International Journal of Infectious Diseases 144 (2024) 107070

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Safety and effectiveness of isavuconazole in real-life non-neutropenic patients

Patricia Monzó-Gallo[1,2], Carlos Lopera[1,2], Ana M Badía-Tejero[3], Marina Machado[4], Julio García-Rodríguez[5,15], Pablo Vidal-Cortés[6], Esperanza Merino[7], Jorge Calderón[8], Jesús Fortún[9], Zaira R. Palacios-Baena[10,15], Javier Pemán[11], Joan Roig Sanchis[12], Manuela Aguilar-Guisado[13,15], Carlota Gudiol[3,15], Juan C Ramos[5,15], Isabel Sánchez-Romero[8], Pilar Martin-Davila[9], Luis E. López-Cortés[10,15], Miguel Salavert[11], Isabel Ruiz-Camps[12], Mariana Chumbita[1,2], Tommaso Francesco Aiello[1,2], Olivier Peyrony[1,14], Pedro Puerta-Alcalde[1], Alex Soriano[1,15,2], Francesc Marco[16,2], Carolina Garcia-Vidal[1,15,2,*]

[1] *Department of Infectious Diseases, Hospital Clinic of Barcelona-IDIBAPS, University of Barcelona, Barcelona, Spain*
[2] *Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), c. Casanova, 143, 08036 Barcelona, Spain.*
[3] *Department of Infectious Diseases, Hospital of Bellvitge, Barcelona, Spain*
[4] *Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid - Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*
[5] *Infectious Diseases Unit, University Hospital La Paz, Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ), Madrid, Spain*
[6] *Intensive Care Unit, University Hospital of Ourense, Ourense, Spain*
[7] *Department of Infectious Diseases, Hospital General Universitario Dr. Balmis – Instituto, Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain*
[8] *Department of Infectious Diseases, University Hospital Puerta de Hierro, Madrid, Spain*
[9] *Department of Infectious Diseases, University Hospital Ramon y Cajal, Madrid, Spain*
[10] *Infectious Diseases and Microbiology Clinical Unit, University Hospital Virgen Macarena, Institute of Biomedicine of Seville (IBiS) and CSIC, Seville, Spain*
[11] *Infectious Diseases Unit (Medical Clinical Department), University and Polytechnic Hospital La Fe, La Fe Health Research Institute (IIS-La Fe), Valencia, Spain*
[12] *Department of Infectious Diseases, University Hospital Vall d'Hebron, Barcelona, Spain*
[13] *Unit of Infectious Diseases, Microbiology and Parasitology, Virgen del Rocío University Hospital, Seville, Spain*
[14] *Emergency Department, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France*
[15] *CIBER Enfermedades Infecciosas (CIBERINFEC), ISCIII, Madrid, Spain*
[16] *Department of Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 29 January 2024
Revised 9 April 2024
Accepted 22 April 2024

Keywords:
Isavuconazole
Non-neutropenic
Invasive fungal infection
Effectiveness
Safety

ABSTRACT

Objectives: Information is scarce on clinical experiences with non-neutropenic patients with invasive fungal infection (IFI) receiving isavuconazole. We aimed to report the safety and effectiveness of this drug as a first-line treatment or rescue in real life.

Methods: A retrospective, observational multicentric study of non-neutropenic patients who received isavuconazole as an IFI treatment at 12 different university hospitals (January 2018-2022). All patients met criteria for proven, probable or possible IFI according to EORTC-MSG.

Results: A total of 238 IFIs were treated with isavuconazole during the study period. Combination therapy was administered in 27.7% of cases. The primary IFI was aspergillosis (217, 91.2%). Other IFIs treated with isavuconazole were candidemia (n = 10), mucormycosis (n = 8), histoplasmosis (n = 2), cryptococcosis (n = 2), and others (n = 4). Median time of isavuconazole treatment was 29 days. Only 5.9% (n = 14) of cases developed toxicity, mainly hepatic-related (10 patients, 4.2%). Nine patients (3.8%) had treatment withdrawn. Successful clinical response at 12 weeks was documented in 50.5% of patients.

