Clinical Infectious Diseases

BRIEF REPORT

Superiority Trials in Invasive Aspergillosis: A Harsh Reality Check With the IA-DUET (HOVON502) Trial

Hanne Lamberink,[1,a] Sammy Huygens,[1,2,a] Robina Aerts,[3,4,a] Katrien Lagrou,[4,5] Elena van Leeuwen-Segarceanu,[6] Tom Lodewyck,[7] Laurens Nieuwenhuizen,[8] Maarten F. Corsten,[9] Ine Moors,[2] Sophie Servais,[10] Julien De Greef,[11] Maya Hites,[12] Astrid Demandt,[13] Alexander Schauwvlieghe,[7] Johan Maertens,[3] and Bart Rijnders[1]

[1]Department of Internal Medicine, Section of Infectious Diseases and Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Hematology, Ghent University Hospital, Ghent, Belgium; [3]Department of Hematology, University Hospitals Leuven, Leuven, Belgium; [4]Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium; [5]Department of Laboratory Medicine and National Reference Center for Mycosis, Excellence Center for Medical Mycology (ECMM), University Hospitals Leuven, Leuven, Belgium; [6]Department of Internal Medicine, St Antonius Hospital, Nieuwegein, The Netherlands; [7]Department of Hematology, AZ St-Jan Brugge-Oostende Hospital, Bruges, Belgium; [8]Department of Hematology, Maxima Medical Center, Eindhoven/Veldhoven, The Netherlands; [9]Department of Hematology, Meander Medical Center, Amersfoort, The Netherlands; [10]Department of Hematology, University Hospital of Liège, Liège, Belgium; [11]Department of Internal Medicine and Infectious Diseases, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium; [12]Clinic of Infectious Diseases, Hôpital Universitaire de Bruxelles, Brussels, Belgium; and [13]Division of Hematology, Department of Internal Medicine, GROW–School for Oncology and Developmental Biology, Maastricht University Medical Center, The Netherlands

The IA-DUET study aimed to compare azole-echinocandin combination therapy with azole monotherapy for invasive aspergillosis. Recruitment was hindered by patient ineligibility, competing studies, and guidelines favoring combination therapy when azole resistance was unknown. The low IA-attributable mortality suggests future trials may benefit from cluster randomization or composite endpoints to enhance efficiency.

Keywords. azole; combination therapy; echinocandin; invasive aspergillosis.

Invasive aspergillosis (IA) challenges the clinical management of patients undergoing treatment for hematologic malignancies. Triazoles are the preferred first-line therapy, but the short-term all-cause mortality is still 25%–30% [1]. Animal data suggest a synergistic effect of echinocandins and triazoles [2]. Although a lower overall 6-week mortality was seen with this combination therapy in a clinical trial (19.3% vs 27.5%, $P = .087$), the results were inconclusive [3]. This was not surprising because the study design anticipated an overly optimistic 60% reduction in overall mortality with combination therapy. Studies to confirm or refute these findings are therefore required. Moreover, the increasing prevalence of azole resistance worldwide underscores the need for research on the use of upfront combination therapy while waiting for azole susceptibility test results, if available at all [4]. Indeed, the overall mortality of patients infected with an azole-resistant *Aspergillus fumigatus* who initially receive azole monotherapy is high [5, 6].

Against this background, the IA-DUET study (ClinicalTrials.gov identifier NCT04876716) was conceived to confirm or refute the survival advantage of combination therapy. Designed as a pragmatic, nonblinded, multinational, superiority trial, it aimed to include a diverse population of immunocompromised patients, as well as those critically ill with influenza. By embracing real-world scenarios, the study sought to provide robust recommendations for daily clinical practice.

METHODS

The design of the study is summarized in Supplementary Figure 1. The full study protocol is available as an online supplement. A summary is provided below. The primary objective was to investigate whether combination therapy offered a survival advantage over azole monotherapy at 6 weeks in patients with an azole-susceptible IA.

Study Population

Adult immunocompromised patients with radiological abnormalities on chest computed tomography and a positive mycological test as well as intensive care unit patients with a Sequential Organ Failure Assessment score <12 who fulfilled a definition of influenza-associated IA [7] could be enrolled. To allow the inclusion of patients who are considered to suffer from IA in clinical practice, patients with a host factor and pulmonary infiltrates but without classic radiological signs (eg, halo, cavity) were also included if they had a positive culture or galactomannan test (≥1.0 in bronchoalveolar lavage or ≥0.5 in serum). Those with acute leukemia or severe graft-versus-host disease could be included based on clinical criteria but were excluded after 7 days if mycology test results turned out negative, azole resistance was detected, or testing for resistance was unsuccessful.

