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BRIEF REPORT

Isavuconazole for the treatment of fungal infections: a real-life experience from the Fungal Infection Network of Switzerland (FUNGINOS)

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This analysis of 116 isavuconazole therapy courses shows that hepatic test disturbances (HTD) were relatively frequent (29% cases), but rarely led to treatment interruption (5%). Importantly, patients with baseline HTD, including those attributed to a first-line triazole, did not exhibit a higher risk of subsequent HTD under isavuconazole therapy.

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INTRODUCTION

Invasive fungal infections (IFI) are important causes of mortality among immunocompromised patients, such as those with hematologic cancer or long-term immunosuppressive therapies [1, 2]. The limited therapeutic options and their associated toxicities are factors that may contribute to poor outcomes [3, 4]. Triazoles are widely used antifungals for the treatment of IFI because of their large antifungal spectrum and the availability of both intravenous and oral formulations [5]. However, their drug-drug interactions and liver toxicity limit their use [5]. Isavuconazole (ISA), the most recently marketed triazole, displays some advantages over other drugs of this class, such as broad anti-mold activity, fewer drug-drug interactions and less hepatotoxicity [6]. ISA has been approved for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) [7-10]. It has been available in Switzerland since 2017. This study of the Fungal Infection Network of Switzerland (FUNGINOS) aimed to investigate the current place of ISA for the treatment of IFI in Switzerland, as well as its related outcomes and safety in a real-life clinical setting.

MATERIALS AND METHODS

Patients treated with ISA between January 1st 2017 and December 31st 2020 were identified via the pharmacology databases in three university hospitals (Geneva, Lausanne and Zurich). Patients having received ≥7 days of ISA therapy with clinical follow-up were included. Demographic characteristics, underlying diseases, characteristics of IFI, type and duration of antifungal therapy, outcomes and potential adverse events were collected in medical records. When ISA was administered as second or subsequent therapeutic line, the reason for therapy change was analyzed. Patients were retrospectively followed until the end of ISA therapy or the date of last follow-up and no later than December 31st 2021. IFI were classified according to criteria of the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group Education and Research Consortium (MSGERC) [11].

The outcome analysis included only patients fulfilling criteria of proven, probable or possible IFI. Patients who received ISA as a subsequent line of therapy beyond 28 days from the start of antifungal treatment, which was considered as a maintenance therapy, were excluded. Response to therapy was assessed at week 6 from the start of ISA therapy. Success was defined as complete or partial response, and failure as stable disease, progression or death, according to standard criteria [12].

For the safety analysis, medical records were screened for adverse events that led to interruption of ISA or were potentially attributed to ISA. Hepatic test values, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl

transferase (GGT) and total bilirubin (TB), were recorded just before and until the end of ISA therapy. Hepatic test disturbances (HTD) were defined as a ≥2-fold increase from baseline value of any of the liver parameters (ALT, AST, ALP, GGT or TB) during ISA therapy.

Patient consent statement: This study was approved by the local ethics committee for retrospective data use (CER-VD, project-ID: 2020-01641).

RESULTS

A total of 113 patients who developed 114 IFI episodes and received 116 courses of ISA therapy were included in the analysis. Characteristics of patients and IFI are shown in **Table 1**. Most patients (81/113, 72%) had hematologic cancer. Criteria of proven/probable or possible IFI were met in 62/114 (54%) and 37/114 (32%) cases, respectively. In 15/114 (13%) cases, there was no IFI criteria. Proven/probable IFI (n=62) consisted of 40 (65%) IA, 12 (19%) IM, 2 (3%) mixed IA/IM and 8 (13%) other IFI. ISA was administered as first-line therapy in 45/116 (39%) cases, subsequent therapeutic line in 66/116 (57%) cases and prophylaxis in 5 (4%) cases. The median duration of ISA therapy was 97 days (range: 7 – 953). Among the 68 patients who received ISA as subsequent therapeutic line (66 as therapy and 2 as prophylaxis), the reasons for switching to ISA were: toxicity attributed to the previous antifungal treatment (n=33, 49%), failure of the previous antifungal treatment (unsatisfactory response, non-achievement of therapeutic drug monitoring target or drug-drug interactions, n=14, 21%), convenience (switch for oral medication, n=11, 16%), and undetermined (n=10, 15%).

