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Coadministration of isavuconazole and sirolimus in allogeneic hematopoietic stem cell transplant recipients

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Abstract

Background: Invasive fungal infections (IFIs) represent a major cause of morbidity among allogeneic hematopoietic stem cell transplantation (allo-HSCT). Isavuconazole (ISA) is a broad-spectrum triazole with favorable safety profile.

Objectives and design: Herein, we evaluate the real life coadministration of ISA and sirolimus in allo-HSCT recipients in a single-center retrospective analysis, describing clinical efficacy, safety, and therapeutic drug monitoring (TDM) of both drugs.

Methods: All consecutive allo-HSCT recipients who received the coadministration of ISA and sirolimus for at least 2 weeks between July 2017 and December 2022 were included in this retrospective analysis. TDM was longitudinally performed during treatment. IFIs were classified according to the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus criteria.

Results: A total of 51 recipients were included in the analysis. A total of 17 patients received ISA as continuous antifungal treatment for IFI diagnosed before transplant: one patient experienced a probable invasive pulmonary aspergillosis, and one patient switched from ISA to liposomal amphotericin B for a possible IFI. A total of 34 patients started ISA as antifungal therapy for IFI diagnosed after transplant. Sixteen of 34 were treated for a proven/probable breakthrough IFI during mold-active prophylaxis: 6/16 patients died for IFI after a median of 51 days of ISA. Eighteen of 34 started ISA as empirical therapy for a possible IFI: 15/18 patients were alive with resolution of infection after 6 weeks, 1 died for disease progression, and 2 had empirically changed antifungal therapy due to pneumonia progression. Clinical and radiological response rate was 68% after 90 days from IFI diagnosis. No toxicities related to drug–drug interaction have been registered in patients reaching concomitant therapeutic levels of ISA and sirolimus.

Conclusion: The coadministration of ISA and sirolimus was safe and feasible in this cohort, confirming favorable clinical efficacy in patients with multiple-drug coadministration.

Keywords: allogeneic transplantation, IFI, isavuconazole, sirolimus, TDM

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Introduction

Despite the well-known infection risk in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), the early post-transplant mortality rate progressively decreased in recent years, thanks to the development of new antimicrobial agents for infection prophylaxis and treatment.[1] Invasive fungal infections (IFIs) are still one of the leading causes of infection-related morbidity among allo-HSCT recipients, raising

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interest in implementation of antifungal prophylaxis (AFP).[2–4]

In allo-HSCT setting, both yeasts and molds are potentially responsible for serious IFIs; therefore, a mold-active primary AFP is strongly recommended, particularly for patients at high risk for IFI.[5] The third European Conference on Infections in Leukemia (ECIL-3) proposed phase-specific recommendations for allo-HSCT according to the different risk factors for IFI in the pre- and post-engraftment period, as described by Gruppo Italiano Trapianto Midollo Osseo (GITMO).[5,6] Currently, posaconazole and voriconazole are approved for primary AFP in allo-HSCT, but are associated with several potential drug–drug interactions and possible breakthrough invasive fungal infections (b-IFIs).[7]

Despite the usage of mold-active AFP, a significant rate of b-IFIs was reported: in patients receiving posaconazole, prospective and retrospective trials reported b-IFIs rate ranging between 0% and 10.9%.[8–10] Scientific societies have established a series of recommendations for AFP based on prospective studies performed with different drugs, and patients may receive different azoles (from fluconazole to posaconazole and voriconazole) or liposomal amphotericin B or echinocandin according to drug approval status, local epidemiology, individual risk factors, and the usage in empirical therapy.[11]

Isavuconazole (ISA) is a new-generation triazole with broad-spectrum antifungal activity, approved for the treatment of invasive aspergillosis (IA) and mucormycosis. In the prospective, double-blind, randomized SECURE trial, ISA proved noninferior to voriconazole for the primary treatment of IA and IFI caused by non-*Aspergillus* molds, being well tolerated and showing significantly fewer drug-related adverse events compared to voriconazole.[12] ISA has not been studied for prophylaxis in randomized controlled trials, but its efficacy is supported by retrospective observational studies that underline its favorable pharmacokinetics, tolerability, and drug–drug interaction profile. However, there are still concerns on a possible increased incidence of b-IFIs in neutropenic hematologic malignancy patients and HSCT recipients during ISA prophylaxis up to 5–8%.[13–16]