Received 16 July 2024; editorial decision 18 September 2024; accepted 05 October 2024; published online 8 October 2024

[a]H. L., S. H., and R. A. contributed equally to this work.

Correspondence: B. Rijnders, Department of Internal Medicine, Section of Infectious Diseases and Department of Medical Microbiology, Erasmus University Medical Center, PO Box 9101, 3015 GD Rotterdam, The Netherlands (b.rijnders@erasmusmc.nl).

Clinical Infectious Diseases® 2025;80(2):367–70

https://doi.org/10.1093/cid/ciae501

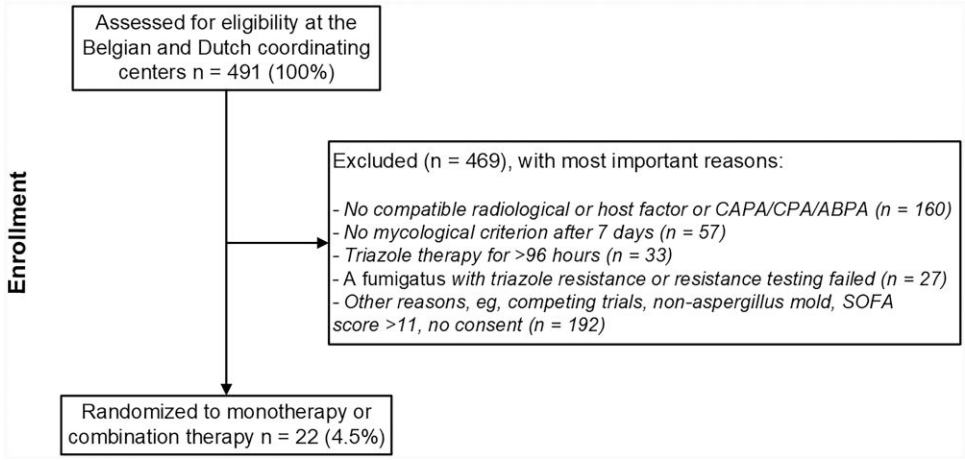

Figure 1. Screening failures from the Belgian and Dutch coordinating centers. Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CAPA, coronavirus disease 2019–associated pulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; SOFA, Sequential Organ Failure Assessment.

Patients had started azole therapy <96 hours prior to inclusion. After randomization, monotherapy was continued or anidulafungin was added. The main exclusion criteria were chronic pulmonary aspergillosis, prolonged use of azole or echinocandin prophylaxis, and, in the Netherlands, unavailability of resistance testing results due to negative cultures or failed polymerase chain reaction (PCR)–based resistance testing.

Sample Size Calculation

With an expected 35% overall mortality, 237 evaluable patients were needed per arm (power 80%, $\alpha = .05$ for superiority) to show a reduction in overall mortality of 33% (from 35% to 23.3%).

Study Design

The study was designed as simple and pragmatic as possible. In brief, echinocandin therapy was given for at least 7 but no more than 28 days. On day 1, week 6, week 12, and week 24, questionnaires on quality of life and loss of income were completed and data were extracted from the electronic patient file without additional hospital visits. In case of fatality, the local investigator registered whether or not the IA was the primary cause of death or contributed to the death of the patient, according to the guidance provided in the study protocol.

RESULTS

Since data regarding the reasons for noneligibility of patients can help to improve recruitment or improve the design of future trials, we describe the accrual in the 2 largest study sites. All patients at these 2 sites who started on voriconazole/posaconazole/isavuconazole, or with a positive galactomannan or *Aspergillus* PCR, were reviewed several times a week by the study team. As such, 491 patients were prescreened but only 22 (4.5%) fulfilled all study criteria and could be approached for inclusion. The wide spectrum of reasons for noneligibility is illustrated in Figure 1 and Supplementary Figure 2. Unfortunately, in May 2023, 30 months after the first patient was enrolled, the decision was made to end the study due to slow enrollment. Indeed, it would have taken up to 10 more years to get to 474 evaluable patients. Sixty-six patients had been enrolled; all were immunocompromised according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) 2020 criteria [8], and none had influenza-associated IA: 31 were randomized to combination therapy and 35 to azole monotherapy. As per protocol, 17 high-risk patients were excluded when mycological confirmation of IA was not obtained within 7 days after exclusion. Additionally, 8 patients were excluded per protocol if triazole resistance could not be ruled out within 1 week, aligning with Dutch guidelines that advise against using triazole monotherapy in such cases. In the end, 39 evaluable patients were included in the final analysis (Supplementary Figure 2).