The response to therapy could be assessed in 62 cases, for which ISA was administered as first-line or subsequent therapeutic line within 28 days from the start of antifungal treatment. The success rate for all IFI was 36/62 (58%) at week 6. No significant difference was observed between patients with versus without hematologic cancer (63% vs 44%, respectively, p=0.2). Among proven/probable IFI, the success rate was 22/41 (54%) and did not differ between invasive aspergillosis (52%) and other IFI (55%).

For the analysis of adverse events, all 116 ISA therapy courses were included. A total of 34/116 (29%) patients experienced HTD (**Table 2**), occurring at a median of 20 days (range 2 – 318) from the start of ISA therapy. Mild HTD (2-5-fold increase of any parameter) and moderate HTD (5-10-fold increase of any parameter) were observed in 26/34 (76%) and 8/34 (24%) cases, respectively. ALP/GGT rise was the predominant HTD (**Table 2**). Among the 34 patients with HTD, ISA therapy was interrupted for attributed hepatotoxicity in 6 (18%) and for other causes (rash, therapy failure) in 2 cases. The rate of discontinuation was similar between patients with mild and moderate HTD (23% and 25%, respectively). Considering the entire population, the rate of ISA discontinuation for attributed hepatotoxicity was 6/118 (5%). Following ISA interruption, partial resolution of HTD was observed in 4 cases, while. 2 patients died from causes not attributed

to hepatotoxicity. When ISA therapy was continued despite HTD (n=26), complete/partial resolution was observed in 15 (58%) cases, while it remained stable in other cases.

Half of patients (n=58) received ISA despite baseline HTD (mild in 60% and moderate in 40% cases). The occurrence of HTD under ISA therapy in these patients did not significantly differ from that in patients without baseline HTD (31% vs 28%, p=0.8, **Table 2**). Among patients with baseline HTD attributed to a first-line azole therapy (voriconazole or posaconazole, n=19), 3 (16%) experienced recurrent HTD under subsequent ISA therapy.

Other ISA-attributed adverse events leading to its interruption were skin rash (n=1) and gastro-intestinal disorders (n=1).

DISCUSSION

In this multicenter retrospective study, we analyzed the practices of ISA prescription in Switzerland and its related outcomes and toxicity. While the efficacy and safety of ISA for the treatment of IFI have been assessed in randomized controlled trials [8, 9], post-hoc surveillance studies are needed to assess the drug profile in real clinical settings that differ from the selected population of clinical trials [13-18].

ISA is currently approved for the treatment of IA and IM [7, 10]. In our study, these IFI accounted for most cases (87%) where ISA was used as targeted therapy. Success rate for proven/probable IFI was 54%, which is superior to those reported in prospective trials [8, 9], but similar to those of other real-life observational studies [14, 17]. In addition, ISA was used as empiric therapy for possible IFI. In this setting, ISA represents an alternative to amphotericin B, because of its broad-spectrum, oral bioavailability and lower risk of nephrotoxicity. As observed in other settings [15, 17], ISA was mainly used as a second-line therapy in our study (57% of cases). Toxic issues of previous antifungal drugs motivated the switch to ISA in about half of cases. Compared to other anti-mold triazoles, ISA has less drug-drug interactions and a lower risk for hepatotoxicity [6]. In the SECURE trial, ISA was associated with less hepatobiliary disorders compared to voriconazole [8]. A meta-analysis confirmed the lower rate of ISA-related hepatotoxicity when compared to other antifungals [19]. Similar observations were made when ISA was used as prophylaxis, with a rate of hepatotoxicity-related ISA discontinuation of about 5% (lower compared to voriconazole or posaconazole) [20-23].

We observed a similarly low rate of hepatotoxicity-related ISA discontinuation in our study, although HTD occurred in about 30% of cases using a low cut-off (≥2-fold increase of any hepatic test). At least partial resolution of HTD was observed in more than half of these cases despite ISA continuation, which suggests that their origin was possibly not ISA-related. Indeed, causes and mechanisms of HTD under azole therapy are often multiple and complex [24]. Most interestingly, half of the patients in our study had baseline HTD at start of ISA therapy. In that sense, our patient

population differed from that of previous prospective trials excluding such patients [8, 9]. The main observation of our relatively large cohort (n=116) was that patients with baseline HTD or previous hepatotoxicity attributed to another triazole were not more susceptible to develop HTD under ISA therapy, which is in line with results of previous smaller studies [13, 15, 25].

