LRAs United as a Novel Anti-HIV strategy (LUNA): a randomized controlled trial.

Published: 31-10-2017
Last updated: 12-04-2024

The longitudinal assessment of the BAFi pyrimethamine and of the HDACi valproic acid on the HIV reservoir size in HIV patients on antiretroviral therapy.

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

Summary

ID

NL-OMON50727

Source
ToetsingOnline

Brief title
LUNA

Condition

- Viral infectious disorders

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Erasmus MC 2016 MRace PhD project beurs

Intervention

Keyword: Eradication, HIV, Latency

Outcome measures

Primary outcome

The change in HIV reactivation in the reservoir in vivo at treatment initiation and at the end of treatment measured as the change in cell associated HIV-RNA. The change in reactivation is compared between the treatment arms.

Secondary outcome

The secondary endpoints are exploratory. 2.1 The change in reservoir size in vivo at treatment initiation week 0, at the end of treatment week 2, and after treatment, measured as the number of CD4 T-cells with multiply spliced HIV-RNA with nested PCR based tat/rev induced limiting dilution assay (TILDA, Procopio et al. EBiomedicine 2015). The change in reservoir size is compared within and between the treatment arms. 2.2 The potential synergism or additive effects of the administration of both drugs will be assessed. 2.3 The change in cell-free HIV-RNA as measured by routine PCR and single copy assay, cell associated HIV-RNA, and cell-associated HIV-DNA at week 0, week 2 and week 6 within and between the treatment arms. 2.4 The change in the level of histone acetylation and expression of BAF subunits at the RNA and at the protein level at week 0, week 2 and week 6 within and between the treatment arms. 2.5 The change of the functionality and phenotype of innate immune cells, HIV specific CD4+ and CD8+ T cells and HIV specific B-cells using proliferation assays, flow cytometry, cytokine and cytotoxicity analysis at week 0, week 2 and week 6 within and between the treatment arms. 2.6 Explore and correlate clinical and markers of the viral reservoir (HIV-DNA, HIV-RNA), immune function and phenotype, and the

level of acetylation/BAF expression with the change in reservoir size (TILDA) within and between the treatment arms. 2.7 Correlate the latency reversal activity with pyrimethamine and valproic acid in vitro in cell line based HIV latency models, in primary CD4 T cells ex vivo, and in vivo with TILDA, HIV-RNA, HIV-DNA and the level of acetylation/BAF expression. 2.8 Number and percentage of clinical and biochemical AE according to the latest version of the Common Toxicity Criteria. 2.9 Number and percentage of patients with HIV-1 RNA level greater than or equal to 20, 50 and 200 c/mL at week 0, week 2 and week 6 within and between the treatment arms. 2.10 The effect of vaproic acid on dolutegravir exposure in vivo. 2.11 Assess the pharmacokinetic profile of pyrimethamine and valproic acid in relation to the primary endpoint

Study description

Background summary

The retrovirus HIV integrates as proviral DNA in the genome of our CD4+ T cells. A subset form a reservoir of latently infected long-lived memory T-cells with nearly absent HIV-DNA transcription. This persistent latent HIV reservoir is the major obstacle for a cure. HIV latency is sustained by multiple host factors that restrict the viral promotor and expression of the viral genome. Latency reversing agents (LRA) can remove these restrictive components and mediate HIV latency reversal. LRA monotherapy with histone deacetylase inhibitors (HDACi), including valproic acid, vorinostat, romidepsin, panobinostat, reactivates HIV but seems insufficient to eliminate the reservoir in vivo. Our research group has identified the BAF complex as a repressive factor that maintains HIV latency (Rafati et al. PLoS Biol 2011). We investigated the activity of a panel of recently identified small molecule inhibitors of BAF (BAFi) as a new LRA group and showed that BAFi, including the clinically approved drug pyrimethamine at tolerable concentrations, are capable of reversing HIV latency and act synergistic with HDACi in vitro and in CD4+ T cells obtained from HIV infected patients on suppressive antiretroviral therapy (Stoszko et al. 2016 EBiomedicine). This offers new opportunities for cure research. We want to conduct the first study with BAFi and assess the potential

synergism of 2 LRA with different modes of action on the reservoir in HIV patients.

