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Itraconazole Versus Amphotericin B for the treatment of Penicilliosis (IVAP)

Submission date
10/10/2011

Recruitment status
No longer recruiting

Registration date
19/12/2011

Overall study status
Completed

Last Edited
23/01/2019

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
This is a study of adults (both male and female) with human immunodeficiency virus (HIV) infection who become infected with Penicillium marneffei, which causes a deadly infection known as penicilliosis . There are two drugs used to treat this infection in Viet Nam: amphotericin B and Itraconazole. Itraconazole is taken by mouth and is less expensive, while amphotericin B is taken through intravenous infusion, which is less convenient, causes more drug reactions, is more expensive and requires a higher level of care. Current WHO and Vietnamese guidelines recommend amphotericin B as the treatment of choice. Amphotericin B is not available in many resource-limited settings and doctors still use itraconazole to treat this disease. Experience in these settings shows that this treatment is effective. This study is designed to find out if itraconazole works as well as amphotericin B.

Who can participate?
Participants have to be HIV positive, be over 18 years old and suffer from penicilliosis (identified from blood, skin lesion scrapping, lymph node or bone marrow biopsy).

What does the study involve?
Participants will randomly be allocated to one of the two treatments: amphotericin B (0.7 mg/kg /day) through a vein in their arm or itraconazole by mouth (600 mg/day for 3 days, then 400 mg /day) for the first 2 weeks. Then everyone will be given itraconazole by mouth (400 mg/day) for the remaining 10 weeks of the treatment.

What are the possible benefits and risks of participating?
Participants will be treated according to regular clinical care when participating to the study. As we do not know if the drugs work in the same way, participants may not benefit directly from being in the study. The study results will help understanding how to best treat this fungal infection and it may help others with this disease in the future.
The risks associated with this study are the same as those which patients will experience in clinical care. Both drugs are routinely used in clinical care and study procedures will follow regular guidelines. A small amount of additional blood will be taken for laboratory tests which are not routine, but may improve diagnosis and understanding of the disease.

Where is the study run from?
There will be four study sites in Viet Nam: Hospital for Tropical Diseases in Ho Chi Minh City, Bach Mai Hospital, National Hospital for Tropical Diseases in Hanoi, Uong Bi Viet Nam Sweden Hospital in Quang Ninh Province and Viet Tiep Hospital in Hai Phong Province.

When is the study starting and how long is it expected to run for?
The study started in October 2012 and should last about four years.

Who is funding the study?
Funders of this trial are: The Department for International Development, the Wellcome Trust and the Medical Research Council in the UK.

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Contact details
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Additional identifiers

Protocol serial number
11CN

Study information

Scientific Title
A randomized, open-label, comparative study of the effectiveness of itraconazole versus amphotericin B in the induction treatment of penicilliosis in HIV-infected adults

Acronym
IVAP

Study objectives

Itraconazole is at least as effective as amphotericin B for the acute-phase treatment of penicilliosis by conducting a randomized, open-label, comparative non-inferiority trial of the efficacy and safety of itraconazole versus amphotericin B.

As of 15/02/2012, the following changes have been made on the trial record.
Scientific title: Updated from A randomized, open-label, comparative study of the effectiveness of itraconazole versus amphotericin B in the induction treatment of penicilliosis in HIV-infected persons to A randomized, open-label, comparative study of the effectiveness of itraconazole versus amphotericin B in the induction treatment of penicilliosis in HIV-infected adults.
Anticipated start date of trial was updated from 01/10/2010 to 01/05/2012.
Anticipated end date of trial was updated from 31/12/2013 to 31/12/2015.

