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BRIEF REPORT

# Breakthrough Invasive Fungal Infection After Coadministration of Venetoclax and Voriconazole

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Venetoclax requires a 75% dose reduction when coadministered with voriconazole. In a 10-year historical cohort of treatment with venetoclax, we did not observe a worse hematologic outcome in patients who received voriconazole prophylaxis versus those who did not. Subtherapeutic voriconazole levels and a triazole exposure history may contribute to breakthrough invasive fungal infection.

**Keywords.** breakthrough; invasive fungal infection; venetoclax; voriconazole.

Patients with hematological malignancy (HM) are at increased risk of invasive fungal infection (IFI). In a recent article by Zhang et al [1], the risk of IFI in patients receiving BCL-2 inhibitor venetoclax (VEN) was demonstrated. In this cohort, a small number of patients who received antifungal prophylaxis did not develop IFI [1]. A similar study conducted by Rausch et al [2] showed the efficacy of antifungal prophylaxis but 7.8% breakthrough IFI (bIFI) in patients with HM receiving VEN and prophylaxis with echinocandins or triazoles [3].

Antifungal prophylaxis in this context has 2 beneficial effects: reducing the IFI risk and decreasing the cost of treatment with VEN. In the presence of voriconazole (VORI), a potent CYP3A4 inhibitor, it is recommended to reduce the VEN dose by 75%, or from 400 mg routine daily dose to 100 mg daily [4]. Considering this drug interaction, the therapeutic effect of VEN is the focus of attention when the patient is on antifungal prophylaxis, and VORI therapeutic drug monitoring (TDM) may not be routinely done in the outpatient setting. Observational studies are required to estimate the IFI and bIFI risk in patients receiving VEN with and without VORI.

## METHODS

In a retrospective cohort at Princess Margaret Cancer Centre, we compared the outcomes of IFI, bIFI, morbidity and mortality among adult patients with HM who received VEN with or without concomitant prescription of VORI, from January 1, 2010, to December 31, 2020.

Eligible patients were identified through hospital pharmacy and prescribing records. The index date was the date of commencement of VEN, and the duration of follow up was at least 90 days. Two groups were identified: (1) participants who received VEN without coadministered VORI (VEN group): and (2) participants who were simultaneously coprescribed VEN with VORI (VEN + VORI group). Acute myeloid leukemia (AML) was characterized by European LeukemiaNet (ELN) classification [5]. All IFI episodes were recorded as "proven", "probable" or "possible" according to the 2019 revised European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [6]. The outcomes of interest were proven or probable IFI and death. Each discrete IFI episode was classified as de novo, persistent, refractory, relapsed, and breakthrough IFI as per recently suggested criteria [7]. Similar to Rausch et al [2], IFI occurring >5 days after continuous azole exposure or within 14 days of discontinuation were considered bIFI. This definition was applied to both groups and considered a secondary outcome.

We use VORI 6 mg/kg twice daily for 2 doses followed by 4 mg/kg twice daily and routinely monitor VORI trough level during prophylaxis or treatment targeting 1.0–5.5 μg/L (Supplementary Appendix) [8, 9]. Count recovery was defined as neutrophils $\geq 1.0 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L [5].

We compared the outcomes in participants receiving VEN or VEN + VORI using $\chi^2$ or Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables, considering $P < .05$ as the significance level.

### Patient Consent Statement

The design of the work has been approved by the University of Toronto-University Health Network, Research Ethics Board.

## RESULTS

One hundred nineteen patients with HM receiving VEN (Supplementary Table 1) were included in this cohort. Median age was similar between the 2 groups (Table 1).

