The Effect of Rosuvastatin on Immune Activation Markers in Treatment-naïve HIV-Positive Patients; a Randomized Placebo-Controlled Trial

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Primary Objective: to investigate the effect of rosuvastatin 20 mg qd on subsequent immune activation markers in treatment-naïve HIV-patients: circulating LPS (LAL assay), TLR mRNA expression in whole blood, circulating IL-6, D-dimer, hsCRP, CD38...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON35121

Source
ToetsingOnline

Brief title
StatHiv trial

Condition

- Immune disorders NEC
- Viral infectious disorders

Synonym
HIV infection; immune activation

Research involving
Human

Sponsors and support

Primary sponsor: Onze Lieve Vrouwe Gasthuis
Source(s) of monetary or material Support: Stichting Research Interne Geneeskunde OLVG

Intervention

Keyword: HIV infection, immune activation, statins

Outcome measures

Primary outcome

circulating LPS (LAL assay), TLR mRNA expression in whole blood, circulating IL-6, D-dimer, hsCRP, CD38 and HLA-DR expression on lymphocytes, and microparticles and endogenous thrombin potential as indicators of endothelial damage.

Secondary outcome

HIV viral load, CD4 cell count, total cholesterol and cholesterol subfractions, ApoB/ApoA1 ratio, CK, liver enzymes, renal function, and complete blood count as well as on markers of quality of life measured with the EuroQol-6D questionnaire in treatment-naïve HIV-patients throughout the study period.

Study description

Background summary

Despite the enormous success of highly active antiretroviral therapy (HAART) in the Western world, life expectancy of HIV infected patients still lags behind the general population. Nowadays, excess mortality is largely due to non-AIDS defining diseases such as cardiovascular diseases and non-AIDS defining malignancies. Many factors can be held responsible for this increase in non-AIDS defining morbidity and mortality, such as smoking, toxicity of HAART, or socioeconomic factors. Recently, a number of studies have indicated that ongoing immune activation may play an important role in the pathogenesis of

these non-AIDS defining conditions. Early in HIV infection, mucosa-associated lymph nodes in the gut are largely destroyed. Decreased host defense at the level of the gut mucosa with ensuing low-grade translocation of bacteria and bacterial products such as lipopolysaccharide (LPS) contributes to ongoing immune activation in HIV infected patients. In a recent small study, microbial translocation was associated with sustained failure in CD4+ T-cell reconstitution in HIV infected patients on HAART. LPS induces a broad activation of macrophages and circulating monocytes with increases in the production of proinflammatory cytokines and activation of coagulation. Circulating LPS was significantly increased in chronically HIV-infected individuals and in pathogenic simian immunodeficiency virus (SIV)-infected rhesus macaques, and interestingly also in non-HIV infected patients with idiopathic CD4 lymphopenia. In a recent nested case control study derived from the SMART study, mortality of HIV patients correlated strongly with increased concentrations of the pro-inflammatory cytokine interleukin-6 (IL-6) and D-dimer, a marker of coagulation activation. It has been postulated that modulating this residual inflammatory activation in HIV infected patients receiving HAART may be beneficial for countering the increased risk of non-AIDS defining conditions.
After binding to lipopolysaccharide binding protein (LBP), LPS stimulates CD14 positive monocytes and macrophages through its receptor Toll-like receptor 4 (TLR4). This complex process leads to intracellular signal transduction and the subsequent production of pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF alpha) and IL-6. HIV infection is associated with increased TLR expression and responsiveness. Polymorphisms in the TLR4 gene have been described to influence signal transduction and thus modulate the inflammatory cascade. In HIV patients, the TLR4 Asp299Gly polymorphism seems to increase the risk of active tuberculosis.