As of 25/07/2013, the following changes have been made on the trial record:
Anticipated start date of trial was updated from 01/05/2012 to 8/10/2012.
Anticipated end date of trial was updated from 31/12/2015 to 31/3/2016.
Other changes are indicated in the corresponding fields.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee, 03/12/2010, ref: 12-09
Hospital for Tropical Diseases' Committee of Scientific and Medical Ethics, 09/09/2010, ref: CS /ND/10/18

Added as of 15/02/2012:
National Hospital for Tropical Diseasess Committee of Ethics in Biomedical Research, 12/12 /2011, ref: 17/HDDD-NDTU
Bach Mai Hospitals Committee of Ethics in Biomedical Research, 12/12/2011, ref: 39/HDDD
Uong Bi Hospitals Committee of Science and Technology, 16/01/2012, ref: 49/HDKHKT-BV
Viet Tiep Hospitals Committee of Science, 12/01/2012, ref: 01/BVVT/HDKH

Added as of 25/07/2013:
Vietnamese Ministry of Healths Evaluation Committee on Ethics in Biomedical Research, 12/09 /2012, ref: 781/CN-BYT

Primary study design
Interventional

Study design
Randomized open-label comparative study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Penicillium marneffei

Interventions
Current interventions as of 15/02/2012:
This study is a randomized, open-label, comparative, multi-center trial designed to assess the

efficacy and safety of itraconazole versus amphotericin B for the acute-phase treatment of penicilliosis in patients infected with HIV in Viet Nam. Patients will be randomized at 1:1 ration to the following treatment arms:

Group 1: intravenous amphotericin B 0.7 mg/kg/day for 2 weeks
Group 2: oral itraconazole 600 mg/day x first 3 days + 400 mg/day x 11 days

After the 2-week acute phase therapy, all patients will continue on to the maintain-phase therapy with oral itraconazole 400 mg/day for 10 weeks, followed by the suppressive phase therapy with itraconazole 200 mg/day until CD4 count rises above 100 for 6 months on antiretroviral therapy for HIV.

Randomization will be stratified by study site.

Previous interventions
This study is a randomized, open-label, comparative, multi-center trial designed to assess the efficacy and safety of itraconazole versus amphotericin B for the acute-phase treatment of penicilliosis in patients infected with HIV in Viet Nam. Patients will be randomized at 1:1 ration to the following treatment arms:

Group 1: intravenous amphotericin B 0.6 mg/kg/day for 2 weeks
Group 2: oral itraconazole 400 mg/day for 2 weeks

After the 2-week acute phase therapy, all patients will continue on to the maintain-phase therapy with oral itraconazole 400 mg/day for 10 weeks, followed by the suppressive phase therapy with itraconazole 200 mg/day until CD4 count rises above 100 for 6 months on antiretroviral therapy for HIV.

Randomization will be stratified for the following variables:
1. Study site
2. Presence of fungemia

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Amphotericin B, itraconazole

Primary outcome(s)
Current primary outcome as of 15/02/2012:
Absolute risk of death during the first 2 weeks after randomization

Previous primary outcome:
Mortality at 2 weeks of treatment (most deaths from penicilliosis occur in the acute phase of the disease and are reasonably assumed to have occurred by week 2 of presentation)

Key secondary outcome(s)

Current secondary outcomes as of 25/07/2013:
1.Clinical endpoints
1.1 Overall survival until week 24
1.2 Time to treatment success (defined by absence of fungal growth in follow up culture, temperature <38°C for 3 days, and complete resolution of lesions or lesions in the final stage of healing as judged by treating clinicians)
1.3 Relapse-free survival until week 24 of therapy (i.e., time from treatment success to the first treatment relapse or death). (Relapse is defined as recurrence of culture-confirmed penicilliosis after achieving treatment success at week 12)
1.4 Deaths from penicilliosis until week 24 (causes of death will be determined by investigators)
1.5 Time to change of therapy from assigned study therapy
1.6 Total number of patients with Grade 3 and Grade 4 AEs and SAEs, and the cumulative incidence of Grade 3 and Grade 4 AEs and SAEs, associated with cessation of randomly assigned therapy between treatment arms
1.7 Antifungal medication adherence
1.8 Incidence of Immune Reconstitution Diseases
2. Microbiological endpoints
2.1 Time to blood culture sterilization
2.2 Rate of early fungicidal activity as determined by serial blood samplings during therapy and measured by the decrease in log colony forming units per mL of blood (CFUs/mL)
2.3 Frequency and patterns of itraconazole and amphotericin B resistance emergence
3. Pharmacological endpoints
3.1 Antifungal concentration time curves
3.2 Maximum antifungal concentrations/MIC, area under the curve (AUC) of antifungals/MIC over time

