Azole-echinocandin combination therapy for invasive aspergillosis. A randomized pragmatic superiority trial (IA-DUET)

Published: 06-08-2020
Last updated: 08-04-2024

Primary objective 1. Evaluate if the survival in patients with a triazole susceptible IA can be improved when the initial therapy consists of triazole and echinocandin combination therapy instead of triazole monotherapy. (This objective is captured...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON52868

Source
ToetsingOnline

Brief title
IA-DUET/HOVON 502

Condition

- Fungal infectious disorders

Synonym
Aspergillus infection, invasive aspergillosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW in NL en KCE in Belgie

Intervention

Keyword: azole, combination therapy, echinocandin, invasive aspergillosis

Outcome measures

Primary outcome

Overall survival 6 weeks after the start of antifungal therapy in the MITT population

Secondary outcome

1. Overall survival 6 weeks after the start of antifungal therapy in the ITT population

2. Overall aspergillus attributable mortality 12 weeks after the start of antifungal therapy.

3. Overall survival 12 weeks after the start of antifungal therapy in the MITT population

4. Overall survival 6 weeks after the start of therapy in the subgroup of patients in the MITT population with a positive serum galactomannan test at baseline.

5. Overall survival 6 weeks after the start of therapy in the subgroup of non-ICU patients who fulfill the EORTC/MSG probable or proven definition (MITT population).

6. Overall survival 6 weeks after the start of therapy in the subgroup of non-ICU patients with an underlying haematological disease (MITT population)

7. Overall survival 6 weeks after the start of therapy in the subgroup of non-ICU patients without an underlying haematological disease (MITT population)

8. Overall survival 6 weeks after the start of therapy in patients that started

with triazole monotherapy and in which triazole resistance is detected during follow-up

9. Overall survival 6 weeks after the start of therapy in patients that started with triazole-anidulafungin combination therapy and in which triazole resistance is detected during follow-up

10. In the subgroup of patients with a positive serum galactomannan; Kinetics of serum galactomannan levels with combination versus monotherapy

11. Outcome of patients in which resistance testing was unsuccessful

12. Time to hospital discharge (in the MITT subgroup of patients admitted to the hospital at baseline)

13. Time to hospital discharge (in the ITT subgriup of patients admitted to the hospital at baseline)

14. Cost-effectivity of azole-anidulafungin combination therapy

Study description

Background summary

Patients with underlying haematological malignancies or immunocompromised for various other reasons, are prone to fungal infections. Invasive aspergillosis (IA) is a common complication during remission inducing chemotherapy for acute leukemia or other hematological malignancies, as well as those who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT). For more than 15 years voriconazole, a drug of the triazole class, has been the recommended treatment for this life-threatening infection after a pivotal randomized trial showed an improved survival with voriconazole compared with amphotericin B deoxycholate. However, also with voriconazole the overall 6-week mortality is still unacceptably high at 25-30% (Herbrecht et al., 20021). Therefore, a randomized controlled trial assed the efficacy of voriconazole with or without anidulafungin for the treatment of IA in haematology patients to prove that combination therapy can improve outcome.2 Among the 277 patients with IA in this study, the 6-week mortality with

combination therapy was 30% lower (19.3%) than with monotherapy (27.5%), p=0.087. In a post-hoc analysis of the 222 patients with radiographic abnormalities and a positive galactomannan antigen test, a statistically significant difference in mortality was observed (p=0.037). Though, this study did not result in conclusive evidence in favor of combination therapy, it is a credible study which adds to the already existing in vitro and animal studies in support of echinocandin triazole combination therapy for IA and thus paves the way for a second larger and pragmatic clinical trial. Another important and new consideration about the management of IA is the upcoming of infections with triazole-resistant A.fumigatus. This is increasingly becoming a worldwide problem and leads to longer hospital stay, higher costs and is associated with a very high mortality. It is very likely that the excessive use of antifungals of the triazole class in agriculture has formed the basis of this problem. Since 2018 the Dutch Working Party on Antibiotic therapy (SWAB) guideline on the management of invasive fungal infections therefore recommends upfront combination therapy (azole plus echinocandins or liposomal-amfotericine B) until resistance can be excluded as one of the treatment options for IA.

Given the evidence in favor of voriconazole-echinocandin combination therapy as well as the increasing incidence of voriconazole-resistant A. fumigatus in Belgium and the Netherlands, a large clinical study on the value of combination therapy is urgently needed.