Sirolimus, an inhibitor of the mammalian target, rapamycin, is used for Graft-versus-Host-Disease (GvHD) prophylaxis and is extensively metabolized by cytochrome P450 3A4 (CYP3A4). Posaconazole and voriconazole strongly inhibit CYP3A4, so their coadministration with sirolimus is challenging and their interactions are important to be considered in the clinical management of transplant recipients.[17,18] Experiences in the usage of sirolimus and azoles are reported, showing a safe and well-tolerated sirolimus and posaconazole coadministration through a close monitoring of serum levels, particularly in the first month of treatment.[19] Being a moderate CYP3A4 inhibitor, ISA has lower potential drug–drug interactions compared to other azoles.[20] In allo-HSCT patients, modest increases in sirolimus concentration/dose (C/D) ratio were observed within the first 2 weeks after initiation of ISA[21]; also a recent study described mild increases in the tacrolimus C/D ratio from baseline after starting ISA therapy.[22]

Letermovir, currently used as primary prophylaxis for cytomegalovirus (CMV) in serology-positive allo-HSCT recipients, is reported as a moderate inhibitor of CYP3A4 and can decrease 'first-generation azoles' area under the curve by 33% in allo-HSCT recipients.[23,24]

In this study, we describe our experience with ISA and sirolimus coadministration in allo-HSCT recipients.

Methods

This single-center retrospective analysis was conducted to evaluate the real-life usage of ISA in allo-HSCT setting between July 2017 and December 2022. In this period, a total of 377 allo-HSCTs have been performed in our center. All consecutive HSCT recipients (age ⩾18 years) who received ⩾2 weeks of ISA have been included in the analysis.

Patient charts were reviewed to collect baseline characteristics: demographics, underlying malignancy, disease status at transplant, conditioning regimen, donor type, prior antifungal use, presence of acute and chronic GvHD, prophylaxis with letermovir, indications for ISA use (including reasons for switching to ISA), duration of antifungal therapy, b-IFIs, and ISA steady-state concentrations.

All patients were treated according to institutional guidelines, upon written informed consent

for transplant procedures and use of medical records for research.

GvHD prophylaxis was based on sirolimus, given from day +5, maintaining until day +100 immunosuppressive therapeutic concentrations, and then proceeding with gradual tapering until discontinuation at day +180. Sirolimus was monitored twice weekly in order to maintain a target therapeutic plasma level of 5–14 ng/mL. Mycophenolate mofetil from day +5 until day +30 was added, except for HLA-identical transplants.[25] All patients received post-transplant cyclophosphamide (PTCy) on day +3 and +4, except for cord-blood transplant recipients. Letermovir was administered in all CMV-seropositive transplant recipients after March 2019 from day 0 to day +100 after transplant. All patients received antiviral prophylaxis with acyclovir.

Both acute and chronic GvHD were diagnosed and scored according to standard criteria.[26,27]

As per local practice, ISA serum levels were measured weekly, and doses were adjusted according to therapeutic drug monitoring (TDM) to achieve a TDM within the therapeutic range of 3–9 ng/mL. ISA was administered orally, or intravenously until patients could receive oral medications.

All breakthrough proven-probable IFIs (b-PP-IFIs) were classified according to the revised 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) 2020 criteria.[28] Galactomannan assay was routinely monitored weekly on peripheral blood and on three consecutive tests in case of fever. Significant organ toxicities [higher than grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03)] were recorded.

No a priori sample size calculation was performed for this analysis. Categorical variables are presented with frequencies and percentages, and continuous variables with median and absolute range. Descriptive statistics were used to summarize patient characteristics and clinical outcomes. Dichotomous variables were analyzed by means of Fisher exact test, continuous variables by means of unpaired two-sided t-tests, as appropriate. A p value of <0.05 was considered significant. GraphPad Prism 8 and Microsoft Excel 2013 were used for data tabulation, statistical analyses, and compilation of diagrams.