Statins are potent lipid lowering agents that are extensively used in the primary and secondary prevention of atherosclerotic diseases. They are generally well tolerated. There is an ongoing debate on the possible pleiotropic effects of statins. A number of studies have shown anti-inflammatory effects of statins and two recent studies found that statins have an inhibitory effect on the TLR4-mediated inflammatory response. Moreover, retrospective studies found that prior statin use was associated with improved outcome of pneumonia, and this finding was recently confirmed in one prospective study. In these studies, C-reactive protein (CRP) levels were lower in statin-treated patients. In the recently published JUPITER study, high-dose rosuvastatin resulted in significant decreases in vascular events in patients with slightly elevated high sensitivity CRP (hsCRP) levels without further risk factors. Rosuvastatin caused a significant decrease in hsCRP levels compared to placebo-treated patients, indicating an anti-inflammatory effect. A recent study showed that high-dose atorvastatin decreased cellular immune activation markers in treatment-naïve HIV patients without affecting HIV viral load. Taken together, these studies point to an antiinflammatory effect of statins that does not impair host response to infections, and that may be explained by

influencing TLR4-mediated inflammatory responses. In the present study, we want to investigate the effect of high-dose rosuvastatin on markers of immune activation in treatment-naïve HIV patients. Immune activation can be expected to be more pronounced in treatment-naïve patients than in patients on HAART. A number of markers will be studied that represent subsequent steps in the process of immune activation: circulating LPS (LAL-assay),TLR-messenger RNA in whole blood, the pro-inflammatory cytokine IL-6, D-dimer, hsCRP, markers of T-cell activation (CD38 and HLA-DR expression on CD4 and CD8 cells), and microparticles and endogenous thrombin potential as indicators of endothelial damage. Also, TLR4 polymorphisms will be determined and related to the levels of immune activation. Since both immune activation and statin use may cause fatigue, a standardized questionnaire (the EuroQol-6D questionnaire) estimating the quality of life will be used. Other parameters studied will include CD4- and CD8-positive T lymphocytes, HIV viral load, total cholesterol and cholesterolsubfractions, apolipoprotein

Study objective

Primary Objective: to investigate the effect of rosuvastatin 20 mg qd on subsequent immune activation markers in treatment-naïve HIV-patients: circulating LPS (LAL assay), TLR mRNA expression in whole blood, circulating IL-6, D-dimer, hsCRP, CD38 and HLA-DR expression on lymphocytes, and microparticles and endogenous thrombin potential as indicators of endothelial damage.

Secondary Objective: to investigate the effect of rosuvastatin 20 mg qd on HIV viral load, CD4 cell count, total cholesterol and cholesterol subfractions, ApoB/ApoA1 ratio, CK, liver enzymes, renal function, and complete blood count as well as on markers of quality of life measured with the EuroQol-6D questionnaire in treatment-naïve HIV-patients throughout the study period.

Study design

This is a double blind, randomized, placebo-controlled therapeutic intervention study with a cross-over design. The patients will be assigned to random groups: one receives rosuvastatin 20 mg daily, and the other receives placebo. Patients remain in their treatment groups for 8 weeks. After 8 weeks all patients, in both study groups, will be required to discontinue all study-related medications for 4 weeks. After that period, patients receiving placebo will take rosuvastatin, and vice versa. The study will proceed for another 8 weeks, followed by a period of stopping study-related medications and patients being observed for 4 weeks. Throughout the study, patients will have regularly scheduled visits at the clinic every 4 weeks. At those visits there will be collection of blood samples, assessments of symptoms, physical examinations, and questionnaires to complete.
To obtain reliable reference values for the experimental laboratory

investigations, ten healthy, age and sex-matched volunteers will be asked to donate blood samples twice for all the parameters investigated in the patients. Laboratory investigations include complete blood count, sodium, potassium, creatinine, BUN, glucose, ALAT, ASAT, LDH, alkaline phosphatase, gammaGT, bilirubin, CK, total cholesterol, HDL-, LDL-cholesterol, triglycerides ApoB/ApoA1 ratio. Moreover, circulating IL-6 , D-dimer, microparticles and endogenous thrombin potential, hsCRP, LPS (LAL-assay), TLRmRNA and TLR4 polymorphism, T-cell activation markers (CD 38; HLA-DR), CD4- and CD8-cell count, and HIV viral load are measured.
Blood is drawn for baseline measurements on28 days and one day before the start of study medication. After the start of study medication, blood is drawn on days 28, 56, 84, 112, 140 and 168 (weeks 4, 8, 12, 16, 20 and 24). The study medication consists of rosuvastatin 20 mg daily.
To ensure the double blind character of the study, the treating physician will not be informed about the results of blood tests during the study period. A local supervising committee will weekly review laboratory results throughout the study period, and will intervene in study participation of individual patients whenever serious adverse events occur.