Previous secondary outcomes (15/02/2012 to 25/07/2013):
1.Clinical endpoints
1.1 Overall survival until week 24
1.2 Time to treatment success (defined by absence of fungal growth in follow up culture, temperature <38°C for 3 days, and complete resolution of lesions or lesions in the final stage of healing as judged by treating clinicians)
1.3 Relapse-free survival until week 24 of therapy (i.e., time from treatment success to the first treatment relapse or death). (Relapse is defined as recurrence of culture-confirmed penicilliosis after achieving treatment success at week 12)
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2.1 Time to blood culture sterilization
2.2 Rate of early fungicidal activity as determined by serial blood samplings during therapy and measured by the decrease in log colony forming units per mL of blood (CFUs/mL)
2.3 Frequency and patterns of itraconazole and amphotericin B resistance emergence
3. Pharmacological endpoints
3.1 Antifungal concentration time curves
3.2 Maximum antifungal concentrations/MIC, area under the curve (AUC) of antifungals/MIC over time
4. Serological endpoints

4.1 Time to P. marneffei urinary antigen clearance
4.2 Rate of decrease in P. marneffei urinary antigen titers

Original secondary outcomes (until 15/02/2012):
1. Clinical endpoints:
1.1. Overall survival until week 24
1.2. Time to treatment success (defined by absence of fungal growth in follow up culture, temperature <38°C for 3 days, and complete resolution of lesions or lesions in the final stage of healing as judged by treating clinicians)
1.3. Relapse-free survival until week 24 of therapy (i.e. time from treatment success to the first treatment relapse or death). (Relapse is defined as recurrence of culture-confirmed penicilliosis after achieving treatment success at week 12)
1.4. Time to change in randomly assigned therapy
1.5. Total number of patients with Grade 3 and Grade 4 AEs and SAEs, and the cumulative incidence of Grade 3 and Grade 4 AEs and SAEs, associated with cessation of randomly assigned therapy between treatment arms
1.6. Antifungal medication adherence
2. Microbiological endpoints:
2.1. Time to blood culture sterilization
2.2. Rate of early fungicidal activity as determined by serial blood samplings during therapy and measured by the decrease in log colony forming units per mL of blood (CFUs/mL)
2.3. Frequency and patterns of itraconazole and amphotericin B resistance emergence by E-test
3. Pharmacological endpoints:
3.1. Antifungal concentration time curves in central (plasma) and PBM intracellular compartments
3.2. Maximum antifungal concentrations/MIC, area under the curve (AUC) of antifungals/MIC over time
4. Serological endpoints:
4.1. Time to P. marneffei urinary antigen clearance
4.2. Rate of decrease in P. marneffei urinary antigen titers

Completion date
15/06/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 15/02/2012
1. HIV positive
AND
2. Age ≥18 years
AND
3. Syndrome consistent with penicilliosis (primary or relapse) PLUS culture-confirmed diagnosis of penicilliosis (from blood, skin lesion scrapping, lymph node or bone marrow biopsy).

Previous inclusion criteria
1. HIV positive
2. Age ≥ 15 years
3. Male and female participants