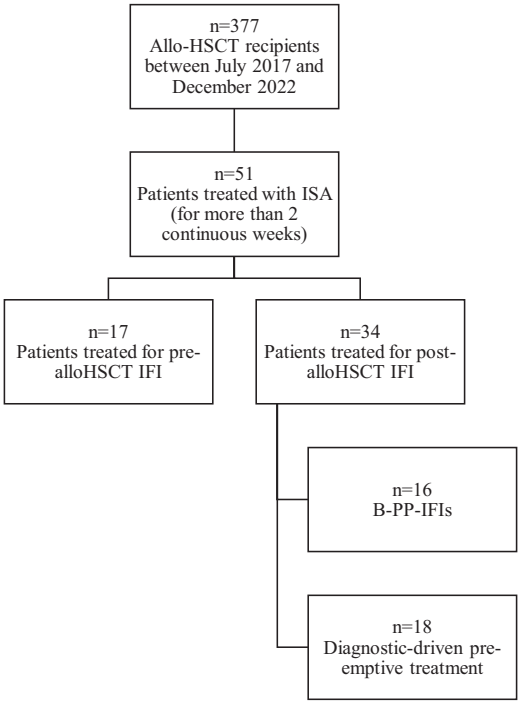

Figure 1. Patients selection and subgroups.
allo-HSCT, allogeneic hematopoietic stem cell transplantation; b-PP-IFI, breakthrough proven and probable IFI; IFI, invasive fungal infection; ISA, isavuconazole.

Results

A total of 377 patients received allo-HSCT between July 2017 and December 2022, 51/377 received more than two continuous weeks of ISA (Figure 1). Median treatment duration with ISA was 140 days (range 14 days–40 months).

The median age at transplant was 52 years (range 24–75). Median follow-up was 374 days (range 14 days–62 months). Complete patient and transplant characteristics are summarized in Table 1. Acute GvHD occurred in 22 patients: grade I–II in 14 patients and grade III–IV in 8 patients. Nine patients developed classic chronic GvHD (four mild, one moderate, and one severe chronic GvHD).

Table 1. Patient and HSCT characteristics.

Characteristics of patients	Overall population, *n*	%
Age		
20–50 years	25	49
51–65 years	18	35
>65 years	8	16
Sex		
Male	29	57
Female	22	43
Disease		
Acute myeloid leukemia	31	60
Acute lymphoblastic leukemia	6	12
Myelodysplasia and myeloproliferative neoplasms	5	10
Lymphoma	8	16
Severe aplastic anemia	1	2
Disease status		
First complete remission	21	41
Second complete remission	17	33
Active disease	13	26
Allo-HSCT		
I transplant	48	94
II transplant	3	6
Donor type		
Matched-related donor	6	12
Matched-unrelated donor	13	25
Mismatched-related donor	27	53
Cord blood unit	5	10
aGvHD		
Yes		
Grade I–II	14	27
Grade III–IV	8	16
No	29	57
cGvHD		
Yes		
Mild	4	8
Moderate	1	2
Severe	4	8
No	42	82
Letermovir		
Yes	24	47
No	27	53

allo-HSCT, allogeneic hematopoietic stem cell transplantation; aGvHD, acute GvHD; cGvHD, chronic GvHD.

A total of 17 patients underwent allo-HSCT while receiving ISA as continuous treatment for a previously diagnosed IFI (17/377, 4.6%), which occurred during either induction or consolidation therapy. Among them, only one patient (1/17, 0.06%), who was on ISA for a possible IFI during induction chemotherapy, experienced a b-PP-IFI, showing a probable invasive pulmonary aspergillosis with positive galactomannan assay on serum. Median ISA TDM in this patient was lower (2.5 mg/L) compared to median TDM values (4.5 mg/L) of patients without b-PP-IFIs. This case of invasive pulmonary aspergillosis was successfully treated with the association of liposomal amphotericin B and voriconazole. One patient empirically switched from ISA to liposomal amphotericin B for persistent unexplained fever with progressive respiratory distress, and died few days later without any microbiologically documented infections.

