Pharmacokinetics, safety and efficacy of atazanavir /dolutegravir/lamivudine regimen as maintenance regimen in patients with intolerance and/or resistance to NRTIs, NNRTIs and RTV: a pilot study (PRADA II study)

Published: 19-01-2015
Last updated: 21-04-2024

Primary objective:To assess the pharmacokinetics of the alternative maintenance QD regimen combining atazanavir, dolutegravir and lamivudine in HIV infected patients.
Secondary objectives:To asses short term efficacy of the combination of atazanavir...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON42090

Source
ToetsingOnline

Brief title
PRADA II

Condition

- Viral infectious disorders

Synonym
HIV, human immunodeficiency virus

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dolutegravir, HIV-1 infection, maintenance regimen, pharmacokinetics

Outcome measures

Primary outcome

Pharmacokinetic parameters (AUC0-24h, Cmax, Ct, C24h, Tmax, T1/2) for

atazanavir, dolutegravir en lamivudine. Values will be compared to historical

data.

Secondary outcome

HIV viral load and CD4 count (efficacy) and adverse events (safety).

Study description

Background summary

During the past years the treatment of HIV-1 infection has transformed towards chronic treatment. Patients are being treated with antiretroviral drugs for many years and become older. The risk of developing side-effects due to long term antiretroviral therapy is therefore more and more likely. New alternative once-daily maintenance regimes are needed for those who are extensively pre-treated and experience side-effects or toxic-ity on standard treatment combinations. A possible once-daily, fully active maintenance regimen, with a mild side-effect profile is the combination of atazanavir (unboosted), dolutegravir and lamivudine (PRADA II regimen). Dolutegravir has shown to be highly potent in reducing the HIV-1 RNA viral load and was generally safe and well tolerated. Compared to other inte-grase inhibitors dolutegravir has a higher barrier to resistance. Dolutegravir showed low rates of discontinuation due to adverse events and has a low potency to cause drug interactions. The use of once daily unboosted atazanavir leads to improved safety without compromising virological efficacy in patients having achieved virological

suppression on other combination therapies. Combining dolutegravir and atazanavir with lamivudine adds a third fully active agent to the regimen. The combination of unboosted atazanavir, dolutegravir and lamivudine would thus be expected to be a safe, once-daily maintenance regimen with a favorable side-effect profile. This combination suits patients with intolerance and/or resistance to NRTIs, NNRTIs and ritonavir, who have a suppressed viral load. However, for this new combination the pharmacokinetic profile is unknown and there are no data on short-term and long-term safety and efficacy.

Study objective

Primary objective:
To assess the pharmacokinetics of the alternative maintenance QD regimen combining atazanavir, dolutegravir and lamivudine in HIV infected patients.

Secondary objectives:
To asses short term efficacy of the combination of atazanavir, dolute-gravir and lamivudine as maintenance regimen in HIV infected patients.
To evaluate the safety and tolerability of the combination of atazanavir, dolutegravir and lamivudine as maintenance regimen in HIV infected patients.

Study design

Pilot, open-label, multi-centre, phase IIA, prospective longitudinal observational pharmacokinetic study in 20 HIV-infected patients.
Treatment: once daily maintenance regimen containing atazanavir 400 mg / dolute-gravir 50 mg / lamivudine 300 mg.
Treatment period: 2 weeks until pharmacokinetic sampling. Total duration of treatment will be 12 weeks.

Intervention

HIV therapy will be adapted.

Study burden and risks

The study participants are HIV infected patients in need for a switch of medication regimen, for example due to side-effects or toxicities. Switching to the combination of atazanavir, dolutegravir and lamivudine could possibly relief or prevent progression of troublesome or unpleasant side-effects.

A potential risk due to switching to the combination of atazanavir, dolutegravir and lamivudine is treatment failure, resulting in a detectable viral load. Patients can develop side-effects after switching to the combination of atazanavir, dolutegravir and lamivudine.

Participants will visit the clinical research centre for a screening visit, 3 short visits (approximately 1 hour) and 1 full day (9-10 hours). Short visits at week 6 and week 12 after switching to a new regimen are part of standard care. The duration of the entire trial (excluding screening period) and duration of treatment with study medication is 84 days.

For pharmacokinetic purposes 10 blood samples will be taken in total. For safety assessment (haematology and clinical chemistry), hCG blood test, blood glucose, pharmacogenetic testing and determination of VL and CD4-count a total of 30 blood samples will be collected. The total blood volume taken will be approximately 195.5-205.5 mL. During the day that blood samples will be collected for a pharmacokinetic curve an intravenous cannula will be inserted to facilitate blood sampling and limit the amount of venous punctions.

Risk assessment is 'moderate'.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. HIV-infected as documented by positive HIV antibody test and confirmed by Western Blot.
2. Subject is in need for a switch in maintenance regimen due to adverse effects, toxicities, simplification and/or resistance.
3. Subject is at least 18 years of age at the day of screening.
4. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
5. HIV-1 RNA < 40 copies/mL for at least 6 months on antiretroviral therapy prior to inclusion.
6. Subject has no documented resistance mutations to PIs, INSTIs or lamivudine.

Exclusion criteria

1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
2. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
3. Inability to understand the nature and extent of the trial and the procedures required.
4. Pregnant female (as confirmed by an HCG test performed less than 3 weeks before the first dose) or breast-feeding female.
5. Abnormal serum transaminases determined as levels being > 5 times upper limit of normal (see Appendix A for normal ranges of clinical laboratory values).
6. Renal failure determined as an estimated Glomerular Filtration Rate (eGFR) < 50 ml/min (MDRD-based).
7. Concomitant use of medications that interfere with atazanavir, dolutegravir or lamivudine pharmacokinetics: oxcarbamazepine, phenytoin, phenobarbital, carbamazepine, St. John*s wort, rifampicin, clarithromycin, H2 receptor antagonists, proton pump inhibitors, irinotecan, midazolam, triazolam, buprenorfine, aprepitant, modafinil, imatinib, co-trimoxazole, other antiretroviral drugs.
8. Concomitant use of medications that are contraindicated for use with atazanavir, dolutegravir or lamivudine: alfuzosin, pimozide, quetiapine, kinidine, bepridil, simvastatin, atorvastatin, lovastatin, sildenafil (as for use in pulmonary arterial hypertension), cladribine.
9. Active hepatobiliary or hepatic disease (including chronic hepatitis B or C infection).
10. Alcohol abuse.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-09-2015
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epivir
Generic name:	lamivudine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Reyataz
Generic name:	atazanavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tivicay
Generic name:	dolutegravir
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-01-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	23-07-2015
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
EudraCT	EUCTR2014-004488-19-NL
CCMO	NL52048.091.14

Study results

Date completed:	31-12-2016
Actual enrolment:	9

Summary results
Trial is onging in other countries