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**Table 1. Comparison of Venetoclax and Venetoclax Plus Voriconazole**

| Variable | Venetoclax, n = 78 (%) | Venetoclax and Voriconazole, n = 41 (%) | *P* Value |
|---|---|---|---|
| Male sex | 49 (62.8) | 30 (73.1) | .26 |
| Median age (IQR), years | 66 (54–76.5) | 65.5 (53.75–72) | .47 |
| Current smoker | 6 (7.7) | 3 (7.32) | .94 |
| Underlying Disease | | | |
| Acute myeloid leukemia | 59 (75.6) | 39 (95.1) | .008 |
| IFI[a] before cohort | 14 (17.9) | 13 (31.7) | .09 |
| Transplant before venetoclax | 5 (6.41) | 5 (12.2) | .28 |
| Median (IQR) duration of venetoclax | 63 (28–140) | 56 (65–84) | .56 |
| Best Response to Venetoclax | | | .4 |
| (n = 106)[b] | | | |
| CR | 13 (20) | 5 (12.2) | |
| CRi | 13 (20) | 7 (17.1) | |
| MLFS | 6 (9.2) | 1 (2.4) | |
| Refractory/progressive | 28 (43.1) | 21 (51.2) | |
| Aplastic | 1 (1.5) | 2 (4.9) | |
| Unknown | 4 (6.2) | 5 (12.2) | |
| IFI, probable and proven | 4 (5.1) | 6 (14.6) | .07 |
| All-cause death | 30 (38.4) | 16 (39) | .9 |
| Directly associated with IFI | 1 (1.3) | 2 (4.8) | .2 |
| Count recovery (n = 106)[c] | 17 (26.2) | 8 (19.5) | .1 |
| Median (IQR) time to count recovery | 43 (35–89) | 41 (37–78) | .92 |
| MRD by Flow Cytometry (n = 106)[b] | | | .1 |
| Negative | 9 (13.8) | 1 (2.4) | |
| Positive | 22 (33.8) | 14 (34.1) | |
| Unknown[d] | 34 (52.3) | 26 (63.4) | |
| Hospitalization during treatment | 42 (51.3) | 32 (78) | .004 |
| Hospitalization Episodes | | | |
| 1 | 32 (41) | 24 (58.5) | |
| 2 | 8 (10.2) | 5 (12.2) | |
| 3 or more | 2 (2.6) | 3 (7.3) | |
| Infection-related hospitalization[e] | 17 (21.8) | 14 (34.1) | .14 |
| Median (IQR) length of stay, days | 18 (9–46) | 16 (4–33) | .2 |
| Admission due to febrile neutropenia | 16 (20.5) | 11 (14.1) | .4 |
| Proceeded to transplant | 15 (19.2) | 6 (14.6) | .5 |

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; IFI, invasive fungal infection; IQR, interquartile range; MRD, measurable residual disease; MLFS, morphologic leukemia-free state.

[a]Includes possible, probable, and proven IFI.

[b]Only including acute myeloid leukemia, acute lymphocytic leukemia, and myeloid disorders. In this analysis, the percentages are based on 65 patients in venetoclax and 41 patients in venetoclax plus voriconazole group.

[c]Count recovery was defined as neutrophils $\geq 1.0 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L[5].

[d]Patients who achieved CR or CRi but their MRD status was not known.

[e]Infection-related hospitalization in the venetoclax group (n = 17) were due to bacterial = 10, fungal = 1, viral = 3, mixed fungal, bacterial or viral = 3; venetoclax and voriconazole group (n = 14) due to bacterial = 5, fungal = 3, viral = 2, mixed fungal, bacterial, or viral = 4.

There was a higher proportion with de novo AML in the VEN + VORI group compared with VEN (27 of 39 [69.2%] versus 25 of 59 [42.4%], respectively; $P = .009$). In those participants receiving VORI (Supplementary Table 1), 10 of 44 (22.7%) experienced adverse effects, with deranged liver function tests (7 of 44, 15.9%) the most common. In the VEN group, 15 of 78 (19.2%) received antifungal agents including caspofungin (n = 7) and posaconazole (n = 8) after the commencement of venetoclax at a median of 43 days (interquartile range, 10–120).

