ISRCTN73411795 https://doi.org/10.1186/ISRCTN73411795

Efficacy of switch to lopinavir/ritonavir in improving cognitive function in efavirenz treated patients

Submission date
16/08/2012

Recruitment status
No longer recruiting

Registration date
16/08/2012

Overall study status
Completed

Last Edited
28/03/2019

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Recent studies have suggested that some HIV-infected patients experience mild problems with 'cognitive impairment'. Mild cognitive impairment means a slight slowing of brain processes, which could lead to problems with memory or concentration. Currently it is not fully understood why these problems occur or what we may be able to do to improve them. In particular it is not known what role anti-retroviral medications (anti-HIV drugs) may have in affecting brain function, and whether certain anti-retroviral drugs may lead to a greater tendency to develop problems, or whether some may be better than others at preventing the problems. Efavirenz (EFV) is currently one of the most commonly used anti-retroviral drugs. It is also known as Sustiva® and is a component of Atripla®. We know that Efavirenz can have effects on the brain in the first few weeks of treatment such as bad dreams and dizziness, but these usually settle. However, recent research suggests that Efavirenz may have some longer term effect on brain function (although this does not appear to be very severe in the vast majority of cases). This study aims to find out whether switching treatment away from Efavirenz to another anti-retroviral medication (Kaletra®) may improve brain function. Kaletra® is another commonly used anti-retroviral medication and does not appear to have the same potential effect on brain function.

Who can participate?
Patients infected with HIV-1 who are 18 years old or over and are receiving a highly active anti-retroviral therapy (HAART) combination which contains efavirenz, and have a suppressed HIV viral load.

What does the study involve?
We will switch your medication from Efavirenz to Kaletra® for 12 weeks, and look for any change in brain function. We will make measurements at the beginning and end of the study to see how they change. These will include: a special kind of MRI scan, which measures chemicals in the brain, a computerised test of brain function ('memory games'), sleep diaries and blood tests. If impairment in brain function is due to Efavirenz use, this may change and possibly improve on switching to Kaletra. This is a pilot study and therefore any changes seen would need to be

confirmed in further studies. There is a possibility that there will be no significant changes and no improvement or change in brain function that is detectable.

What are the possible benefits and risks of participating?
The main purpose of the study is to better understand the effect of different anti-retroviral drugs on brain function in HIV infection to help clinicians guide treatment choices in the future. It is possible that patients may see an improvement in their cognitive function (e.g. memory or concentration) and quality of sleep; however, this may not be solely due to the study drug. Both Efavirenz and Kaletra® are licensed for treatment of HIV infection and they are considered to be equally effective. There is therefore a negligible risk of virological failure (rise in HIV viral load) from a switch to Kaletra®. Patients viral load will be monitored for any problems during the study. Kaletra® is a commonly used anti-retroviral medication and has been shown to be safe and well-tolerated in large clinical trials. There are possible side effects associated with taking Kaletra®; these include nausea and a slightly higher rate of diarrhoea compared with Efavirenz. If these do occur they are usually mild. The rate of serious adverse events with Kaletra has been shown to be low. Some patients also show increases in levels of cholesterol and triglycerides on their blood tests. These changes would not be expected to lead to any problems within the short duration of this study. The blood tests will be monitored regularly to check for any problems during the study.

Where is the study run from?
The study will be run by the Clinical Research Facility which is designed specifically for conducting clinical trials at Royal Victoria Infirmary Newcastle (UK).

When is the study starting and how long is it expected to run for?
The study started in October 2012 and will run for two years and six months. Each patient will participate in the study for 15 weeks.

Who is funding the study?
This study is funded by a research grant from Abbott Laboratories Limited. They are also providing the study drug Kaletra® at no cost for the duration of the study. Abbott is the company who is licensed to sell Kaletra in the UK at present. Abbott has no role in the design or running of the study or ownership of the data. The Newcastle Clinical Trials Unit is managing the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is the legal sponsor of the study.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
12779

Study information

Scientific Title
Efficacy of Switch to Lopinavir/Ritonavir in Improving Cognitive function in Efavirenz treated patients

Acronym
SLICE

Study objectives
Efavirenz (EFV) is currently one of the most commonly used anti-retroviral drugs. It is well recognised that cognitive side-effects are common in the first 4-6 weeks of EFV therapy and it is thought that these effects disappear entirely after treatment, however recent data suggests that EFV may have long-term detrimental effects in brain function.

Recent research studies have suggested that many HIV-infected patients experience mild problems with 'cognitive function'. This means that there may be slight slowing of brain processes and this may lead to problems with memory or concentration. These problems tend to be mild, but may potentially have an impact on daily life. We currently do not know why these problems occur or what we may be able to do to improve them. In particular we do not know what role anti-retroviral medications have in brain function and whether certain antiretroviral drugs may lead to a greater tendency to develop problems or may be better than others at preventing the problems.