In conclusion, this study shows that HTD under ISA therapy, albeit frequent, rarely requires its interruption. In particular, ISA could be safely used in patients with mild/moderate baseline HTD, provided that liver tests are closely monitored. ISA may also be used as second-line therapy in patients who needed to interrupt first-line voriconazole or posaconazole therapy because of hepatotoxicity, as it is associated with a low rate of HTD recurrence in this setting.

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Conflict of interests

Outside of the submitted work:

FL received research funding from Gilead, MSD and Novartis, and speaker honoraria from Pfizer, Gilead, MSD, Mundipharma and Becton-Dickinson. All contracts were made with and fees paid to his institution.

PWS received travel grants from Pfizer and Gilead, speaker's honorary from Pfizer and fees for advisory board activity from Pfizer and Gilead.

Appendix

Members of the scientific committee of the Fungal Infection Network of Switzerland (FUNGINOS):

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REFERENCES

1. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis **2010**; 50:1091-100.
2. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis **2010**; 50:1101-11.
3. Lamoth F, Calandra T Pulmonary aspergillosis: diagnosis and treatment. Eur Respir Rev **2022**; 31.
4. Lamoth F, Kontoyiannis DP Therapeutic Challenges of Non-Aspergillus Invasive Mold Infections in Immunosuppressed Patients. Antimicrob Agents Chemother **2019**; 63.
5. Lass-Florl C Triazole antifungal agents in invasive fungal infections: a comparative review. Drugs **2011**; 71:2405-19.
6. Miceli MH, Kauffman CA Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. Clin Infect Dis **2015**; 61:1558-65.
7. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis **2019**; 19:e405-e21.
8. Maertens JA, Raad, II, Marr KA, 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**; 387:760-9.
9. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis **2016**; 16:828-37.
10. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect **2018**; 24 Suppl 1:e1-e38.
11. 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.
12. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis **2008**; 47:674-83.
13. DiPippo AJ, Kontoyiannis DP Lack of Toxicity With Long-term Isavuconazole Use in Patients With Hematologic Malignancy. Clin Infect Dis **2019**; 69:1624-7.
14. Fernandez-Ruiz M, Bodro M, Gutierrez Martin I, 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**; 107:762-73.

15. Kronig I, Masouridi-Levrat S, Chalandon Y, et al. Clinical Considerations of Isavuconazole Administration in High-Risk Hematological Patients: A Single-Center 5-Year Experience. Mycopathologia **2021**; 186:775-88.
16. Nwankwo L, Gilmartin D, Matharu S, et al. Experience of Isavuconazole as a Salvage Therapy in Chronic Pulmonary Fungal Disease. J Fungi (Basel) **2022**; 8.
17. Pieragostini R, Xhaard A, Sauvageon H, Madelaine I, Touratier S, Denis B Context of instauration and evolution under isavuconazole, a 2-year prospective real-life study. Med Mycol **2023**; 61.
18. Silva JT, Husain S, Aguado JM Isavuconazole for Treating Invasive Mould Disease in Solid Organ Transplant Recipients. Transpl Int **2023**; 36:11845.
19. Kato H, Hagihara M, Asai N, et al. A systematic review and meta-analysis of efficacy and safety of isavuconazole for the treatment and prophylaxis of invasive fungal infections. Mycoses **2023**; 66:815-24.
20. Bogler Y, Stern A, Su Y, et al. Efficacy and safety of isavuconazole compared with voriconazole as primary antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients. Med Mycol **2021**; 59:970-9.
21. Samanta P, Clancy CJ, Marini RV, et al. Isavuconazole Is as Effective as and Better Tolerated Than Voriconazole for Antifungal Prophylaxis in Lung Transplant Recipients. Clin Infect Dis **2021**; 73:416-26.
22. Scott SA, Perry C, Mahmoudjafari Z, et al. Incidence of breakthrough fungal infections on isavuconazole prophylaxis compared to posaconazole and voriconazole. Transpl Infect Dis **2023**; 25:e14045.
23. Stern A, Su Y, Lee YJ, et al. A Single-Center, Open-Label Trial of Isavuconazole Prophylaxis against Invasive Fungal Infection in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant **2020**; 26:1195-202.
24. Tverdek FP, Kofteridis D, Kontoyiannis DP Antifungal agents and liver toxicity: a complex interaction. Expert Rev Anti Infect Ther **2016**; 14:765-76.
25. DiPippo AJ, Rausch CR, Kontoyiannis DP Tolerability of isavuconazole after posaconazole toxicity in leukaemia patients. Mycoses **2019**; 62:81-6.

