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An adaptive pharmacological approach for the individualisation of voriconazole antifungal therapy

Submission date
14/07/2014

Recruitment status
No longer recruiting

Registration date
24/10/2014

Overall study status
Completed

Last Edited
12/06/2019

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Progressive (invasive) fungal infections are a major cause of many diseases and even death in patients with tumors affecting the blood and in those needing a treatment called haematopoietic stem cell transplantation. Invasive fungal infections often prevent the affected patient being able to have chemotherapy or transplantation. New ways to give an ideal antifungal therapy are urgently required. A drug called Voriconazole can be used for the prevention of invasive fungal infections. Research suggests that voriconazole exhibits clinically relevant drug exposure-response and drug-exposure toxicity relationships. Invasive fungal infections are deadly; therefore it is important to monitor the drug intake to ensure individual patients drug exposures are ideal. But there are no computer programs that can tell us how much drug should be given and at what intervals that enable the correct dosage in a timely and optimally precise manner. A computer program for this purpose has been developed. The software is used to individualise voriconazole regimens in patients to ensure they achieve desired levels and are deemed by that clinician to be safe and effective. The aim of this study is to find out how safe and effective this computer software is.

Who can participate?
Patients requiring treatment for invasive fungal infections..

What does the study involve?
Patients are required to stay in hospital and receive treatment every 12 hours for 5 days. In addition, patients have 13 blood samples taken during treatment. As part of the standard treatment patients are required to return to hospital on day 14, and day 35. During these visits patients have a medical examination, a blood sample taken, provide details of any other medications they are taking and on day 35 they may have a CT scan.

What are the possible benefits and risks of participating?
It is hoped that the treatments will help patients. However, this cannot be guaranteed. The information from this study may help to improve the future treatment of patients with invasive fungal infections. Voriconazole is generally well tolerated. The most common side effects

experienced with voriconazole are liver disturbances, visual disturbances, skin rash, neurological disturbances, cardiovascular events, blood disorders, kidney disturbances, fever, vomiting, nausea, diarrhoea, headache, peripheral oedema, abdominal pain. Patients are required to have extra blood tests as part of the study. These may cause some bruising and soreness however this should be minor.

Where is the study run from?
Royal Liverpool University Hospital (UK)

When is the study starting and how long is it expected to run for?
August 2014 to August 2016

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof. William Hope
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2013-002578-34

ClinicalTrials.gov (NCT)
NCT01887457

Protocol serial number
UoL001025

Study information

Scientific Title

An adaptive Pharmacological approach for the Individualisation of VOriconazole AntifungaL therapy (PIVOTAL): a Phase II registered single-centre medical device study

Acronym
PIVOTAL

Study objectives
Increasing evidence suggests that voriconazole exhibits clinically relevant drug exposure-response and drug-exposure toxicity relationships. Trough concentrations < 1 mg/L are associated with a higher probability of clinical failure, while trough concentrations > 5.5-6 mg/L are associated with a higher probability of toxicity. Invasive fungal infections are rapidly lethal; therefore, there are strong grounds to offer therapeutic drug monitoring to ensure individual patients drug exposures are optimal.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North West – Liverpool Central, 09/12/2014, ref: 14/NW/1323

Study design
Phase II registered single-centre medical device study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Invasive fungal infection

Interventions
Voriconazole is administered over 5 days. Treatment will be given every 12 hours, each treatment will be given over 2 hours via an intravenous drip, so there will be ten 2-hour treatments in total. After consenting initially through part 1 of the consent patients will receive three of these treatments, which are the same as standard treatment.

In addition, five blood samples will be taken, one 10 ml sample before the second treatment and then 5 ml samples taken 1, 3, 6 and 12 hours after the second infusion. Half of the first sample will be stored for future research, the other samples will be used to identify the best dose.

In addition, 5 ml blood samples will be taken before the fifth and tenth treatments, and further 5 ml blood samples taken at 1, 3, 6 and 12 hours after the fifth and tenth treatments. The samples taken before and after the fifth dose will be used to identify the best dose. The samples taken before and after the tenth dose will be used to assess whether the dose given was effective.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Voriconazole

Primary outcome(s)
The safety and efficacy of computer software to attain pre-defined plasma concentrations of voriconazole for immunocompromised patients. Successful therapy is a trough concentration of 1-3 mg/L at the end of the 10th dosing interval on day 10.

Key secondary outcome(s))
1. Toxicity of patients receiving individualised voriconazole dosing at 35 days
2. Mortality of patients receiving individualised voriconazole dosing at 35 days

Completion date
31/08/2017

Eligibility

Key inclusion criteria
1. Patients ≥18 years old
2. Patients where a new course of voriconazole is indicated for prevention or treatment of an invasive fungal infection
3. Patients with sufficient venous access to enable repeated blood samples
4. Estimated creatinine clearance ≥ 50 mL/min
5. Able to give written informed consent
6. Able to remain in the hospital for at least 5 days
7. Willing to use adequate contraception if necessary

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
19

Key exclusion criteria

1. Estimated creatinine clearance < 50 mL/minute
2. Use of haemodialysis or haemofiltration
3. Hepatic insufficiency (Childs B or C)
4. Hepatitis with LFTs > three-times upper limit of normal
5. Pregnancy, breastfeeding or planning pregnancy during the study
6. Past history of intolerance to voriconazole
7. Microbiological evidence of resistance to voriconazole
8. QT prolongation (see 20.6 page 68)
9. Use of other medications that contraindicate the use of voriconazole
10. Hypersensitivity to voriconazole, its excipients or other triazole antifungal agents

Date of first enrolment
01/08/2014

Date of final enrolment
01/08/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Liverpool
Liverpool
United Kingdom
L69 3GE

Sponsor information

Organisation
University of Liverpool (UK)

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	27/03/2019	12/06/2019	Yes	No
HRA research summary			28/06/2023	No	No