Primary Endpoint

The overall 6-week mortality was 6 of 19 (31.6%) with combination therapy and 1 of 20 (5%) in the control arm. The very small sample size makes a formal statistical analysis futile.

Secondary Endpoints

The overall 12-week mortality was 10 of 39 (25.6%): 6 of 19 (31.6%) in the intervention arm and 4 of 20 (20%) in the control arm. According to the principal investigators' opinion, in 5 of 10 deaths at week 12, and 5 of 12 deaths at week 24, IA was the cause of or at least contributed to the death, corresponding to a low IA-attributable mortality of 12.8% (5/39) at weeks 12 and 24. This included 3 of 19 (15.8%) with combination therapy and 2 of 20 (10%) with monotherapy. Other causes

of death comprised refractory hematological disease, metastases from solid malignancy, bacterial infections, acute renal failure, and ischemic cerebrovascular accident. As only 13 and 14 patients were alive at week 24 of the study in each group, we were unable to analyze any other secondary endpoints.

DISCUSSION

The IA-DUET trial aimed to evaluate whether azole-echinocandin combination therapy decreases overall mortality of IA at 6 weeks compared to azole monotherapy. Despite its pragmatic design, the trial was discontinued after 3.5 years because of poor accrual. Although the final sample size does not allow for any conclusions on the primary endpoint, there are still some important observations made. While the overall mortality at 12 weeks was 25.6% (10/39), IA was considered to have at least contributed to death in only 12.8% (5/39) of cases, comparable to or lower than found in previous studies [9, 10]. This low attributable mortality rate suggests that as of 2024, a superiority trial on IA has become very difficult to execute. Even with a trial design to detect a large treatment effect (50% decrease in attributable mortality, which was ±15% in this study), the overall mortality would be expected to be reduced from ±30% to ±22.5%. Based on these assumptions, a superiority trial with overall mortality as the primary endpoint and the optimistic 50% reduction in attributable mortality would need 537 *evaluable* patients in each arm (80% power, $\alpha = .05$). This is twice as many patients ever enrolled in a phase 3 interventional trial on IA to date.

Limitations to this study include, first, that recruitment in the trial turned out to be very challenging. Despite a definition of IA somewhat broader than the EORTC/MSGERC 2020 criteria and the limited number of exclusion criteria, <5% of the "screened" patients were eventually eligible.

Second, our study sites were tertiary care hematology centers where competing trials, sometimes with more substantial funding, influenced enrollment priorities. Indeed, many trial protocols prohibit patients from participating in another intervention study once enrolled in a therapy-focused hematology trial, including ours. Additionally, in times of limited funding and personnel, hematology trials, especially those targeting novel agents, are typically prioritized by both clinicians and patients, which further impacted our trial's enrollment. Finally, at the time of the study, the Dutch guideline on the treatment of IA recommended against azole monotherapy when azole resistance cannot be excluded by culture or CYP51A PCR-based resistance testing in culture-negative cases [11]. Although this recommendation is controversial, it resulted in a substantial number of ineligible patients.

IA is a relatively rare infection, at least compared with urinary tract infections, *Staphylococcus aureus* bacteremia, or community-acquired pneumonia. However, it is still 10 times more frequent than other invasive mold infections like mucormycosis or fusariosis. Studying the prevention and treatment of these invasive mold infections with "simple" randomized trials is therefore challenging or not possible at all. Still, the growing immunocompromised population, as well as azole resistance, underscores the need for novel therapeutic antifungal options. The use of cluster randomization, composite endpoints as part of a win ratio analysis (eg, attributable mortality, biomarker evolution, toxicity, breakthrough or refractory infections) or the use of nonrandomized controls may help to improve the efficiency of studies on invasive mold infections and help to find answers to the many questions regarding their management [12].

