose and in those on reduced TDF dose.

- The relation between plasma TFV, urine TFV and intracellular TFV-DP levels

and the occurrence of KPTD in studygroup 1.

- The percentage of patients in studygroup 1, meeting the criteria for dose

reduction, maintaining adequate viral suppression.

Study description

Background summary

For extensive information regarding background, see also study protocol text, page 10-14.

After its recent approval for use in the treatment of chronic hepatitis B virus (HBV)-infection (cHBV) tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor, has become a preferred first line drug in this pathology. TDF is a first line drug in HIV treatment as well. The last few years increasing evidence has emerged relating TDF use to the development of kidney proximal tubular dysfunction (KPTD), renal insufficiency and osteomalacia in HIV-infected individuals. KPTD, with renal losses of phosphate, small proteins, amino acids, glucose and uric acid, is found in up to 22-53% of asymptomatic HIV-infected patients on TDF containing ART. The pathophysiology behind its development has not been elucidated and may be multifactorial. Risk factors for its development in HIV identified from studies performed to date include increased age, low body weight, pre-existing decrease in kidney function, and concomitant use of nephrotoxic drugs. As recently shown in HIV-infected persons, the intracellular tenofovir-diphosphate (TFV-DP, its active metabolite) increases 8% with every 10 mL/min decrease in glomerular filtration rate and with every 1-L/h decline in TFV renal clearance. Currently, in the TDF package insert TDF dose adjustment is recommended in patients with renal clearances < 50 mL/min but not in patients with mild renal impairment (CCl 50-80 mL/min). This advice however has to be taken with caution as it is

based on pharmacokinetic studies with single dose TDF monotherapy in non-HIV infected volunteers.
There are no data on the occurrence of KPTD in HBV-monoinfected individuals on TDF. Furthermore no data exist on drug levels of TDF and its metabolites in cHBV treatment. Also, there are few data on the reversibility of tenofovir associated KPTD and no prospective studies on the effect of TDF dose reduction in patients with KPTD.

Study objective

The main objective of this study is to assess incidence of, clinical determinants for, dose reduction in and reversibility of tenofovir associated renal insufficiency and KPTD.
Secondary objectives are to assess kidney tubular function in patients with cHBV on entecavir and without treatment, to relate plasma and intracellular levels of tenofovir (diphosphate) to the occurrence of renal insufficiency and KPTD, to report on plasma and intracellular levels of tenofovir (diphosphate) in cHBV.

Study design

Cross-sectional and prospective, observational study.

Intervention

Dose reduction:

Subjects in group 1 meeting the following criteria at inclusion (weeks 0 and 4), will have TDF dose reduction from TDF 300 mg qd to TDF 300 mg eod (Monday-Wednesday-Friday):
Patients with:
• tenofovir plasma levels above the upper limit of normal (normal range 0.05-0.30 mg/L) at weeks 0 and 4.
• KPTD at weeks 0 and 4.
• Renal insufficiency: a confirmed renal clearance of < 80 mL/min, or a confirmed >25% decrease in renal clearance since initiation of TDF.

Definition of baseline renal clearance: estimated GFR (eGFR) at TDF initiation, or at least within 6 months before as determined by CG formula.

Definition of confirmed renal clearance: best of two values for eGFR as determined by the CG formula at weeks 0 and 4.

After TDF dose reduction urine and laboratory tests will be performed at 4, 8, 12, 24, 36 and 48 weeks (at week 8 HBV-DNA only).
If renal dysfunction/KPTD in a patient is not fully reversible after 24 weeks

(reversible is GFR within 10% of baseline eGFR/no KPTD criteria) we will leave it to the treating physician to decide whether to switch from TDF to another antiviral drug or to continue TDF.

Definition of and course of action in case of viral blip and virologic failure in patients on reduced TDF-dose:
1. In patients with an undetectable HBV-viral load before dose reduction on at least two consecutive occasions virologic failure is defined as an HBV-viral load > 1000 IU/mL. In these patients this finding will be confirmed in a second sample. If confirmed genotypic testing will be performed to search for resistant viral genetic variants. Patients then will be excluded from the study and we leave it to the treating physician to decide whether to switch from TDF to another antiviral drug, to add another antiviral drug or to increase the TDF dose.

2. In patients with an undetectable HBV-viral load before dose reduction on at least two consecutive occasions a viral blip is defined as an HBV-viral load >50 and <1000 IU/mL. In patients with a viral blip a repeat HBV-viral load test will be done 4 weeks after the last measurement. If undetectable (< 50 IU/mL) the patient will continue the reduced TDF dose. If >50 IU/mL, genotypic testing will be performed to search for resistant viral genetic variants. Patients then will be excluded from the study and we leave it to the treating physician to decide whether to switch from TDF to another antiviral drug, to add another antiviral drug or to raise the TDF dose.

3. In patients with detectable HBV-viral load previous to dose reduction, virologic failure is defined as an increase in HBV-viral load of at least 1 log. In these patients this finding will be confirmed in a second sample. If confirmed genotypic testing will be performed to search for resistant viral genetic variants. Patients then will be excluded from the study and we leave it to the treating physician to decide whether to switch from TDF to another antiviral drug, to add another antiviral drug or to raise the TDF dose.

NOTE: In the aforementioned inclusion period for selection of patients meeting the criteria for dose reduction (week 0 and 4), we expect to find adequate numbers. However, if the number of patients meeting these criteria is below 20 the authors aim to extend the inclusion period. The medical ethical commission of the Erasmus MC (METc) will be notified if this should be the case.

Study burden and risks

People already receive standard of care (physical examination, blood and urine testing and treatment). During 52-96 weeks they are observed, using blood parameters of routinely taken samples in the frequency used in daily practice. Urine samples are taken each visit (6 times in the first 48 weeks and twice in the second 48 weeks), where in daily clinical practice twice yearly would be advised.

The extra 'burden' of this research consists of
- a questionnaire each visit (2 minutes extra)
- urine sample each visit (3 minutes extra)
- 3 extra blood tubes each visit (no extra vena puncture required)
- 1 extra blood tube once (pharmacogenetic research, additional informed consent) (no extra vena puncture required)

Benefit:
close monitoring and intervention (dose reduction) in case of meeting criteria for dose reduction, with the potential benefit of early detection of renal side effect and reversibility upon dose reduction.

Group relatedness: because it involves monitoring for adverse events, this study can only be performed on patients with chronic hepatitis B.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
3015 CE Rotterdam
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
3015 CE Rotterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

all adult, cHBV-infected patients on tenofovir or entecavir or without treatment are eligable

Exclusion criteria

HIV-infection

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2012
Enrollment:	180
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	baraclude
Generic name:	entecavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Viread

Generic name:	tenofovirdisoproxilfumarate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2011
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
EudraCT	EUCTR2011-004272-11-NL
CCMO	NL38009.078.11