Table 1. Characteristics of patients, invasive fungal infections (IFI) and isavuconazole therapy courses

Patients	**N = 113**
Age (years)	58 (16 – 83)
Female / Male	42 (37) / 71 (63)
Underlying conditions	
Allogeneic HSCT	59 (52)
Hematologic cancer, non-HSCT	22 (19)
Solid-organ transplantation	12 (11)
Auto-immune disease	3 (3)
Influenza or COVID-19	2 (2)
No host criteria[1]	15 (13)
Invasive fungal infections (IFI)	**N = 114[1]**
IFI classification[2]	
Proven	39 (34)
Probable	23 (20)

Possible	37 (32)
No IFI[3]	15 (13)
Documentation of IFI	N = 62
Invasive aspergillosis[4]	40 (65)
Invasive mucormycosis[5]	12 (19)
Mixed aspergillosis/mucormycosis	2 (3)
Other IFI[6]	8 (13)
Localization of IFI	
Pulmonary only	81 (71)
Extrapulmonary (single site)	10 (9)
Multiple sites	16 (14)
No clinical site	7 (6)
Isavuconazole courses	**N = 116[7]**
Type of treatment	
First line therapy	45 (39)
Subsequent line of therapy	66 (57)
Prophylaxis[8]	5 (4)
Isavuconazole monotherapy	100 (86)
Other concomitant antifungal drug[9]	16 (14)

Numbers are N (%) for proportions and median (range) for continuous variables.

HSCT: hematopoietic stem cell transplantation.

[1] One patient developed two IFIs at 202 days apart.

[2] According to definitions of the European Organization for Research and Treatment of Cancer – Mycoses Study Group Education and Research Consortium (EORTC – MSGERC) [11].

[3] "No IFI" includes chronic pulmonary aspergillosis (n=5), antifungal prophylaxis (n=5) and suspected IFI not meeting EORTC-MSGERC criteria (n=5).

[4] Documentation of *Aspergillus* spp. (culture or PCR) or positive galactomannan (serum or bronchoalveolar lavage fluid).

[5] Documentation of Mucorales by PCR or culture or presence of broad septate hyphae at histopathology

[6] Fungal pathogens: Scedosporium apiospermum (1), Phaeoacremonium spp. (1), Blastoschizomyces capitatus (1), Fusarium spp. (1), Conidiobolus spp. (1), Trichosporon asahii and Kodamaea ohmeri (1), Aureobasidium spp. (1), positive histopathology only (septate hyphae) (1).

[7] Two patients had two distinct courses of isavuconazole therapy for the same IFI episode. The time interval between each course was 12 and 29 days, respectively.

[8] First-line prophylaxis (3), second-line prophylaxis (2).

[9] If administered for at least 7 days: echinocandin drug (8), liposomal amphotericin B (7), terbinafine (1).

Table 2. Hepatic tests disturbances (HTD) during isavuconazole therapy

Occurrence of HTD[1]	
All isavuconazole courses (n=116)	34 (29)
Patients with baseline HTD (n=58)	18 (31)
Patients without baseline HTD (n=58)	16 (28)
Patients with previous azole-related HTD (n=19)[2]	3 (16)
HTD Type (n=34)	
ALP/GGT only	19 (56)
ALP/GGT and ALT/AST	8 (24)
ALT/AST only	4 (12)

TB only	1 (3)
ALP/GGT and TB	1 (3)
ALP/GGT and ALT/AST and TB	1 (3)
Intervention / outcome (n=34)	
ISA interruption (not HTD-attributed)	2 (6)
ISA interruption (HTD-attributed)	6 (18)
Improvement[3]	4 (67)
ISA continuation	26 (76)
Improvement[3]	15 (58)

Numbers are N (%).

Pts: patients, ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TB: total bilirubin, ISA: isavuconazole

[1] Increase of ≥2-fold from baseline value of any parameter (ALP, GGT, ALT, AST, TB).

[2] Patients who received isavuconazole as second-line therapy following hepatotoxicity attributed to another azole drug (voriconazole n=18, posaconazole n=1).

[3] Complete or partial resolution of HTD.