Invasive fungal infection occurred in 10 of 119 (8.4%) participants, with 8 of 119 (6.7%) probable IFI and 2 of 119 (1.7%) proven IFI (Supplementary Table 2). In sensitivity analysis, the cumulative incidence of IFI in the subcohort of patients with AML and high-risk myelodysplastic/myeloproliferative neoplasm (MDS/MPN) was 9.6% (10 of 104). The specific characteristics of probable and proven IFI are detailed in Supplementary Table 3. There were 2 proven IFI episodes in the VEN + VORI group, which were classified as bIFI. These bIFI episodes occurred in 2 participants with relapsed AML, who were both receiving dose-reduced VEN at 200 mg daily (physician preference) with VORI at the same time. They experienced bIFI with culture and biopsy-proven angioinvasive fungal sinusitis, requiring surgical debridement and a change in therapy to liposomal amphotericin-B at 5 mg/kg intravenously

daily. The culture was positive for zygomycete species in one participant and *Alternaria* species in the other participant.

The incidence of proven or probable IFI (Table 1) was not significantly different between participants in the VEN versus VEN + VORI groups (4 of 78 [5.1%] vs 6 of 41 [14.6%], $P = .07$). Seven patients (5.8%) developed bIFI, including 6 patients in the VEN + VORI group and 1 in the VEN group, with no influence on overall mortality nor IFI-related death. All participants with bIFI had a history of possible IFI before commencement of venetoclax (7 of 7, 100%). In the VEN + VORI group, 3 of 6 patients with bIFI (50%) and 14 of 35 patients without bIFI (40%) had subtherapeutic VORI trough levels on ≥75% of measurements in the outpatient setting ($P = .645$) (Supplementary Table 3). In the VEN group, the bIFI episode (Supplementary Table 3) occurred in a participant receiving several months of posaconazole modified release 300 mg daily for possible pulmonary IFI, which was commenced after VEN.

In the comparison of the 2 groups, in participants with AML, acute lymphocytic leukemia, and myeloid disorders, there was no difference in the best response to VEN (n = 106), count recovery, measurable residual disease, and the number of participants proceeding to hematopoietic stem cell transplantation (Table 1). A substantial burden of hospitalizations was recorded in this cohort, with 74 of 119 (62.2%) participants requiring at least 1 hospitalization (Supplementary Table 2). There was a higher frequency of hospitalization (Table 1) in the VEN + VORI group than the VEN group ($P = .004$) but no difference in admission for febrile neutropenia.

## DISCUSSION

We retrospectively assessed all patients with HM at our institution receiving VEN with or without VORI. Overall, we found a considerable IFI risk in this cohort (8.4%) and the subcohort of patients with AML and high-risk MDS/MPN (9.6%), highlighting the requirement for preventive strategies in patients receiving VEN. Patients with underlying AML and increased IFI risk were more likely to receive VORI. Therefore, the nonsignificant difference in IFI outcome between VEN and VEN + VORI groups should be cautiously interpreted. Interventional studies and clinical trials are needed to determine the efficacy of antifungal prophylaxis in balanced risk groups of patients with HM receiving VEN.

The bIFI incidence in our cohort (5.8%) was similar to Rausch et al's [2] study (2.9% for posaconazole, 4.8% for voriconazole, and 5.7% for isavuconazole) [2]. However, we demonstrated a risk of bIFI in patients receiving VEN + VORI, possibly due to several contributing factors, including subtherapeutic VORI levels in the outpatient setting (although this cannot be casually associated), a high number of participants with a history of prior possible IFI episodes that may predict future IFI risk, and a significantly higher proportion of patients with AML [10–12]. The bIFI risk in patients who received VEN + VORI can be secondary to a higher proportion of patients with precohort IFI in this group than patients in the VEN group. These contributing factors should be considered in studies estimating the bIFI risk in patients receiving VORI prophylaxis.