Thirty-four patients (34/377, 9%) started ISA for IFI diagnosed after transplant. ISA was introduced at a median time of 44 days after allo-HSCT infusion; 22/34 patients received ISA during engraftment phase.

A total of 16 patients (16/34, 47%) were treated for a b-PP-IFI during mold-active prophylaxis (seven posaconazole, seven voriconazole, and two amphotericin B); both posaconazole and voriconazole TDM were in prophylactic range at b-PP-IFI occurrence. Three IFIs were proven (one *Candida glabrata* sepsis, one disseminated aspergillosis, and one *Aspergillus flavus*–biopsy-proven sinus aspergillosis) and 13 were probable invasive pulmonary aspergillosis. In this group of 16 patients, median ISA TDM was 3.7 mg/L (range 1.1–7.6 mg/L). Six of 16 patients (38%) died from IFI at a median time of 51 days (range 14–93 days) after the start of ISA. Median ISA TDM in patients who died from IFI was 2.7 mg/L (range 1.1–3.8 mg/L), which was lower than median ISA TDM in patients in whom the IFI solved (4.4 mg/L, range 2.6–7.6 mg/L, $p = 0.04$).

Six weeks after b-PP-IFI diagnosis, 10/16 patients (63%) were still alive, the IFI had resolved in 8/16 (50%) patients, two patients had a persistent IFI (1 of which was fatal), five patients had already died from IFI, and the disease had progressed in one patient (Figure 1). During long-term follow-up, even during immunosuppressive therapy, all patients that continued ISA after b-PP-IFI had no further IFI episodes.

A total of 18 patients (18/34, 53%) were treated with ISA as diagnostic-driven pre-emptive therapy in patients with fever and pulmonary infiltrates. Median ISA TDM was 4.1 mg/L (range 1.5–5.9 mg/L). Six weeks after the start of ISA, 1 patient had died from disease progression, 2 patients had empirically changed antifungal therapy due to pneumonia progression, and 15 patients were alive with resolution of infection (Figures 2 and 3).

The clinical and radiological response rate (RR) at 90 days after ISA start was 68% (23/34 patients); the radiological response was complete in 16 (70%) and partial in 7 (30%) cases. RR was higher in possible IFIs (15/18, 83%) than in proven and probable IFIs (8/16, 50%). ISA showed better RR in pulmonary IFI than in extra-pulmonary IFI (20/28, 71% *versus* 3/6, 50%). All patients received concomitant ISA and sirolimus.

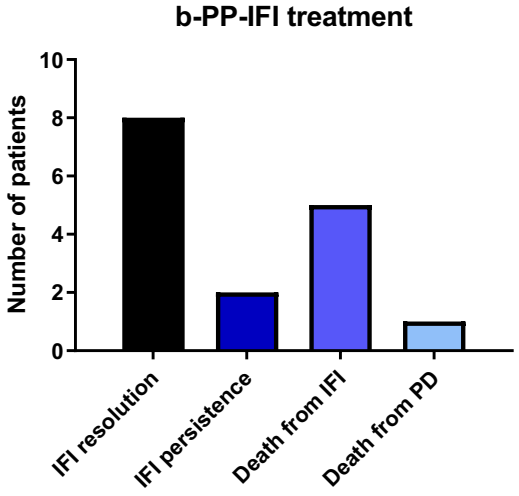

Figure 2. Outcome for b-PP-IFI subgroup patients at 6 weeks after ISA start.
b-PP-IFI, breakthrough proven and probable IFI; IFI, invasive fungal infection; ISA, Isavuconazole; PD, progression of disease.

