ISRCTN11847553 https://doi.org/10.1186/ISRCTN11847553

King's invasive aspergillosis study II (KIASII)

Submission date
06/03/2017

Recruitment status
No longer recruiting

Registration date
07/06/2017

Overall study status
Completed

Last Edited
15/02/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Invasive fungal disease (IFD) is an infection caused by a fungus. It is a major cause of death and disease in people who have weakened immune systems (the body's natural defences), such as those undergoing cancer treatment or those taking medications to reduce their immune response after a transplant. Fungal infections are difficult to diagnose and the number of people affected is not known for sure. Diagnosis of IFD at present is largely based on the failure of patients to respond to second line antibiotics for persistent fevers. The study team recently finished a study looking at the diagnostic and management strategies for invasive aspergillosis, a type of aggressive fungal infection. In this study it was found that using a combination of diagnostic tools was the best way of diagnosing IFD. By using a combination of diagnostic tools, it was found that 1 in 5 patients developed IFD during the course of their treatment. Moreover, patients who developed IFD had a worse outcome compared to those with no IFD. Similarly short follow-up periods were shown to miss out cases of IFD which can develop many months after transplantation for instance. Since then, the centre has changed strategy for prevention of IFD in high risk patients and now uses a more broad-spectrum anti-fungal agent (posaconazole) which was previously shown to be better at preventing IFD. The aim of this study is to assess the impact of using posaconazole on the incidence of IFD in patients at high risk of developing IFD.

Who can participate?
Adults who are at risk of developing IFD.

What does the study involve?
All patients are given 300 mg posaconazole tablets to take twice/day on the first day and then once a day for as long as required. In addition to standard care, patients have a CT chest scan at the start of the study. In addition patients also have one and half tablespoon of additional blood taken at the same time as their routine blood collections. These blood samples are used to find out whether the level of certain proteins in patients' blood, called cytokines, before starting their chemotherapy or transplant, can predict risk of developing IFD. In addition, the clinical performance of potential newer laboratory tests for IFD diagnosis will be examined to help improve the sensitivity of the diagnostic tests for IFD either on its own or in combination with other tests currently available. These laboratory tests are also done on fluid samples from lungs, obtained by a procedure called bronchoscopy, which is a test using a small camera to look down the airways and will only be undertaken when clinically indicated. These research samples are securely stored and any spare samples will be used for future ethically approved research.

Finally, clinical, laboratory and radiological (scan) information taken as part of patients' normal care is also collected.

What are the possible benefits and risks of participating?
There is unlikely to be any direct medical benefit to patients in the study, but it is hoped that the information learned from this study will benefit other people in the future. There is a risk of side effects from the medication used. In addition, patients will receive a dose of radiation in CT scanning. This risk is considered to be very minor in relation to the advantages of the examination. If patients are a female of child bearing age, they will also be required to undergo pregnancy test prior to any planned CT scans. This is to avoid any potential risk to developing baby with radiation exposure. There is also s risk of fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site when blood samples are taken.

Where is the study run from?
Kings College Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2015 to July 2018

Who is funding the study?
Merck Sharp and Dohme (UK)

Who is the main contact?
Dr Varun Mehra
varun.mehra@nhs.net

Contact information

Type(s)
Public

Contact name
Dr Varun Mehra

ORCID ID
https://orcid.org/0000-0001-6572-0971

Contact details
Department of Haematology
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS
+44 20 3299 5378
varun.mehra@nhs.net

Additional identifiers

ClinicalTrials.gov (NCT)

NCT02875743

Clinical Trials Information System (CTIS)
2016-001223-31

Protocol serial number
31824

Study information

Scientific Title
Incidence of Invasive Fungal Disease in Patients receiving Immunosuppressive Therapy, Intensive Chemotherapy or Reduced Intensity Haematopoietic Stem Cell Transplantation on Posaconazole Prophylaxis

Acronym
KIASII

Study objectives
The aim of this study is to assess the impact of using posaconazole tablet (an anti-fungal agent) prophylaxis on the incidence of invasive fungal disease (IFD) in patients with aplastic anaemia, Myelodysplasia (MDS) or Acute Myeloid Leukaemia (AML), undergoing immunosuppressive therapy, intensive chemotherapy or reduced intensity conditioning (RIC) allogeneic haematopoietic stem cell transplant (HSCT).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leeds East Research Ethics Committee, 11/10/2016, ref: 16/YH/0370

Study design
Non-randomised; Interventional; Design type: Diagnosis, Prevention, Drug, Active Monitoring

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Haematology, Primary sub-specialty: Haematology; UKCRC code/ Disease: Infection/ Other bacterial diseases

Interventions
Participants are given 300 mg posaconazole tablets to take twice/day on day 1 and then 300 mg daily thereafter as long as prophylaxis is indicated. Posaconazole will be administered until no longer clinically indicated, i.e. when neutrophils > 0.5 X 109/L for two consecutive days, patient not receiving immunosuppressive drugs for GVHD treatment, and no GVHD.