* Corresponding author: Carolina Garcia-Vidal, Infectious Diseases Department, Hospital Clinic of Barcelona, C/ Villarroel 170, 08036 Barcelona, Spain.
E-mail address: cgarciav@clinic.cat (C. Garcia-Vidal).

https://doi.org/10.1016/j.ijid.2024.107070

Conclusion: Isavuconazole is an adequate treatment for non-neutropenic patients with IFIs. Toxicity rates were low and its effectiveness was comparable to other antifungal therapies previously reported.

Introduction

There is a notable change in the profile of patients with invasive fungal infections (IFI): there has been a progressive rise of such infections in non-neutropenic population (i.e., COVID-19, influenza, biologic agents, corticosteroids, cancer, chronic obstructive pulmonary disorder [COPD] or cirrhosis) [1–3]. However, information concerning the management of non-neutropenic patients with IFI remains limited. Caution should be exercised before these patients are treated like those who are neutropenic, given a considerable variability in pathogenesis and clinical manifestations of IFI [4].

Approved in 2015, isavuconazole is a new broad-spectrum, second-generation triazole that treats invasive aspergillosis and mucormycoses [5,6]. It increases the antifungal arsenal and has several benefits compared to other azoles (broad-spectrum, more predictable pharmacokinetics (PK), good oral bioavailability and tissue diffusion, fewer side effects, lower potential drug interactions, etc.) [7].

However, impact by this new azole has not been well established in relation to outcomes and side effects in non-neutropenic patients who are diagnosed with possible, probable, or proven IFI. The randomised trial that led to the approval of isavuconazole included mainly patients with haematological malignancies and neutropenia [5]. Moreover, data on real-life patients with IFI treated with isavuconazole is scarce. This holds especially true for patients with chronic kidney disease or hepatopathy, who were excluded from pivotal studies [5,6].

Therefore, the aim of this multicentre study is to report the safety and effectiveness of isavuconazole as either first-line treatment, salvage therapy or sequential treatment in all consecutive, real-life non-neutropenic patients who were diagnosed with IFI according to consensus criteria.

Material and methods

Patients, data collection and study design

This is a retrospective, observational and multicentre study conducted in 12 Spanish tertiary hospitals collaborating within the Spanish Society of Infectious Diseases and Clinical Microbiology (GEMICOMED/SEIMC) Medical Mycology Study Group. We included all consecutive, non-neutropenic patients diagnosed with IFI receiving isavuconazole for at least 24 hours as first-line treatment or salvage therapy between January 2018 and January 2022. Both intravenous and oral isavuconazole prescriptions were considered. We excluded non-solid organ transplantation (SOT). We also excluded all cases wherein isavuconazole was used as prophylaxis or empiric therapy if it did not follow a confirmed probable or proven IFI diagnosis.

Data from prescription registers was provided by the pharmacy departments. A consensus team in each hospital reviewed episodes to verify the fulfilment of inclusion and exclusion criteria. Data from every patient included was anonymised, introduced and stored in a database made especially for the study via REDCap®.

The following variables were recorded: demographics and baseline variables (underlying diseases, viral co-infection, use of immunosuppressants or corticosteroids or previous intensive care unit [ICU] stay); IFI characteristics (type, date of diagnosis, diagnostic category, site of infection, clinical characteristics, microbiologic characteristics and antifungal susceptibility, if known); antifungal therapy (length of therapy, previous antifungals, indication of isavuconazole use, serum level of antifungals, if available; occurrence of adverse events related to antifungal therapy); clinical response and all-cause and IFI-attributable mortality.

The Ethics Committee of Clinical Research of the Hospital Clinic of Barcelona approved the study protocol (Reg. HCB/2020/0969) and granted a waiver of informed consent due to its retrospective, observational design.