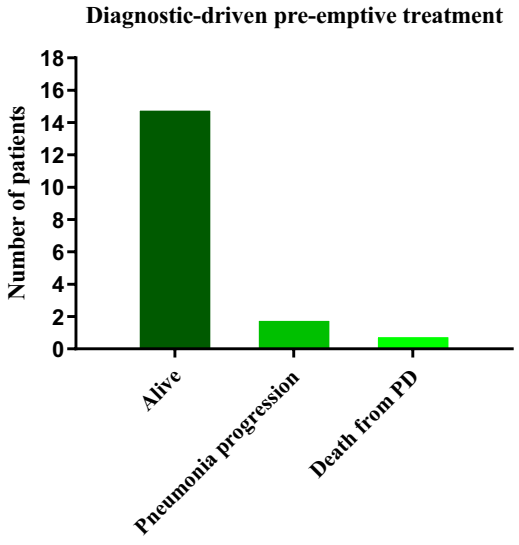

Figure 3. Outcome for diagnostic-driven pre-emptive treatment subgroup patients at 6 weeks after ISA start.
ISA, Isavuconazole; PD, progression of disease.

No overdosing of either sirolimus or ISA was observed during coadministration. During the study period, no patients had sirolimus serum concentration above 14 ng/mL. Significantly, no

patients had ISA and/or sirolimus-related toxicities (i.e. liver toxicity, sinusoidal obstructive syndrome, thrombotic microangiopathy, or neuropathy). No patients needed to stop ISA for the presence of adverse events of any grade. All patients that continued ISA for a longer time after b-PP-IFI had no toxicities. A total of 23 patients received letermovir in coadministration with ISA and sirolimus: in patients treated with ISA, there was no need to change on institutional protocol for both sirolimus and letermovir dosage. Interestingly, no overdosing of sirolimus and ISA was observed also in this subgroup of patients, but a stringent sirolimus and ISA TDM monitoring was needed and dosing changes were adjusted according to that.

After a median follow-up of 1 year, 22/51 patients had died (35%). The mortality attributable to IFI was 8/51 (16%). The 1 year-survival rate was 78% in ISA-responding patients, which was significantly better than the corresponding rate in ISA- non responding patients (18%, $p = 0.002$).

Discussion

IFIs represent an important complication in allo-HSCT, and their management is still challenging. AFP and treatment are based on the use of different pharmacological agents, such as posaconazole, voriconazole, and liposomal amphotericin B, with concerns regarding dose-limiting toxicities and drug–drug interactions that are responsible for difficulties in managing IFIs.[6,29] In allo-HSCT setting, the strong inhibition of CYP3A4 enzyme mediated by posaconazole and voriconazole can increase plasma concentrations of immunosuppressive drugs, generally requiring a close monitoring of pharmacological drug levels.

ISA is a potential alternative to minimize adverse events and pharmacological interactions. Its effectiveness in allo-HSCT setting as AFP and treatment is supported by some studies with promising results.[13–16] However, so far, ISA has been studied within the traditional GvHD prophylaxis platform based on cyclosporine, and no studies have been performed on its coadministration with sirolimus and letermovir, with no real-life data regarding toxicity, outcomes, and drug–drug interactions in allo-HSCT recipients.

In this monocentric observational analysis, we describe the real-life experience on the coadministration of ISA and sirolimus, in the context of allo-HSCT.

ISA registration trial showed a good toxicity profile in adult patients affected by invasive mold disease caused by *Aspergillus* spp. or other filamentous fungi; ISA was well tolerated compared with voriconazole, with fewer study-drug-related adverse events.

Previous experiences that studied the usage of ISA in allo-HSCT setting confirmed the better tolerability with similar b-IFI rates compared to historical data for posaconazole and voriconazole.[15,30] In 2019, a real-life multicenter observational SEIFEM study showed that ISA was well tolerated in most patients, including those undergoing allo-HSCT, in the treatment of all possible/probable/proven IFIs. Adverse events were reported in 12% of the population treated with ISA, with grade 3–4 adverse events that led to ISA discontinuation only in 4% of cases.[30]

In this study, we confirm the good tolerability of ISA in a high-risk setting population. ISA therapy was well tolerated, and no patient had to stop ISA due to occurrence of adverse events.

