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Letter to the Editor

Real-life use of isavuconazole outside the hematological wards

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Dear Editor,

Real-world data on efficacy and safety of isavuconazole (ISV) are mostly based on cohorts of patients with hematological malignancies, stem cells or solid organ transplants (i.e., HSCT or SOT) [1,2].

In these settings, invasive fungal infections (IFI) are responsible for considerable morbidity and mortality, although recent studies showed that, aside of the classic risk factors, low doses of corticosteroids, chronic obstructive pulmonary disease (COPD), liver cirrhosis, systemic connective tissue diseases, influenza infection, diabetes mellitus, and advanced solid cancer represent a favorable environment for IFI, especially for invasive pulmonary aspergillosis (IPA) [3,4].

According to the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) [5], IPA is categorized into *proven*, *probable*, *possible* and Blot et al. externally validated this classification in the Intensive Care Unit (ICU) [6]. Although the host factors described in EORTC/MSG statements were extended to patients with SOT, hereditary immunodeficiencies, connective tissue disorders, and immunosuppressive agents, different groups of non-neutropenic patients with not negligible risk of IFI are still left out from EORTC/MSG criteria [5].

We report here a case series of patients treated with isavuconazole for IFI outside the hematological wards in two referral hospitals in Turin, Italy. All adults receiving at least three doses of ISV from 1st March 2017 to 30th June 2019 were enrolled in the study. ISV was administered at the standard dosage of isavuconazonium sulfate 372 mg either intravenously or orally every 8 h for 48 h (loading dose), then once daily (maintenance dose).

Exclusion criteria were ongoing or new-onset neutropenia, lymphoproliferative disorders, or other hematological diseases.

Diagnosis of *proven*, *probable* or *possible* IFI was defined according to host risk factors, clinical and radiological features, detection of specific markers of fungal infections and mycological isolations, mostly relying on EORTC/MSG [5]. Given the low sensibility and specificity of the following criteria in non-hematological and non-transplanted patients, new risk and host factors have been used to define IFI according to the recent literature on this issue [7,8].

Adverse effects, when reported, were considered as follows: increase in transaminases (aspartate aminotransferase– AST/GOT and alanine aminotransferase– ALT/GPT) levels > 1,5-fold the upper normal limits, increase Na^+ (up to 145 mEq/L) or decrease K^+ (under 3,5 mEq/L) levels, new-onset neurological signs (e.g., confusion, dizziness), neuro visual toxicity (e.g., color vision, decrease in visual acuity), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea, dyspepsia) and skin modifications. Drug and drug interactions were checked before start ISV.

Outcomes were defined as follows: *complete response*, as the resolution of all signs and symptoms and radiographic abnormalities compared with baseline; *partial response*, as a clinical and radiographic improvement compared with baseline; *no response*, not consistent with any of the categories mentioned above [5].

We performed descriptive statistics on the study population. Data were analyzed using standard statistical methods: variables were described with medians [interquartile ranges (IQR)], and data analysis was performed using SPSS software version 25.0 (IBM).

Ten adults were included in the study (Table 1); the median age was 69 year-old (range 42–79). Patients were all Caucasian, without previous history of IFI: five (50%) were managed as outpatients in the Infectious Diseases clinic, 3 (30%) were enrolled during hospitalization at Medical Ward, 2 (20%) at time of discharge from the ICU. Among comorbidities, there were: history of malignancy (5; 50%), chronic pulmonary disease (3; 30%) or diabetes mellitus (2, 20%); five patients (50%) had a history of recent corticosteroid immunosuppressive therapy (in the previous 30 days).

Aspergillosis was the frequent primary diagnosis ($N = 9$, 90%), and one patient was affected by pulmonary mucormycosis. Eight patients (8/9, 88,8%) had a microbiological diagnosis of *Aspergillus* spp. infection, and the remaining was treated according to clinical symptoms and biomarkers positivity. Besides, one adult (1/1, 100%) has reported a microbiological diagnosis of *Mucor* spp. infection (Table 1). Clinical symptoms (e.g., fever, cough, purulent sputum) were present in all patients. Regarding radiological findings, nodules (dense, well-circumscribed lesions, with or without “halo” sign) were described in 6 patients (60%), two patients reported a tree-in-bud pattern (20%), cavitation alone and cavitation with fungus ball in one patient each, respectively (14,3%). Regarding biomarkers, serum galattomannan (GM) resulted positive in two (20%) patients, whilst GM on (bronchoalveolar lavage) BAL was positive in 50% of cases, confirming the usefulness

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Table 1
Host Factors, Microbiological Features, Radiological Findings and Treatment Duration in Moulds Infections.