In conclusion, while addressing logistical challenges and competing trials could improve future antifungal treatment trials, the current low mortality rate attributable to IA suggests that superiority trials on overall mortality for triazole-susceptible IA are becoming unrealistic. Future studies may need to focus on alternative trial designs or endpoints to address this evolving landscape.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank all of the patients who participated in the trial, together with all trial assistants from local study teams who made the study possible.

Financial support. This work was supported by the Netherlands Organisation for Health Research and Development (ZonMw) and the Belgian Health Care Knowledge Centre under project number 80-85200-98-18558.

Potential conflicts of interest. S. H. received travel support from Gilead Sciences and payment for teaching activities from Gilead Sciences and Pfizer. R. A. received research grants from the Flemish Cancer Society (Kom Op Tegen Kanker), Gilead Sciences, and Pfizer; payment for teaching activities from Gilead Sciences and Pfizer (all paid to the institution); and travel support from Gilead Sciences and Pfizer. K. L. received consultancy fees from MRM Health and Mundipharma; speaker fees from Pfizer, Gilead, and FUJIFILM Wako chemicals Europe GmbH; a service fee from Thermo Fisher Scientific and TECOmedical; and a fee for advisory board participation from MSD and Pfizer. I. M. received a travel grant from the European Hematology Association. M. H. received a research grant from EU-RESPONSE; payment for teaching activities from Gilead Sciences, MSD, GSK, and INSMED, and travel support from Pfizer, Gilead Sciences, and MSD, all paid to the institution; participated on the advisory board of the DisCoVeRy Trial; and is the president of the Belgian Society of Infectious Diseases and Clinical Microbiology. A. S. received speaker's fees from Gilead Sciences, Pierre Fabre, and AbbVie; received support for attending meetings or travel from Gilead Sciences and AstraZeneca; and participated on the advisory boards of Merck, Sobi, and MaaT Pharma. J. M. received consulting fees, payment for lectures, and travel support from Gilead Sciences, Mundipharma, Astellas, Pfizer, Takeda, and F2G; and participated in advisory boards from Gilead Sciences, Mundipharma, Astellas, Pfizer, Takeda, and F2G. B. R. received research grants from Gilead Sciences; received consulting fees from F2G Ltd; was paid for teaching activities by Gilead Sciences; and was a member of advisory boards for Pfizer, Gilead Sciences, and F2G Ltd. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. van de Peppel RJ, Visser LG, Dekkers OM, de Boer MGJ. The burden of invasive aspergillosis in patients with haematological malignancy: a meta-analysis and systematic review. J Infect **2018**; 76:550–62.
2. Petraitis V, Petraitiene R, Sarafandi AA, et al. Combination therapy in treatment of experimental pulmonary aspergillosis: synergistic interaction between an antifungal triazole and an echinocandin. J Infect Dis **2003**; 187:1834–43.
3. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. Ann Intern Med **2015**; 162: 81–9.
4. Morrissey CO, Kim HY, Duong TN, et al. *Aspergillus fumigatus*—a systematic review to inform the World Health Organization priority list of fungal pathogens. Med Mycol **2024**; 62:myad129.
5. Lestrade PP, Bentvelsen RG, Schauwvlieghe AFAD, et al. Voriconazole resistance and mortality in invasive aspergillosis: a multicenter retrospective cohort study. Clin Infect Dis **2019**; 68:1463–71.
6. van der Linden JW, Snelders E, Kampinga GA, et al. Clinical implications of azole resistance in *Aspergillus fumigatus*, The Netherlands, 2007–2009. Emerg Infect Dis **2011**; 17:1846–54.
7. Verweij PE, Rijnders BJA, Brüggemann RJM, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med **2020**; 46:1524–35.
8. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis **2020**; 71:1367–76.
9. van de Peppel RJ, van Grootveld R, Hendriks BJC, et al. Implementation of a clinical decision rule for selecting empiric treatment for invasive aspergillosis in a setting with high triazole resistance. Med Mycol **2021**; 60:myab060.
10. Slobbe L, Polinder S, Doorduijn JK, et al. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia–myelodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin Infect Dis **2008**; 47:1507–12.
11. Dutch Working Party on Antibiotic Policy. SWAB guidelines for the management of invasive fungal infections. 2017. Available at: https://swab.nl/nl/exec/file/download/86. Accessed 5 May 2024.
12. Walsh TJ. Meeting the therapeutic challenges of emergent and rare invasive fungal diseases through novel clinical trial designs. Open Forum Infect Dis **2024**; 11:ofae257.