In SEIFEM study, at 90 days after ISA start, an RR of 67.2% was described, which is comparable to the RR of other antifungal treatments and is quite similar to the RR of 62% observed at 84 days in the SECURE study. In our study at 90 days after ISA start, an RR of 68% is described, in line with previous reports. As reported in SEIFEM study, also in our cohort, ISA was less effective in subjects with extra pulmonary IFI.[30]

TDM is largely used for triazole antifungal agents such as voriconazole and posaconazole, while it is controversial for ISA. However, interactions among azoles, immunosuppressive drugs, and letermovir prophylaxis are important to be considered in allo-HSCT setting. In this context, little is known about the impact of ISA on sirolimus. Some studies have been conducted on the coadministration of ISA and tacrolimus, showing that ISA exerts a moderate effect in increasing tacrolimus whole blood concentration, highlighting the necessity of close tacrolimus levels monitoring.[31] Kieu *et al.*[21] showed in allo-HSCT patients a modest increase in sirolimus TDM from baseline within the first 2 weeks after starting ISA therapy with no statistically significant differences for the

remaining timepoints. In our experience, sirolimus and ISA TDM were maintained in the therapeutic range, without cases of overdosing, also in the context of letermovir prophylaxis.

A recent study reported high incidence of b-PP-IFIs in the context of both non- and mold-active prophylaxis: 48.8% of patients were changed to liposomal amphotericin-B with a mortality at 100 days of 47.1% with an essential factor in 61.4% of cases.[32] Our results showed a 47% of b-PP-IFI on mold-active prophylaxis with a 38% of b-PP-IFI attributable mortality. Although in our study the majority of patients shifted from an azole to ISA, a reduction of mortality is described: this could be explained by the aggressive and rapid diagnostic approach performed in our center and the early changed of antifungal drug. The SEIFEM 2010-C study showed that in patients affected by acute myeloid leukemia (AML) in posaconazole as antifungal prophylaxis (FAP), it is common to apply an empirical approach in treating b-PP-IFIs, with no differences between liposomal B amphotericin and voriconazole.[33] However, especially in high-risk HSCT patients, it is needed to better understand the optimal subsequent antifungal drugs in patients on azole prophylaxis.

Our study has several limitations due to its retrospective design, the wide heterogeneity in patient characteristics, and the possible selection bias for the choice of antifungal therapy. Moreover, only a small number of patients are included that does not allow us to perform a deep statistical analysis.

Further studies will help clinicians in the unmet clinical needs and questions about the optimal antifungal approach as new antifungal drugs are upcoming (e.g. olorofim), epidemiology will be more extensively evaluated as reported recently for Australian guidelines and EORTC/MSG criteria will be discussed in this setting.[34]

Conclusion

This retrospective analysis supports the real-life use of ISA in combination with sirolimus after allo-HSCT, also in the context of letermovir prophylaxis. Here, we confirmed favorable clinical efficacy and safety of ISA antifungal therapy, even during the most critical early post-transplant phases. The use of ISA in combination with sirolimus was not associated with any case of sirolimus overexposure, under close supervision of both sirolimus and ISA TDM, which allowed safe pharmacological profile to be maintained, and therefore, no adverse events related to that were reported.

Declarations

Ethics approval and consent to participate

The patients were treated according to current Institutional programs, upon written informed consent for transplant procedures, and use of medical records for research, within the noninterventional 'ALMON study'. The observational protocol 'ALMON' has been approved by the Ethics Committee of the IRCCS San Raffaele Hospital, Milan on 19/10/2007 and the last amendment on 04/06/2015.

Consent for publication

Not applicable.

Author contributions

Francesca Farina: Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

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Chiara Oltolini: Conceptualization, Writing – original draft, Writing – review & editing.

Matteo Chiurlo: Writing – review & editing.

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Iacopo Peccatori: Writing – review & editing.

Fabio Ciceri: Conceptualization, Writing – review & editing.

Raffaella Greco: Conceptualization, Writing – original draft, Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets generated for this study are available on request to the corresponding author.

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