Study objective

The longitudinal assessment of the BAFi pyrimethamine and of the HDACi valproic acid on the HIV reservoir size in HIV patients on antiretroviral therapy.

Study design

Open label 6 week randomized controlled intervention trial.

Intervention

Group 1 receives valproic acid (Depakine enteric) 30mg/kg, divided over 2 doses per day, orally on day 1-14.
Group 2 receives pyrimethamine 200mg QD orally on day 1 and 100mg on day 2-14.
Group 3 receives valproic acid (Depakine enteric) 30mg/kg, divided over 2 doses per day, orally on day 1-14 in combination with pyrimethamine 200mg QD orally on day 1 and 100mg on day 2-14.
Group 4 receives no intervention.

Study burden and risks

There is no direct benefit for the patient to participate. Potential beneficial observed effects would have an impact on future research in the HIV cure field. This study can only be done in HIV infected patients and is therefore related to this group only. The total study time for a patient is 6 weeks in which patients have 10 study related visits: 1 pre-treatment screening, 5 during treatment, and 4 post-treatment. Only with additional consent, 1 additional phlebotomy will be done at least 6 months after the visit at day 42. The risks are associated with the study procedures and the administered compounds. The study procedures are blood sampling by phlebotomy. Patients are informed on the sampling methods and will have sufficient time for consideration prior to inclusion. The team ensures that participants have understood the potential risks.

Phlebotomy is a safe well-defined procedure with a negligible low complication rate. The total amount of blood volume is 738mL over 6 weeks at 10 time-points. This is comparable to the maximum of blood donations in the same period (max of 2 of 500mL per donation, drawn in one setting of one hour). The maximum amount will be 174mL, which happens at 2 occasions. Patients are selected on adequate hemoglobin levels and ferritin levels are monitored. Only with additional consent, 1 extra blood donation of 100mL will be done at least 6 months after the day 42 visit.

Both pyrimethamine as BAFi and valproic acid as HDACi are FDA/EMA approved for clinical use for other medical conditions in patients. Their safety profiles are therefore well characterized. Pyrimethamine is an inhibitor of dihydrofolate reductase, resulting in a blockade of folic acid metabolism. Pyrimethamine and valproic acid are used in their approved dosages and for a shorter duration (2 weeks) than usual in the treatment of toxoplasmosis or epilepsy in HIV patients. The pyrimethamine concentration at which we observed effects on the HIV reservoir is well within the therapeuric range in humans with approved dosing.(Jacobson. AAC 1996; Klinker. AAC/Infection 1996; McLeod. AAC 1992; Schmidt. Eur J Pediatr 2006). For valproic acid, the effects on HIV are also observed at therapeutic dosing.(Ylisastigui et al. 2004 AIDS 1101-1108)

The study drugs have no known or predicted interaction on each other or with current approved recommended first line antiretroviral drugs for HIV. Valproic acid and pyrimethamine have a risk of side effects, intolerability and allergy. The main side effects of valproic acid are gastro-intestinal, skin, psychological, central nervous system, and bone marrow depression. Patients with significant cytopenias at baseline cannot participate. The main side effects of pyrimethamine are bone marrow depression and electrolyte disturbances. Due to its working mechanism, patients on pyrimethamine will receive prophylactic folinic acid suppletion.

Exclusion criteria are used to prevent drug exposure in certain patient categories. Women in the reproductive age cannot participate. Male patients must consent to condom use. Participation is stopped if any AIDS defining illness classified as CDC C occurs. Patients with strong glucuronidation interacting comedication cannot participate because valproic acid is metabolized by this pathway. To minimize the risk associated with participation in this trial, biochemical and clinical safety is frequently monitored, and expert consultants in the field of clinical pharmacology and hematology are involved.