Study definitions

IFI diagnosis was established according to updated criteria proposed by the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) and the aspICU algorithm [8,9]. The diagnosis of coronavirus 2019-associated pulmonary aspergillosis (CAPA) was created using consensus criteria endorsed by the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) [10]. Influenza-associated pulmonary aspergillosis diagnosis was made following expert case definitions and chronic cavitary and fibrosing pulmonary and pleural aspergillosis was defined as three months of chronic pulmonary symptoms or chronic illness or progressive radiologic abnormalities; other microbiologic data and no or minimal immunocompromised status, usually with one or more underlying pulmonary disorders [11,12]. Disseminated IFI was defined by the involvement of two or more non-contiguous anatomic sites.

The treatment-emergent adverse event (TEAE) was defined as either any event that was not present prior to treatment initiation or any already present event that worsened in either intensity or frequency following treatment exposure.

The clinical response was defined based on clinical and radiologic evolution after 12 weeks of treatment. It was classified as either success or failure to treatment. Success included total and partial responses. Total response comprised the resolution of symptoms and radiologic improvements when present, whilst partial response represented some clinical and radiologic improvements. Failure included stable disease without clinical changes or mild radiologic improvements and disease progression with clinical and/or radiologic deterioration.

Attributable IFI mortality included patients with fungal infection as main cause of death. It also comprised patients who died from another cause; however, IFI had also contributed to the process.

Laboratory procedures

Microbiologic tests included cultures from blood, cerebrospinal fluid, respiratory airways (bronchoalveolar lavage [BAL], bronchoalveolar aspirate [BAS] and sputum) and all types of biopsy samples. We performed follow-up testing with fungal RT-PCR detection and galactomannan. The threshold used to consider a positive galactomannan antigen was either an optical density index $\geq$ 0.5 in serum or BAL fluid sample from a susceptible host. We opted

Table 1
Characteristics of patients diagnosed with invasive fungal infection.

Patient characteristic	All cases (N = 238)
Demographics	
Median age, years (IQR)	66 (54-74)
Male sex	171 (71.8%)
Main comorbidities	
Hematologic malignancy[a]	45 (18.9%)
HSCT	25 (10.5%)
Autoimmune disease	19 (8%)
Solid organ malignancy[b]	40 (16.8%)
HIV infection	5 (2.1%)
Chronic lung disease	56 (23.5%)
Chronic kidney disease	20 (8.4%)
Diabetes mellitus	45 (18.9%)
Heart disease	51 (21.4%)
Liver disease	20 (8.4%)
Other predisposing factors	
Corticosteroid therapy	139 (58.4%)
Previous ICU stay	137 (57.6%)
Previous viral infection[c]	120 (50.4%)
Immunosuppressors therapy	54 (22.7%)
Chemotherapy	34 (14.3%)
GVHD	12 (5%)
Previous surgery	32 (13.4%)
Previous fungal infection	15 (6.3%)

GVHD, graft-versus-host disease; HSCT, hematologic stem cell transplant; ICU, intensive care unit.
[a] Lymphoma was the most common type (12, 26.7%), followed by acute myeloid leukaemia (9, 20%), lymphoid chronic leukaemia (7, 15.6%), multiple myeloma (6, 13.3%), lymphoid acute leukaemia (5, 11.1%) and myelodysplastic syndrome (4, 8.9%).
[b] Lung cancer was the most frequent type (11, 27.5%), followed by colorectal cancer (7, 17.5%) and breast cancer (5, 12.5%).
[c] SARS-CoV-2 was the main virus type (95, 79.3%), followed by influenza virus (8, 6.7%), cytomegalovirus (7, 5.8%), rhinovirus (3, 2.5%) and other viruses (7, 5.8%).

to establish 0.5 as a threshold in BAL samples. The reason for this is because the study began in 2018, and many samples were considered positive at that threshold.