Patient	Clinical Risk Factors For Moulds	Site of Infection	Radiological Findings	Sample Specimen	Mould	GM serum	GM BAL	BDG	Treatment (wks)	Outcome
1	Breast Cancer	Post-surgical Endophtalmitis	Normal Chest X-Ray	Vitreous	Aspergillus spp.	Negative	Not Available	Not Available	3	Clinical Response
2	Bronchiectasis, Breast Cancer	Pulmonary Aspergillosis	Nodules, Tree-in-bud	Sputum	Aspergillus spp.	Negative	Not Available	Not Available	4	Clinical Response
3	Lung Cancer	Pulmonary Aspergillosis	Nodules, Ground-glass halo	Sputum	Aspergillus fumigatus	Negative	Negative	Not Available	4	Clinical Response
4	Anorexia Nervosa, Cervical Cancer	Pulmonary Mucormycosis	Nodules	Pulmonary biopsy	Mucor spp.	Negative	Negative	Not Available	2	Deceased
5	Chronic Rhinosinusitis	Fungal Rhinosinusitis	Normal Chest X-Ray	Nasal Mucosa	Aspergillus fumigatus	Negative	Not Available	Not Available	4	Clinical Response
6	Asthma	Pulmonary Aspergillosis	Nodules, Ground-glass halo	Sputum	*A. fumigatus, A. niger*	Negative	Not Available	Not Available	4	Clinical Response
7	Lung Transplant, ICU	Pulmonary Aspergillosis	Cavitation	BAL	Aspergillus fumigatus	Negative	3.99	Negative	2	Deceased
8	Burn (TBSA > 90%), HE	Disseminated Aspergillosis	Nodules	Skin Swab and CVC	A. fumigatus, A.flavus	3.38	Not Available	> 500	4	Deceased
9	DM, COPD, Lung Cancer	Pulmonary Aspergillosis	Nodules, Tree-in-bud	BAL	Aspergillus fumigatus	Negative	4,6	Not Available	1	Clinical Response
10	DM, RA, Leflunomide, CTS (> 5 mg/die)	Fungus Ball	Cavitation with fungus ball	Not Isolated	Not Isolated	1,65	Not Available	350	3	Clinical Response

ICU: Intensive Care Unit; TBSA: Total Body Surface Area; COPD: Chronic Obstructive Pulmonary Disease; DM; Diabetes Mellitus; RA: Rheumatoid Arthritis; GM: Galattomannan; BDG: 1,3 Beta D-glucan; Wks: weeks, HE: Haemodyalisis, CTS: corticosteroid.

also in non-neutropenic patients [9].

ISV was started according to moulds' microbiological susceptibility. Seven patients (70%) switched to ISV from triazole or polyene mostly to reduce drug to drug interactions, only three patients switched due to adverse reactions.

The median time of administration of ISV was 3 (range 2–5) weeks: seven patients (63,6%) reported a clinical cure, defined as resolution of symptoms complained, three patients died before the end of therapy, and one patient did not clinically improve during ISV treatment and was switched to polyene. No patient discontinued ISV treatment due to toxicity.

Uusually IFI have been a major concern among hematological setting and neutropenic patients [3,4,7,8]. In this case series we highlighted the increasing relevance of IFI also in non-neutropenic patients, usually admitted to internal medicine wards, with a mild degree of immunosuppression and without classic predisposing risk factors. Data from literature revealed an increasing incidence of IFI, especially IPA, outside hematological wards, with estimated incidence from 0.3%–19% [4]. In this population, IPA diagnosis is usually challenging due to the lack of standardized classification and the non-specificity of signs and symptoms along with the relatively low diagnostic capacity of the complementary tests [8,9]. Clinical symptoms and changes in radiological CT findings even if aspecific may be the first trigger to suspect IFI in these patients, more than serum biomarkers that could be useful to support the clinical suspect, but they lose their sensitivity and specificity in non-hematological setting [7,8]. Moreover, in our case series, ISV was generally well tolerated and, according to literature short term ISV appears safe and associated with treatment response in 70% of cases [2].

In conclusion, IA has to be considered outside the hematological ward, although achieving a diagnosis of IA is challenging, and diagnostic criteria are urgently needed. The use of ISV in these groups of patients seems to be a good option for the treatment of IFI.

Author contributions

S·S, T.L. and S.C. conceived the ideas; S·S and T.L. collected and analyzed the data; S·S, T.L., S.C. and F.G.D.R led the writing.

Declaration of Competing Interest

None to declare.

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