Study objective

Primary objective
1. Evaluate if the survival in patients with a triazole susceptible IA can be improved when the initial therapy consists of triazole and echinocandin combination therapy instead of triazole monotherapy. (This objective is captured in the primary endpoint as well as secondary endpoints 2 to 7)

Secondary objectives
1. Evaluate if the survival in patients with an IA in whom azole resistance was not detected can be improved by starting triazole/echinocandin combination therapy compared to the local standard of care. This IA study population includes patients in whom resistance testing was successful and resistance was not detected OR patients in whom resistance testing was unsuccessful. This objective is captured in the first secondary endpoint..
2. Evaluate if a triazole/echinocandin combination therapy improves the overall quality of life and if it is a cost-effective intervention (these objectives are captured in secondary endpoint 12, 13 and 14)
23. Evaluate the outcome of patients in which a triazole-resistant A. fumigatus is detected in relation to the initial antifungal therapy they had received (i.e. triazole monotherapy or combination therapy). This objective translates into secondary endpoint 8 an 9.
43. Evaluate the outcome of patients in which resistance testing is unsuccessful in function of the antifungal therapy they received. This

translates into secondary endpoint 11.
45. Evaluate if the baseline serum galactomannan value and the serum galactomannan kinetics are predictive of overall 6-week survival. This translates into secondary endpoint 4 and 10.

Study design

A non-blinded phase 3 randomized pragmatic clinical trial.

Intervention

Intervention:
Treatment with a triazole (voriconazole or isavuconazole or posaconazole) + anidulafungin IV. The triazole is administered for at least 6 weeks while anidulafungin is given for at least 7 and a maximum of 28 days.

Comparator:
Treatment with a triazole (voriconazole or isavuconazole or posaconazole) for at least 6 weeks.

Study burden and risks

The safety of this combination therapy has previously been demonstrated in a large randomization clinical trial. As a result of the underlying disease as well as the chemotherapy, serious adverse events are very frequently observed in this patient population (e.g. bleeding, life threatening infections, death due to progression of the underlying disease). The study will comprise of 4 study visits and as most patients will be hospitalized at the start of therapy few of these will be additional hospital visits on top of the standard of care.

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. 18 years or older
2. Have started or will start voriconazole or isavuconazole (or posaconazole if voriconazole or isavuconazole cannot be given as per treating physician*s decision) as antifungal therapy on the baseline visit.
3. For all patients: presence of one of the EORTC/MSG host factors or being admitted to the ICU with influenza
4 For non-ICU patients or ICU patients without influenza: Meet the EORTC/MSG clinical criterion.
5 For non-ICU patients or ICU patients without influenza: Meet the mycological criterion or fulfil inclusion criterion 7.
6. For ICU patients with influenza we consider an isolated positive sputum culture for Aspergillus spp. insufficient as a mycological criterion.
Therefore, in these patients only one of the following mycological criteria are acceptable; Serum galactomannan >=0.5, BAL galactomannan >=1.0 or Aspergillus spp. cultured in BAL fluid.

Exclusion criteria

1. Known history of allergy, hypersensitivity or serious reaction to triazole or echinocandin antifungals;
2.Patients with chronic invasive aspergillosis or a chronic non-invasive aspergillus infection (e.g. aspergilloma) defined as the clinical or radiological sign of infection being present for >28 days.
3. Receipt of itraconazole, voriconazole, posaconazole as prophylaxis for at least 7 days in the 14 days preceding the date of the first radiological signs of the Aspergillus infection. Patients in which the most recent serum level of the triazole given as prophylaxis was subtherapeutic can be included.

4. Receipt of echinocandin prophylaxis for >96 hours in the preceding 7 days
5 Receipt of systemic antifungal treatment with an echinocandin, a triazole (except fluconazole) or amphotericin B for the current episode of invasive aspergillosis for a duration of > 96 hours.
6.. For patients in the Netherlands only: Diagnostic testing to exclude triazole resistance will not be possible (sputum cultures are negative and BAL sampling will not be performed)
7. ICU patients only: Patients with a sequential organ failure assessment (SOFA) score >11 at the time of screening for the study are excluded. If randomization is done >24 hours after screening the calculation should be repeated before the patient can be randomized (appendix 3)
8. ICU patients only: Patients in which weaning from the ventilator or ECMO system is deemed unlikely due to irreversible lung damage
9. Patients with any condition which, in the opinion of the investigator, could affect patient safety, preclude evaluation of response (e.g. because survival beyond 6 weeks is unlikely due to the underlying disease status)
10. Patient previously included in this study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-07-2021
Enrollment:	325
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ecalta
Generic name:	anidulafungin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-08-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2023
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2020-000627-40-NL
ClinicalTrials.gov	NCT04876716
CCMO	NL72950.078.20