Statistical analysis

The qualitative variables were described as absolute and relative frequencies, whilst continuous variables were presented using the median and interquartile range (IQR). The chi-squared Pearson test and either the Mann-Whitney U-test or Student t test were used to compare the categorical and continuous variables distributions, respectively. The analysis was performed with SPSS version 27.0 software.

Results

Clinical characteristics of the study population

We included 238 non-neutropenic patients treated with isavuconazole. Table 1 details the main baseline patient characteristics. Median age at IFI diagnosis was 66 (IQR 54-74) years; most patients were males (171, 71.8%). Main comorbidities were chronic lung disease (23.5%), heart disease (21.4%), diabetes (18.9%) and haematological malignancies (18.9%). A total of 114 patients (47.9%) received prior antifungal treatment different from isavuconazole per either prophylaxis (7.9%), pre-emptive treatment (50%) or treatment for a previously diagnosed IFI (42.1%). One patient received isavuconazole due to QT prolongation with other azoles.

IFI characteristics

Invasive aspergillosis was the most frequent IFI (217, 91.2%), followed by invasive candidiasis (10, 4.2%) and mucormycoses (8, 3.4%), histoplasmosis (2, 0.8%), cryptococcosis (2, 0.8%), fusariosis (1, 0.4%), *Magnusiomyces clavatus* fungemia (1, 0.4%), *Purpureocillium lilacinum* infection (1, 0.4%) and *Arthrocladium fulmicans* infection (1, 0.4%). Five (2.1%) patients had a mixed infection: 1) *A. fumigatus* and *Lictheimia* spp., 2) *Purpureocillium lilacinum* and *A. alliaceus*, 3) *C. tropicalis* and *A. niger*, 4) *Lichteimia corymbifera, C. glabrata* and *C. albicans*, and 5) *Fusarium* spp. and *Aspergillus* spp.

Table 2
Details of isavuconazole treatment.

Variable	N, (%)
Indication isavuconazole[a]	
First-line therapy	166 (69.7%)
Salvage therapy after prior antifungal toxicity[b]	43 (18.1%)
Sequential treatment	29 (12.2%)
PK/PD advantages	78 (32.8%)
Baseline hepatic abnormality	39 (16.4%)
Treatment interactions	28 (11.8%)
Antifungal de-escalation	10 (4.2%)
Other	31 (13%)
Initial mode of administration	
Oral	83 (34.9%)
Intravenous	155 (65.1%)
Type of antifungal regimen	
Monotherapy	172 (72.3%)
Combination therapy	66 (27.7%)
Anidulafungin	29 (43.9%)
L-AmB	28 (42.4%)
Caspofungin	8 (12.1%)
Micafungin	1 (1.5%)
Occurrence of TEAE	14 (5.9%)
Liver enzyme elevation	10 (4.2%)
Neurological or visual disturbances	1 (0.4%)
Gastrointestinal disturbances	1 (0.4%)
Others	2 (0.8)
TEAE requiring discontinuation	9 (3.8%)

TEAE, treatment emergent adverse effects.
[a] Physicians may describe one or more.
[b] 25 (64.1%) with voriconazole, 8 (20.5%) with L-AmB, 3 (7.7%) with fluconazole, 2 (5.2%) with echinocandins, 1 (2.6%) with Posaconazole and 4 (9.2%) were not described.

A total of 32 (13.4%) episodes fulfilled criteria for proven IFI, 179 (75.2%) for probable, and 27 (11.3%) for possible. Proven IFI diagnosis was confirmed by one or more of the following tests: fungal isolation in blood culture from 5 (21.9%) cases (4 candidemia and 1 *Cryptococcus neoformans*); histopathologic findings of a sterile specimen in 18 (58.1%) cases (8 mucormycosis, 8 aspergillosis, 1 *Cryptococcus neoformans,* 1 *Purpureocillium lilacinum* and 1 *Arthrocladium fulminans*), with 3 being mixed mould infections; and a positive culture of a sterile site with clinical or radiologic significance in 26 (81.2%) cases (15 aspergillosis, 5 candidiasis, 4 mucormycosis, 2 histoplasmosis, 1 cryptococcosis, 1 *Purpureocillium lilacinum,* 1 *Arthrocladium fulminans*), with three being mixed mould infections.