4. Syndrome consistent with penicilliosis (fever, malaise, hepatosplenomegaly, lymphadenopathy, typical skin lesions) plus culture confirmed diagnosis of penicilliosis (from blood, skin lesion scrapping/biopsy, lymph node or bone marrow biopsy)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 25/07/2013:
1. Age <18
2. Pregnancy or urine β-hCG positive
3. History of allergy or severe reaction to either itraconazole or amphotericin B
4. Central nervous system involvement (assessed clinically and by evidence of inflammation and /or infection in the CSF)
5. Use of the following prohibited drugs: phenytoin, barbiturates, carbamazepine, rifampin, HMG-CoA reductase inhibitors, cisapride, terfenadine, midazolam, dihydropyridine Ca channel blocker, cyclosporine, cyclophosphamide, tacrolimus, digoxin, quinidine, ergot derivatives, pimozide, coumadin, or investigational drugs.
6. Baseline AST or ALT ≥400 U/L
7. Absolute neutrophil count <500 cells/μL
8. Creatinine clearance of <30 by Cockcroft-Gault formula or on hemodialysis
9. Concurrent diagnosis of cryptococcal meningitis or active tuberculosis (as amphotericin B is the treatment of choice for cryptococcal meningitis, and tuberculosis treatment with INH and rifampin is contraindicated when used with itraconazole)
10. Current treatment with an antifungal drug for confirmed or suspected penicilliosis for >48 hours

Previous exclusion criteria (15/02/2012 to 25/07/2013):
1. Age <18
2. Pregnancy or urine β-hCG positive
3. History of allergy or severe reaction to either itraconazole or amphotericin B
4. Central nervous system involvement (assessed clinically and by evidence of inflammation and /or infection in the CSF)
5. Use of the following prohibited drugs: phenytoin, barbiturates, carbamazepine, rifampin, isoniazid, H2 blocker, HMG-CoA reductase inhibitors, cisapride, terfenadine, midazolam, dihydropyridine Ca channel blocker, cyclosporine, cyclophosphamide, tacrolimus, digoxin, quinidine, ergot derivatives, pimozide, coumadin, or investigational drugs.
6. Baseline AST or ALT ≥10 times the upper limit of normal
7. Absolute neutrophil count < 500 cells/μL

8. Creatinine clearance of <10 by Cockcroft-Gault formula or on hemodialysis
9. Concurrent diagnosis of cryptococcal meningitis or active tuberculosis (as amphotericin B is the treatment of choice for cryptococcal meningitis, and tuberculosis treatment with INH and Rifampin is contraindicated when used with itraconazole)
10. Current treatment with an antifungal drug for confirmed or suspected penicilliosis for >48 hours

Original exclusion criteria (until 15/02/2012):
1. Age < 15
2. Pregnancy or urine β-hCG positive
3. History of allergy or severe reaction to either itraconazole or amphotericin B
4. Unable to take oral medications
5. Documented treatment failure due to suspected drug resistance to either itraconazole or amphotericin B from another hospital or an outpatient clinic
6. Use of the following prohibited drugs: phenytoin, barbiturates, carbamazepine, rifampin, isoniazid, H2 blocker, HMG-CoA reductase inhibitors, cisapride, terfenadine, midazolam, dihydropyridine calcium channel blocker, cyclosporine, cyclophosphamide, tacrolimus, digoxin, coumadin, or investigational drugs.
7. Baseline aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal
8. Creatinine clearance of < 10 by Cockcroft-Gault formula or on hemodialysis
9. Concurrent diagnosis of cryptococcal meningitis or active tuberculosis (as amphotericin B is the treatment of choice for cryptococcal meningitis, and tuberculosis treatment with Isoniazid (INH) and Rifampin is contraindicated when used with itraconazole)

Date of first enrolment
08/10/2012

Date of final enrolment
18/12/2015

Locations

Countries of recruitment
Viet Nam

Study participating centre
Centre for Tropical Medicine
Ho Chi Minh City
Viet Nam
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Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Current sources of funding as of 15/02/2012:

Funder Name
Joint Global Health Trials Initiative (WT-MRC-DFID) ref:100033

Funder Name
Department for International Development (UK)

Funder Name
The Wellcome Trust (UK)

Funder Name
Medical Research Council (UK)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Previous sources of funding:

Funder Name
Department for International Development (UK)

Funder Name
The Wellcome Trust (UK) ref:100033

Funder Name
Medical Research Council (UK) ref: G1100682

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

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	15/06/2017	23/01/2019	Yes	No