Intervention

rosuvastatin 20 mg qd, or placebo

Study burden and risks

Burden: the main burden for the patients concerns the fact that they will have to visit the outpatient clinic every 4 weeks for a total of 24 weeks. During these visits, blood will be drawn, the treating physician will be visited, en three times a questionaire will have to be filled in. The aliquot of blood drawn will not exceed 50 ml per visit, which cannot be considered a burden or risk.

Risk for the patients concerns the possible side effect of rosuvastatin. The investigators will closely monitor the occurence of any side effect by history taking, controlling CK and liver enzymes, and by evaluating questionaires.

Burden and risk are considered to be acceptable in light of the potential benefit to the patient of finding a therapeutic approach that could possibly postpone the moment to start the patient on HAART and/or partly neutralize the increased cardiovascular rist of HIV-infeced patients. Moreover, rosuvastatin is a widely used registered drug, that is taken by tens of thousands of patients without major side effects.

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

• Adults 18 years of age or older.
• HIV-1 infection, as documented by a licensed ELISA test kit and confirmed by a Western blot assay
• No evidence of acute HIV infection. For the purposes of this study acute HIV infection will be defined as presence of a detectable HIV-1 viral RNA in the presence of a non reactive HIV-1 or HIV-2 antibody assay or an indeterminate western blot.
• Treatment naïve, i.e. no current of previous use of HAART
• Willingness to use a method of contraception during the study period. Adequate methods of birth control include: condoms, male or female, with or without a spermicide; diaphragm or cervical cap with spermicide; intrauterine device; any of the methods that require a prescription (such as contraceptive pills or patch, Norplant, Depo-Provera, and others) or a male partner who has previously undergone a vasectomy.

• Willingness to have blood drawn.
• Non known allergy or contraindication to rosuvastatin use.
• Ability to understand and willingness to sign the informed consent.
• Willingness to have blood stored for future phenotyping and genotyping.
• CD4 cell count greater than 350 cells/ml.
• Two viral loads that average greater than 1000 copies/ml within a 4 week period.
• Liver function tests (AST or ALT) not greater than 1.5 times the upper limit of normal.
Evidence of active hepatitis B or C will not be considered an exclusion criterion if the liver function tests are within normal limits.
• Creatine phosphokinase elevations (CK) not greater than 3 times the upper limit of normal (ULN) on two sequential determinations and, in the opinion of the investigator, without clear association with exercise.
• Laboratory values:
Absolute neutrophil count (ANC) greater than or equal to 1000/mm3.
Hemoglobin greater than or equal to 7.5 mmol/L
Platelet count greater than or equal to 100,000/mm3
Creatinine less than or equal to 2 x ULN.
Serum amylase and lipase less than or equal to 1.25 x ULN.
• Negative serum pregnancy test at randomization.

Exclusion criteria

• Pregnancy or breast feeding.
• Active drug use or alcohol abuse/dependence, which in the opinion of the investigators will interfere with the patient's ability to participate in the study.
• Serious illness requiring systemic treatment and/or hospitalization within 30 days of entry.
• Evidence of active opportunistic infections or neoplasms that require chemotherapy during the study period
• Allergy or hypersensitivity to rosuvastatin or any of its components.
• History of myositis or rhabdomyolysis with use of any statins.
• History of inflammatory muscle disease such as poly- or dermatomyositis.
• Concomitant use of fibric acid derivatives or other lipid lowering agents including statins and ezetimibe.
• Concomitant use of drugs that have significant interactions with rosuvastatin. .
• Concomitant use of St.Johns wort.
• Concomitant use of Valproic acid.
• Patients who are on concurrent immunomodulatory agents
• Serum LDL cholesterol less than 1.0 mmol/L.
• Vaccinations within 6 weeks of study entry.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-04-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Crestor
Generic name:	Rosuvastatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-04-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	24-08-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-019781-85-NL
CCMO	NL31926.100.10
Other	TC=2349