Supplementary Tables 1 and 2 detailed the clinical, radiologic and microbiologic features of the most frequent mould infections, as well as evaluations of different predictors of mortality.

Description of isavuconazole therapy course

Table 2 lists the reasons why physicians decided to treat their patients with isavuconazole. Of note, salvage therapy after prior antifungal toxicity was the reason for isavuconazole use in 43 patients, of whom 10 (23.3%) had baseline hepatic abnormality. Median duration for therapy in the entire cohort was 29 days (IQR: 7-90). There was no statistically significant difference between duration of first-line treatment and salvage therapy due to toxicity (25 [IQR: 6-90] vs 40 [IQR: 7-90] days); however, there was such a difference when first-line treatment was compared with sequential treatment (83 [IQR: 18-229] days; P value <0.004). The median duration of therapy in patients surviving IFI was 64 (IQR: 24-114) days.

Table 3
Clinical response to treatment and mortality related to IFI at week 12.

Response	Aspergillosis (n = 217)[a]					Mucor (n = 8)[a]	Other fungi (n = 18)[a]
	CAPA (n = 91)	IPA (n = 78)	AspICU (n = 30)	CCPA (n =11)	IAPA (n = 7)		
Successful	**41 (45%)**	**44 (56.5%)**	**12 (40%)**	**9 (81.8%)**	**4 (57.1%)**	**2 (25%)**	**11 (61.1%)**
Total	21 (23%)	19 (24.4%)	6 (20%)	4 (36.4%)	4 (57.1%)	1 (12.5%)	7 (38.9%)
Partial	20 (22%)	25 (32.1%)	6 (20%)	5 (45.4%)	0 (0%)	1 (12.5%)	4 (22.2%)
Unsuccessful	**50 (55%)**	**34 (43.5%)**	**18 (60%)**	**2 (18.2%)**	**3 (42.9%)**	**6 (75%)**	**7 (38.9%)**
Stable	17 (18.7%)	14 (17.9%)	5 (16.7%)	2 (18.2%)	1 (14.3%)	1 (12.5%)	3 (16.7%)
Progression	33 (36.3%)	20 (25.6%)	13 (43.3%)	0 (0%)	2 (28.6%)	5 (62.5%)	4 (22.2%)
Attributable IFI mortality	**43 (47.3%)**	**25 (32.1%)**	**19 (63.3%)**	**0 (0%)**	**3 (42.9%)**	**6 (75%)**	**5 (27.8%)**

IPA, invasive pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; CAPA, coronavirus-associated pulmonary aspergillosis; IAPA, influenza-associated pulmonary aspergillosis.
[a] Five patients had a mixed infection: 1) *A. fumigatus* and *Lictheimia* spp., 2) *Purpureocillium lilacinum* and *A. alliaceus*, 3) *C. tropicalis* and *A. niger*, 4) *Lichteimia corymbifera, C. glabrata* and *C. albicans*, and 5) *Fusarium* spp. and *Aspergillus* spp.

Most patients received initial intravenous treatment (65.1%). Isavuconazole was used as combination therapy in 66 (27.7%) cases, mainly with an echinocandin (38, 57.5%) and intravenous or nebulised liposomal amphotericin B (L-AmB) (28, 42.4%). Regarding the use of combination therapy, there was a tendency for higher frequency in the first-line therapy group than in the other indication groups (30.9% [51/166] vs 20.5% [15/72]), albeit without statistical significance. Also, there was a tendency for higher frequency in the first-line therapy group in both mucormycosis 85.7% (6/7) and invasive aspergillosis 75.9% (41/54).