Our study demonstrated no significant difference in response to VEN versus VEN + VORI in patients with AML. This bears importance given the current paucity of data on the impact of dose-reduced VEN during concomitant azole therapy on treatment responses in AML. The overall low response rate in our cohort may be due to many participants being classified as adverse risk AML. Our findings confirm results of a small substudy in the phase Ib stage of the VIALE-A trial [13], where patients with dose-reduced VEN and concomitant posaconazole achieved similar treatment responses to those receiving VEN without azoles [13, 14].

Our study has some limitations. Overall, the numbers of participants with recorded IFI episodes and bIFI were small, limiting the ability to perform statistical analysis and formulate risk factors and associations for these observations. In addition, owing to the limitations of an observational study, the baseline characteristics of the 2 groups differed. A higher hospitalization rate in the VEN + VORI group is likely due to a higher proportion of patients with AML than those in the VEN group. Retrospective observational studies are susceptible to selection bias, and patients in the VEN + VORI group were likely at a greater IFI risk than patients in the VEN group. Information on the severity of neutropenia was not collected due to neutrophil count fluctuation during VEN treatment; however, there was no difference in count recovery between the 2 groups.

## CONCLUSIONS

Patients with HM who receive treatment with VEN are at risk of IFI. Prophylaxis with VORI may reduce the IFI risk, but VEN dose adjustment is needed. Patients receiving a low VEN dose due to drug-drug interaction with VORI did not have a worse hematologic outcome than those who did not receive VORI. Further assessment is required to elucidate the bIFI risk in patients receiving concurrent VEN + VORI and individuals with inappropriate TDM in an outpatient setting while receiving VORI.

### Supplementary Data

Supplementary materials are available at *Open Forum 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.

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***Author contributions.*** VGH contributed to protocol composition, data collection, data analysis, manuscript writing, and editing. KT contributed to data collection, data analysis, manuscript writing, and editing. SMH-M contributed to protocol composition, data analysis, manuscript writing, and editing. DK, CR, and SH contributed to study design, manuscript writing, and editing. SC and SMC contributed to case identification and data collection.

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## References

1. Zhang A, Johnson T, Abbott D, et al. Incidence of invasive fungal infections in patients with previously untreated acute myeloid leukemia receiving venetoclax and azacitidine. Open Forum Infect Dis **2022**; 9:ofac486.
2. Rausch CR, DiPippo AJ, Jiang Y, et al. Comparison of mold active triazoles as primary antifungal prophylaxis in patients with newly diagnosed acute myeloid leukemia in the era of molecularly targeted therapies. Clin Infect Dis **2022**; 75: 1503–10.
3. Rausch CR, DiNardo CD, Maiti A, et al. Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia. Cancer **2021**; 127: 2489–99.
4. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. Leukemia **2019**; 33:2795–804.
5. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood **2022**; 140:1345–77.
6. 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.
7. Cornely OA, Hoenigl M, Lass-Florl C, et al. Defining breakthrough invasive fungal infection-position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology. Mycoses **2019**; 62:716–29.
8. Luong ML, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother **2016**; 71:1786–99.
9. Antimicrobial Stewardship Program UHN. Voriconazole monitoring and adjustment. Available at: https://www.antimicrobialstewardship.com/_files/ugd/550306_63c688de2fe546aba5d32617c9b3bf0b.pdf. Accessed 15 January 2023.
10. Rausch CR, DiPippo A, Bose P, Kontoyiannis DP. Breakthrough invasive fungal infections (bIFI) are uncommon in patients with newly diagnosed acute leukemia receiving primary antifungal prophylaxis. Blood **2020**; 136(Suppl 1):31–2.
11. Cornely OA, Böhme A, Reichert D, et al. Risk factors for breakthrough invasive fungal infection during secondary prophylaxis. J Antimicrob Chemother **2008**; 61:939–46.
12. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP. Breakthrough fungal infections in patients with leukemia receiving isavuconazole. Clin Infect Dis **2018**; 67:1610–3.
13. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol **2018**; 19:216–28.
14. Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther **2017**; 39:359–67.