A phase IV, interventional, non-blinded, randomized, controlled, multicenter study of posaconazole prophylaxis for the prevention of influenza-associated aspergillosis (IAA) in critically ill patients

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To deliver proof of concept that antifungal prophylaxis with posaconazole in addition to standard of care (SOC) can reduce the incidence of IAA in ICU patients with severe influenza, in comparison with SOC alone.To assess differences in cytokine...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON46362

Source
ToetsingOnline

Brief title
Posaconazole prophylaxis for prevention of IAA
POSA-FLU

Condition

- Immunodeficiency syndromes
- Fungal infectious disorders

Synonym
Influenza-associated aspergillosis; Aspergillus infection on top of influenza

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: 4e Geldstroom: studiegeneesmiddel en financiële ondersteuning door farmaceutische industrie;zie ook G2,Merck Sharp & Dohme (MSD)

Intervention

Keyword: Influenza-associated aspergillosis, Posaconazole, Prophylaxis

Outcome measures

Primary outcome

The difference in IAA incidence at ICU discharge between the intervention and

control group.

Secondary outcome

- Time to IAA diagnosis

- Length of ICU stay

- Length of hospital stay

- Overall mortality

- 30-day mortality

- 90-day mortality

- Presence of markers of MAS in blood

- Cytokine production by peripheral blood mononuclear cells (Nijmegen site only)

- Reactive oxygen species (ROS) production by peripheral blood

polymorphonuclear cells/neutrophils (Nijmegen site only)

- Frequencies in single nucleotide polymorphisms/mutations in relevant genes

(Nijmegen site only)

Study description

Background summary

Invasive aspergillosis (IA) has classically been viewed as an opportunistic infection in patients with specific forms of immunosuppression. Recently, however, IA has been found to occur as a complication of influenza pneumonia in patients admitted to the Intensive Care Unit (ICU) on account of respiratory insufficiency due to their influenza pneumonia, a condition known as influenza-associated aspergillosis (IAA). In the 2015/2016 influenza season, an incidence of 16% of IAA was observed with a mortality rate of 61%, including previously healthy patients. Furthermore, time to initiation of antifungal therapy was significantly shorter in survivors versus non-survivors, emphasizing the importance of early treatment. The antifungal drug posaconazole is the drug of choice for antifungal prophylaxis in neutropenic patients with acute myeloid leukaemia and patients with graft-versus-host disease after allogeneic haematopoietic stem cell transplantation, effectively reducing the incidence of IA. Therefore, we hypothesize that prophylactic use of posaconazole can reduce the incidence of IAA in ICU patients admitted with severe influenza pneumonia.

Study objective

To deliver proof of concept that antifungal prophylaxis with posaconazole in addition to standard of care (SOC) can reduce the incidence of IAA in ICU patients with severe influenza, in comparison with SOC alone.
To assess differences in cytokine production, reactive oxygen species (ROS) production and frequencies in single nucleotide polymorphisms/mutations in relevant genes between patients with severe influenza pneumonia who develop IAA and those who do not develop IAA (Nijmegen site only). Furthermore, to assess differences in presence of markers of macrophage activation syndrome (MAS) between patients with severe influenza pneumonia who develop IAA and those who do not develop IAA.

Study design

A phase IV, interventional, non-blinded, randomized controlled trial.

Intervention

The intervention group receives 300 mg posaconazole once daily intravenously (after a loading dose of 300 mg twice daily) during 7 days, in addition to standard of care (SOC). The control group receives SOC (including, but not limited to, treatment with oseltamivir).

Study burden and risks

The risk classification is regarded as negligible to the patient population receiving the study drug at the current regimens. The study drug has a market authorisation. Patients will be assessed for the most common side effects, including liver enzyme testing by drawing blood and performing electrocardiography (ECG). For the pathophysiological portion of the study, 20-30 ml of blood sample will be collected once (Nijmegen site only). Before inclusion, women of child-bearing age will undergo pregnancy testing in urine. Liver enzyme, pregnancy testing and taking blood samples for the pathophysiological portion of the study can probably be imbedded in standard of care diagnostic work-up, leading to only a minimum of additional blood samples taken as compared to routine standard of care. 30 and 90 days after inclusion, patients will be contacted by telephone for follow-up. Potentially, patients receiving study drug may experience benefit, if this and future studies indicate that prophylactic use of posaconazole can reduce the incidence of IAA in this group of patients.

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. Written informed consent must be obtained from the patient or his/her legal representative prior to any study procedures;
2. Adult patient (>= 18 years);
3. PCR-confirmed influenza in nasopharyngeal swab (NS), bronchial aspirate (BA) or broncho-alveolar lavage (BAL) fluid within 7 days prior to ICU admission or within 48 hours after ICU admission. If PCR is not available, a positive result of a rapid test is required (a negative rapid test does not imply absence of influenza and thus requires confirmation by means of PCR);
4. Influenza symptoms present for no more than 10 days prior to ICU admission;
5. Respiratory distress as the main reason for ICU admission. Respiratory distress will be defined as tachypnea with a respiratory rate >= 25/min. and a PaO2/FiO2 ratio <= 300 with or without (bilateral) infiltrates on radiographic chest studies

Exclusion criteria

1. Pregnant women (based on a positive serum sample);
2. Expected survival on ICU admission <= 48 hours;
3. Patients being transferred from another hospital ward or another hospital who already have mycological evidence of invasive aspergillosis (based on sputum, BA or BAL fluid culture; BAL fluid or serum galactomannan);
4. Patients with known intolerance of or hypersensitivity to posaconazole;
5. Patients actively treated with antifungal agents active against Aspergillus species;
6. Patients actively treated with rifampicin or rifabutin
7. Patients with a QTc interval >= 500 milliseconds on electrocardiography (ECG);
8. Patients with liver cirrhosis (Child-Pugh classification C);
9. Participation in another investigational clinical trial;
10. Any disorder which, in the investigator's opinion, might jeopardize subject's safety or compliance with the protocol

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2018
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Noxafil
Generic name:	Posaconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-07-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2018

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	17-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-003270-14-NL
ClinicalTrials.gov	NCT03378479
CCMO	NL64151.091.18