Safety and efficacy of isavuconazole therapy

Fourteen (5.9%) patients developed at least 1 TEAE during treatment. The most reported event was liver enzyme elevation (10, 4.2%) and gastrointestinal or visual disturbances (2, 0.8%). Only nine (3.8%) patients had isavuconazole withdrawn due to TEAE (mainly due to liver enzyme elevation). Remarkably, TEAE during treatment was reported in 4 of 43 patients who received isavuconazole as salvage therapy after prior antifungal toxicity and in 2 of 39 patients who had baseline hepatic abnormality.

Table 3 describes patient clinical response and mortality, listed by clinical syndrome. The overall rate of successful clinical response by week 12 after isavuconazole initiation was 50.5% (n = 120/238): 52.3% in patients receiving monotherapy (n = 90/172) and 45.5% (n = 30/66) for those patients receiving combination therapy. Overall mortality at 90 days was 48.7% (n = 116/238); attributable IFI mortality was 40.3% (n = 96/238). With respect to attributable IFI mortality, we identified one group in which fungal infection was the main cause of death; mortality rate was 18.9% (n = 45/238). The other group in which death was due to another cause but IFI had played a role had a mortality rate of 21.4% (n = 51/238). For those patients receiving combination therapy, results were 60.6% (n = 40/66) and 56.1% (n = 37/66), respectively, vs 44.2% (n = 76/172) and 34.3% (n = 59/172) in those receiving monotherapy.

Discussion

In this study, we present the most extensive real-life series of non-neutropenic patients with different IFI treated with isavuconazole, aiming to assess both its safety and effectiveness. Diverging from the randomised trial that led to the drug's approval, this study predominantly characterises non-haematological patients, of whom many exhibit prior antifungal toxicities or hepatic dysfunction. Additionally, this patient series constitutes one of the most comprehensive cohorts of individuals diagnosed with aspergillosis-complicating viral infections treated with isavuconazole. It also represents one of the most substantial series describing the use of isavuconazole in IFIs other than *Aspergillus*.

The median duration of therapy in our cohort was comparable to that reported in other published series [13–15], particularly when examining the subset of patients who survived (64 days). The percentage of patients who experienced TEAE during treatment was 5.9%, which is even lower than those reported in other series [16–18]. Only 3.8% of the patients had a TEAE that required treatment discontinuation. These findings helped demonstrate a high level of safety for this drug when administered to the study population. Consistent with previous studies, the most common TEAE included elevation of hepatic enzymes, and gastrointestinal and visual disturbances [5]. Remarkably, TEAE during treatment with isavuconazole was reported in only 9.3% (n = 4/43) of patients who received isavuconazole as salvage therapy after prior antifungal toxicity and in 5.1% (n = 2/39) of those who had baseline hepatic abnormality. The patient who received isavuconazole due to QT prolongation with other azoles did not experience any issues with this antifungal.

It is challenging to compare the overall rate of successful clinical response by week 12 after isavuconazole initiation and 90-day mortality documented in our study with those of previous studies due to differences in populations and the inclusion of patients with varying IFIs. As expected, patients with mucormycosis had the highest mortality, followed by those with aspergillosis diagnosed by the aspICU algorithm. The outcomes observed in the non-neutropenic patient populations diagnosed with CAPA, IAPA and IPA are consistent with previous results in different populations [18–21].

Despite limited information on potential synergies with other antifungals for isavuconazole, which is mainly derived from *in vitro* studies [22], our research demonstrates that physicians relatively employ antifungal combinations on a frequent basis when managing IFIs. In our study, patients who received combined treatment did not exhibit increased toxicity. The attributable IFI mortality rate of patients who underwent combined therapy was higher than those patients with monotherapy. However, the design of our study does not allow for the assessment of combined treatment. It is easy to speculate that patients who received this regimen were those with the most severe conditions within our cohort.Our study has several limitations. It was a retrospective and descriptive study from a particular geographic area without specific endemic mycosis. Secondly, although we used standardised criteria whose application was reviewed, inter-observer variability cannot be ruled out. There was a non-central-independent adjudication committee, and follow-up imaging was not systematically performed. Also, the number of cases of some types of infections was too small for us to draw strong conclusions on this type of IFI. Finally, this study was non-interventional; therefore, some diagnostic methods may have been underused by the attending physicians.