Participants are actively followed up for 12 months.

Patients recruited in the study will receive care similar to non-study patients with a need to start tablet form of posaconazole for IFD prevention, provided no direct contraindication sor exclusion criteria are met. In addition to standard care, patients will have a CT chest scan as baseline on entry of the study (unless they have already had one within 2 weeks of study entry). The initial CT for all study participants is aimed at establishing a "baseline" of normality from which future comparisons can be made. From audit data (previously collected in our unit) it is known that our patients receive between 2-3 CT scans for the purpose of diagnosis and management of IFD as part of normal clinical care. If study patients later require diagnostic and follow up CT scans as part of their standard clinical management, a lower radiation dose will be used in this study for any follow up scans. The low dose follow-up scans will offset the additional baseline CT to ensure that your total radiation is not significantly different from standard care.

As part of the study, patients will also have one and half tablespoon of additional blood taken at the same time as their routine blood collections. These blood samples will look to see if the level of certain proteins in patients' blood, called cytokines, before starting their chemotherapy or transplant, can predict risk of developing IFD. In addition, we want to examine the clinical performance of newer tests such as detection of bis(methylthio)gliotoxin (bmGT), a type of fungal protein and fungal PCR (Polymerase chain reaction) as diagnostic tests for IFD. bmGT and PCR analysis will also be done on any bronchoalveolar lavage (BAL) samples collected on clinical grounds. BAL samples are obtained by a procedure called bronchoscopy, which is a test using a small camera to look down the airways and will only be undertaken when clinically indicated. These research samples will be securely stored in a pseudo-anonymised form and any spare samples will be stored and used for future ethically approved research.

Finally, clinical, laboratory and radiological information taken as part of patients' normal care will be prospectively collected for this study.

Intervention Type
Other

Phase
Phase IV

Primary outcome(s)
Cumulative incidence of IFD in all treatment groups (aplastic anaemia with IST, chemotherapy only, RIC allograft) assessed by clinical, radiological and mycological diagnostic methods for IFD diagnosis documented in clinical notes and investigations from baseline to 24 weeks.

Key secondary outcome(s))
1. Trough plasma levels of posaconazole correlated with the incidence of IFD assessed by weekly plasma posaconazole levels (during the period when patient continues on posaconazole tablet) and clinical, radiological and mycological diagnostic methods for IFD diagnosis documented in patient's clinical notes from baseline to 24 weeks
2. The number of patients who received antifungal treatment assessed by clinical notes and prescription charts from baseline to 24 weeks
3. Whether calcineurin inhibitors such as cyclosporine A or tacrolimus adversely affect plasma posaconazole levels, assessed by regular weekly-twice weekly drug levels testing performed during periods when patient is taking the drugs, from baseline to 24 weeks
4. Clinical response to antifungal therapy assessed by clinical, radiological and mycological

methods as defined by EORTC criteria documented in clinical notes from baseline to 24 weeks.
5. Clinical performance of BDG, GM, bmGT and PCR assessed by laboratory validation techniques correlating with true clinical incidence of IFD documented in clinical notes from baseline to 24 weeks
6. The risk factors for IFD assessed by clinical, laboratory and radiological attributes documented in clinical notes from baseline to 24 weeks

Exploratory Outcome measures
1. IFD incidence, number of patients on antifungal prophylaxis and treatment is assessed by clinical notes from 24 weeks until 12 months
2. Overall survival is measured by number of people alive using Kaplan Meyer survival estimate analysis at 6, 9 and 12 months
3. Pharmaco-economics of IFD diagnosis and treatment is assessed by costs of diagnostics, antifungal drug treatment and hospitalisation rates documented in clinical notes over 12 months

Completion date
27/10/2019

Eligibility

Key inclusion criteria
1. Adult ≥ 18 years
2. Patients with aplastic anaemia, MDS or AML undergoing:
2.1. IST; or
2.2. Intensive chemotherapy such as induction chemotherapy; or
2.3. RIC allogeneic HSCT
3. Able to swallow and retain orally administered medication

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
120

Key exclusion criteria
1. Refusal or inability to consent
2. Autologous HSCT
3. Contraindicated medications

4. Current evidence of IFD diagnosis or treatment
5. Women who are pregnant or lactating
6. Enrolled in another study requiring alternative antifungal prophylaxis or treatment
7. Women who are unable to use and apply with effective contraception without interruption throughout the duration of study drug therapy and not willing to have further pregnancy tests during the course of the study

Date of first enrolment
19/01/2017

Date of final enrolment
31/10/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Sponsor information

Organisation
King's College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No