This study is investigating whether a commonly used anti-retroviral medication (Efavirenz) has an adverse effect on brain function and whether this can be improved by a switch to another drug (Kaletra®).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East - Newcastle & North Tyneside 2, 11/06/2012, ref: 12/NE/0071

Primary study design
Interventional

Study design
Non-randomised interventional study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Infectious diseases and microbiology

Interventions
This is an exploratory single-centre, self-controlled, open-label phase IV pilot study, comparing the efficacy of Efavirenz (EFV) and Kaletra on neurocognitive performance. All subjects will switch from EFV to Kaletra.

Study duration will be 15 weeks from baseline visit (week 1). Each participant will be required to take the study drug for 12 weeks. For the first 2 weeks participants will stay on EFV and complete the first sleep diary and will have baseline cognitive testing and MR scan. At week 3 they will then switch to the study drug (Kaletra). 4 weeks after switch (at week 7) safety monitoring bloods will be performed. 10 weeks after switch (week 13) follow-up cognitive testing and MR scan will be performed. Participants will remain on study drug for a further 2 weeks (until week 15) whilst completing follow-up sleep diary. At end of study patient will revert to original drug regimen or own physician's choice.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Lopinavir, ritonavir, efavirenz

Primary outcome(s)
Change in cognitive test scores from visit 1 (baseline) to visit 3 (10 weeks from switch to Kaletra)

Key secondary outcome(s)
1. Change in resting-state and attentional processing task-based fMRI
2. Change in sleep quality
3. Change in cerebral metabolite profile on magnetic resonance spectroscopy
All outcomes measured from visit 1 (baseline) to visit 3 (10 weeks from switch to Kaletra)

Completion date
27/11/2015

Eligibility

Key inclusion criteria
1. Documented HIV-1 viral load (VL) measurement =200 copies/ml within 4 months preceding study entry and no VL exceeding 200c/ml within 1 year prior to study entry. The constraint of >1 year of HIV infection is to remove any CNS effects of acute retroviral syndrome.

2. Documented HIV-1 RNA viral load (VL) measurement of <50 copies/ml within the 4 months preceding study entry and no VL exceeding 200c/ml within 1year prior to study entry. This constraint is to remove any CNS effects of active viral replication at baseline, and / or potential change in level of viral replication during the study period.
3. On HAART (at least 3 anti-retroviral drugs from at least 2 classes) for at least 12 months prior to study entry.
4. On Efavirenz (EFV, Sustiva) for at least 6 months prior to study entry. This constraint is to remove acute neuropsychiatric effects of EFV which are typically clinically apparent in the first 4-6 weeks of therapy.
5. Patient has provided written informed consent for participation in the study prior to any study specific procedures
6. Age 18 to 65 years inclusive
7. Male and female participants

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria
1. Use of Kaletra or any other HIV protease inhibitor within 6 months of study entry
2. Current self-reported (within last 3 months) recreational drug use
3. Current self-reported weekly alcohol consumption exceeding 35 units/week
4. Known contra-indication to MRI scanning
5. Known hypersensitivity to Kaletra, or to ritonavir in pharmacokinetic boosting doses (100 or 200mg ritonavir daily)
6. Currently (within 6 weeks of study entry) receiving interferon therapy for treatment of chronic viral hepatitis, or expected to commence such treatment with the next 4 months
7. Severe renal or hepatic impairment;
8. Pregnancy, or women planning to become pregnant within next 6 months;
9. Women breastfeeding
10. Use of other investigational study drugs within 30 days prior to study entry (defined as date of randomisation into study)
11. Previous participation in this study

Date of first enrolment
01/01/2013

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle Clinical Research Facility
Leazes Wing
Royal Victoria Infirmary
Queen Victoria Road
Newcastle Upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Abbott Laboratories Ltd (UK)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository (https://eudract.ema.europa.eu/). The data was stored on Elsevier'

s MACRO clinical data management system. The data is archived with Datatron Document Image Archiving Ltd., 6 Mercury, Orion Business Park, North Shields, NE29 7SN. The CI controls access to the archived data. Datatron can provide a turnaround of either 2 hours, next day, or next week (all cost dependent). Informed consent was obtained from all participants. On entry to the trial, participants received a unique study ID number. All data collection forms contained the study number and patient's initials only. Identifiable data and personal details are necessary for the study and were only available to the normal clinical care team and research team, representatives of the sponsor and regulatory authorities, all of whom adhered to DPA 1998, research governance and Caldicott guidelines.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2016		Yes	No
Results article	results	01/11/2017		Yes	No
HRA research summary			28/06/2023	No	No