In conclusion, our study represents the largest multicentre, uncontrolled cohort of non-neutropenic, non-SOT patients with IFI

treated with isavuconazole as first-line, salvage or sequential treatment. Our study underpins that the use of isavuconazole is safe and associated with minimal side effects and even fewer side effects requiring its discontinuation. Clinical response rates and mortality are comparable to those reported in other similar cohorts with other populations. Nevertheless, more prospective studies are needed to gather more information and establish isavuconazole for basic drug use in some new IFI scenarios.

Declarations of competing interest

PP-A has received honoraria for talks on behalf of Merck Sharp and Dohme, Lilly, ViiV Healthcare and Gilead Science. PP-A has participated in advisory boards for Gilead Science. CG-V has received honoraria for talks on behalf of Gilead Science, Merck Sharp and Dohme, Pfizer, Jannsen, Novartis, Lilly and a grant support from Gilead Science and Merck Sharp and Dohme. AS has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, Angelini, as well as grant support from Pfizer. OP has received honoraria for talks on behalf of MSD and Qiagen, and expertise for Sanofi. PMG has received honoraria for talks on behalf of Pfizer. MM has received honoraria for talks from Pfizer, MSD and Gilead.

Funding

This work was supported by a research grant [ISR 61016665] from Pfizer S.L.U. P.P.-A. [JR20/00012, PI21/00498, and ICI21/00103] and C.G.-V. [FIS PI21/01640, ICI21/00103 and SGR 01324 Q5856414G] have received research grants funded by ISCIII and co-funded by the European Union and also AGAUR. The funders had neither a specific role in study design or collection of data nor in writing of the paper or decision to submit.

Ethical approval

The Ethics Committee of Clinical Research of the Hospital Clinic of Barcelona approved the study protocol (Reg. HCB/2020/0969) and granted a waiver of informed consent due to its retrospective, observational design.

Acknowledgements

We would like to thank Anthony Armenta for providing medical language editing assistance for the manuscript at hand. Authors also would like to thank 'la Ligue Nationale Contre le Cancer' for their financial support of OP post-doctoral fellow (convention number: AAPMRC 2022/OP) and la Direction de l'Assistance Publique - Hôpitaux de Paris (APHP). All the authors collected data. P.M-G analysed the data with support from C.G-V. P.M-G wrote the manuscript with input from all authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107070.

References

[1] Cornillet A, Camus C, Nimubona S, Gandemer V, Tattevin P, Belleguic C, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. *Clin Infect Dis* 2006 Sep 1;**43**(5):577–84. doi:10.1086/505870.

[2] Garbino J, Fluckiger U, Elzi L, Imhof A, Bille J, Zimmerli S. Survey of aspergillosis in non-neutropenic patients in Swiss teaching hospitals. *Clin Microbiol Infect* 2011;**17**(9):1366–71. doi:10.1111/j.1469-0691.2010.03402.x.

[3] Monzó-Gallo P, Chumbita M, Lopera C, Aiello TF, Peyrony O, Bodro M, et al. Real-life epidemiology and current outcomes of hospitalized adults with invasive fungal infections. *Med Mycol* 2023;**61**(3):myad021. doi:10.1093/mmy/myad021.

[4] Marr K, Platt A, Tornheim J, Zhang S, Datta K, Cardozo C, et al. Aspergillosis complicating severe coronavirus disease. *Emerg Infect Dis J* 2021;**27**(1):18.

[5] Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016;**387**(10020):760–9. doi:10.1016/S0140-6736(15)01159-9.