In conclusion: only HIV patients who can understand the pros and cons of participation will be included. The main uncertainty is in the use of both pyrimethamine and valproic acid. However, experience exists with valproic acid pyrimethamine in HIV patients with epilepsy or toxoplasmosis. and in this study we use similar dosages of pyrimethamine and valproic acid but for a significantly shorter time. Two specific safety measures will account for these uncertainties: study visits are frequent during the 6 week study period and will include AE monitoring. Furthermore, a contingency plan including predefined safety criteria has been made with rules to interrupt the trial if unexpected toxicity occurs. The remaining risk is low and acceptable; we use approved drugs for other indications at approved dosage for a shorter time than its approved indication. Most AE can be anticipated on, and a safety plan has been installed for unexpected AE. As patients continue their cART during the study, they can immediately resume their routine care after study end. The outcome of the study could be that an effect or that no effect is observed.

This does not affect study continuation. Both positive and negative outcomes are relevant observations for future HIV reservoir research. As the potential risks are minimal with the used drugs which are also used for a shorter duration than usual and the risks with these compounds are well characterised, and as the visits can be planned with the patient (i.e. earlier or later on the study-days according to patients' own schedules), the procedures are well characterised and safe, and the potential outcome of the study can have a major impact, we believe that this justifies participation.

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. HIV-1 infected patients *18 years.
2. WHO performance status 0 or 1.

3. Confirmed HIV-1 infection by 4th generation ELISA, Western Blot or PCR.
4. Wild type HIV infection or polymorphisms associated with at highest low-level resistance to any class of ART according to Stanford HIV drug resistance database. Transmitted mutations and acquired mutations due to virological failure associated with resistance of at highest low-level resistance are allowed.
5. On cART.
6. Current plasma HIV-RNA <50 copies/mL for at least 365 days and measured on at least 2 occasions of which at least 1 must be obtained within 365 and 90 days prior to study entry.
7. Current CD4 count at study entry of *200 cells/mm3.
8. Pre-cART HIV-RNA *10.000 copies/mL.

Exclusion criteria

1. 1. Previous virological failure, defined as either acquired resistance mutations (>low level resistance) on cART or HIV-RNA >1000 copies/mL on two consecutive measurements during cART.
2. Uncontrolled hepatitis B or C co-infection.
3. Prior exposure to any HDACi, BAFi or other known LRA.
4. Prior exposure to cytotoxic myeloablative chemotherapy for hematological malignancies during cART.
5. Concurrent exposure to strong interacting medication on glucuronidation.
6. Exposure within 90 days prior to study entry to immunomodulators, cytokines, systemic antifungals, dexamethasone, vitamin K antagonists, anti-epileptics, antipsychotica, carbapenems, mefloquine, colestyramine, Any documented opportunistic infection related to HIV in the last 90 days.
7. Inadequate blood counts, renal and hepatic function tests
a. Haemoglobin <6.5 mmol/L (males) or <6.0 mmol/L (females), leucocytes <2.5 x109/L, absolute neutrophil count <1000 cells/mm3, thrombocytes <100 x109/L, international standardized ratio >1.6, activated partial thromboplastin time >40 seconds.
b. Estimated glomerular filtration rate <50 mL/min (CKD-EPI),
c. ALAT or total bilirubin >2.5x upper limit of normal.
d. All laboratory values must be obtained within 42 days prior to the baseline visit.
8. Megaloblastic anemia due to folate deficiency.
9. Pancreatitis in last 6 months, or chronic pancreatitis.
10. Active malignancy during the past year with the exception of basal carcinoma of the skin, stage 0 cervical carcinoma, Kaposi Sarcoma treated with cART alone, or other indolent malignancies.
11. Females in the reproductive age cannot participate. Males cannot participate if they refuse to abstain from sex or condom use in serodiscordant sexual contact during the study, except if their sexual partner(s) use PREP.
12. Patients with active substance abuse or registered allergies to the

investigational medical products.
13. Last, any other condition (familial, psychological, sociological, geographical) which in the investigator*s opinion poses an unacceptable risk or would hamper compliance with the study protocol and follow up schedule, will prohibit participation.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2018
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Depakine enteric
Generic name:	Valproic acid
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pyrimethamine
Generic name:	Pyrimethamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2020
Application type:	Amendment
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	EUCTR2017-002837-48-NL
CCMO	NL62552.078.17