[6] Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis* 2016;**16**(7):828–37. doi:10.1016/S1473-3099(16)00071-2.

[7] Ledoux MP, Denis J, Nivoix Y, Herbrecht R. Isavuconazole: a new broad-spectrum azole. Part 2: pharmacokinetics and clinical activity. *J Mycol Med* 2018;**28**(1):15–22. doi:10.1016/j.mycmed.2018.02.002.

[8] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**(12):1813–21. doi:10.1086/588660.

[9] Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med* 2012;**186**(1):56–64. doi:10.1164/rccm.201111-1978OC.

[10] Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021;**21**(6):e149–62. doi:10.1016/S1473-3099(20)30847-1.

[11] Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, 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**(8):1524–35. doi:10.1007/s00134-020-06091-6.

[12] Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003;**37**(Suppl_3):S265–80. doi:10.1086/376526.

[13] Fernández-Ruiz M, Bodro M, Gutiérrez Martín I, Rodriguez-Álvarez R, Ruiz-Ruigómez M, Sabé N, et al. Isavuconazole for the treatment of invasive mold disease in solid organ transplant recipients: a multicenter study on efficacy and safety in real-life clinical practice. *Transplantation* 2023;**107**(3):762–73. doi:10.1097/TP.0000000000004312.

[14] Zimmermann P, Brethon B, Roupret-Serzec J, Caseris M, Goldwirt L, Baruchel A, et al. Isavuconazole treatment for invasive fungal infections in pediatric patients. *Pharmaceuticals* 2022;**15**(3). doi:10.3390/ph15030375.

[15] Kronig I, Masouridi-Levrat S, Chalandon Y, Glampedakis E, Vernaz N, Van Delden C, et al. Clinical considerations of isavuconazole administration in high-risk hematological patients: a single-center 5-year experience. *Mycopathologia* 2021;**186**(6):775–88.

[16] Thompson III GR, Garcia-Diaz J, Miceli MH, Nguyen MH, Ostrosky-Zeichner L, Young JAH, et al. Systemic antifungal therapy with isavuconazonium sulfate or other agents in adults with invasive mucormycosis or invasive aspergillosis (non-fumigatus): a multicentre, non-interventional registry study. *Mycoses* 2022;**65**(2):186–98. doi:10.1111/myc.13412.

[17] Arnau M, Ibai LA, Teresa MGM, David CH, Judith S, Cristina B, et al. Safety and effectiveness of isavuconazole treatment for fungal infections in solid organ transplant recipients (ISASOT study). *Microbiol Spectr* 2022;**10**(1):e01784 e01721. doi:10.1128/spectrum.01784-21.

[18] Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;**347**(6):408–15. doi:10.1056/NEJMoa020191.

[19] Prattes J, Wauters J, Giacobbe DR, Salmanton-García J, Maertens J, Bourgeois M, et al. Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients—a multinational observational study by the European Confederation of Medical Mycology. *Clin Microbiol Infect* 2022;**28**(4):580–7. doi:10.1016/j.cmi.2021.08.014.

[20] Corcione S, Lupia T, Raviolo S, Montrucchio G, Trentalange A, Curtoni A, et al. Putative invasive pulmonary aspergillosis within medical wards and intensive care units: a 4-year retrospective, observational, single-centre study. *Intern Emerg Med* 2021;**16**(6):1619–27. doi:10.1007/s11739-021-02705-z.

[21] Ku YH, Chan KS, Yang CC, Tan CK, Chuang YC, Yu WL. Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections. *J Formos Med Assoc* 2017;**116**(9):660–70. doi:10.1016/j.jfma.2017.06.002.

[22] Buil JB, Brüggemann RJM, Denardi LB, Melchers WJG, Verweij PE. In vitro interaction of isavuconazole and anidulafungin against azole-susceptible and azole-resistant *Aspergillus fumigatus* isolates. *J Antimicrob Chemother* 2020;**75**(9):2582–6.