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EHA EUROPEAN HEMATOLOGY ASSOCIATION

Letter
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Relationship Between Venetoclax Exposure and Undetectable Minimal Residual Disease Rates in Relapsed/Refractory Patients With Chronic Lymphocytic Leukemia: A Pooled Analysis of Six Clinical Studies

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Chronic lymphocytic leukemia (CLL) is a clinically heterogenous malignancy derived from mature B lymphocytes, where leukemic cells accumulate due to a combination of impaired apoptosis and increased proliferation.[1] Minimal residual disease or measurable residual disease (MRD) is a clinical endpoint in CLL[2] and quantifies the proportion of cancer cells remaining in the blood and/or bone marrow. It is conventionally dichotomized into detectable MRD or undetectable MRD (uMRD) status based on a threshold of 10^{-4} (<1 leukemic cell in 10,000 nucleated cells).[3] It has been demonstrated that uMRD is independently associated with progression-free survival (PFS) and overall survival (OS) with chemoimmunotherapy[4] and targeted therapies.[5]

Venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor that induces, particularly in combination with CD20 targeting mAbs, deep remissions, including uMRD.[6–8] The pharmacokinetics (PK) of venetoclax have been well characterized.[9–11] The relationships of venetoclax exposure with clinical efficacy and safety outcomes as monotherapy and in combination were evaluated across several malignancies.[12] In CLL, higher exposures are associated with more rapid reductions in peripheral blood lymphocyte count and tumor burden and with higher rates of complete response with venetoclax monotherapy.[13] Furthermore, coadministration with rituximab provided a substantial synergistic effect in terms of PFS.[14] In general, exposure-response analyses have supported the use of 400 mg as a highly effective dose of venetoclax in CLL for both monotherapy and combination therapy.[12,15]

Given the emerging role of MRD as a clinical endpoint in the era of targeted therapies in CLL, it is important to understand the relationship between dose or PK exposure and uMRD rates in blood and bone marrow to meaningfully inform choice of doses. Therefore, the objective of the current research is to investigate relationships between venetoclax exposures and uMRD rates in blood and bone marrow of patients receiving venetoclax monotherapy or venetoclax in combination with rituximab.

In this analysis, PK and MRD data from 4 venetoclax monotherapy studies and 2 combination studies (venetoclax + rituximab) were included. All studies were conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and were approved by the Human Investigational Review Board, or equivalent, of each study center. Written informed consent was obtained from each patient. In these studies, venetoclax was administered orally at doses ranging from 10 to 1200 mg once daily. Details of the clinical studies have been previously published.[5–7,16–19]

MRD was assessed following standardized flow cytometry or allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR) methods listed in the iwCLL guidelines[3] or by the clonoSEQ platform (Adaptive Biotechnologies, Seattle, WA), which is next-generation sequencing based. A population PK model was developed using venetoclax concentration data collected in clinical studies to obtain PK exposures for individual patients. Exposure-response analysis was conducted separately for uMRD rates in blood and bone marrow in the monotherapy and combination studies using exploratory quintile plots and logistic regression models. The individual steady-state venetoclax concentration (C_{ss}) was the exposure metric used. Refer to

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Supplemental digital content is available for this article.

HemaSphere (2023) 7:12(e983).
http://dx.doi.org/10.1097/HS9.0000000000000983.
Received: August 1, 2023 / Accepted: October 12, 2023

the Supplement for details on MRD assessments, population PK analysis, and exposure-response models.

A summary of study populations and MRD data from the individual clinical studies included in this analysis are provided in Suppl. Table S1. Suppl. Table S2 provides a summary of patient characteristics. A total of 6447 venetoclax concentration samples from 842 patients across the 4 monotherapy studies and 2 combination therapy studies were included in the population PK analysis. The estimated population parameter estimates and covariate effects (Suppl. Table S3) were similar to those observed in previous analyses. The model was able to predict the observed venetoclax concentrations across all the clinical studies adequately, and no systematic bias was noted in the goodness-of-fit plots (Suppl. Figure S1).

With venetoclax monotherapy, increasing exposure-response trends for uMRD rates in bone marrow and blood were observed (Figure 1A,B). There is a clear benefit for concentrations above ~1 µg/mL (median concentration at steady state with 400 mg venetoclax dose). Logistic regression analyses also showed statistically significant ($P < 0.01$) relationships between venetoclax exposures and uMRD rates in bone marrow and blood (Figure 1C,D). The model-predicted median uMRD rates in bone marrow at median exposures of 200 mg, 400 mg, and 800 mg doses of venetoclax were 8% (95% CI, 5-11), 11% (95% CI, 9-14), and 17% (95% CI, 13-22%), respectively. The corresponding predicted uMRD rates in blood were 21% (95% CI, 16-26), 32% (95% CI, 29-36), and 47% (95% CI, 40-53), respectively. The number of prior therapies was a statistically significant ($P < 0.001$) covariate on the intercept in the model for blood MRD. With venetoclax monotherapy at a dose of 400 mg, the predicted uMRD rates in patients with no prior therapies was 45% (95% CI, 38-52), which was 13% higher compared with the median uMRD rates in patients with 3 (median value) prior therapies.

With combination therapy of venetoclax and rituximab, an increasing exposure-response trend for uMRD rates in bone marrow is noted with a tendency for the rate to plateau at higher exposures (Figure 2A), and logistic regression analyses showed a statistically significant ($P < 0.01$) relationship between venetoclax exposures and uMRD rates in bone marrow (Figure 2C). However, the relationship between venetoclax exposure and uMRD rates in blood appeared relatively flat (Figure 2B) with a lack of statistical significance ($P = 0.06$) observed via logistic regression analyses (Figure 2D). The model-predicted median uMRD rates in bone marrow at median exposures of 200 mg, 400 mg, and 800 mg doses of venetoclax in combination with rituximab were 21% (95% CI, 15-30), 33% (95% CI, 27-39), and 47% (95% CI, 38-57), respectively.

The relationship between PK exposures and clinical efficacy plays an important role in driving dose optimization. With several targeted therapies approved and under development for CLL and the consequent role of MRD as a clinically relevant endpoint, there is a definite benefit in evaluating exposure-response analyses of uMRD rates in blood and bone marrow. To the best of our knowledge, this is the first analysis of this type in CLL.

Venetoclax exposures were significantly correlated with uMRD rates in bone marrow and blood, except for uMRD rates in blood when combined with rituximab. The increasing uMRD rates with venetoclax exposures in monotherapy are consistent with similar relationships observed for other efficacy endpoints including rate of reduction in ALC, tumor size, and partial and complete remission, and PFS rates.[13,14] However, safety of higher venetoclax exposures needs to be considered as well in dose selection.[13,16]

Although the number of cross-trial comparisons are limited by different patient characteristics, it does appear that venetoclax in combination with rituximab results in higher uMRD rates in blood and bone marrow compared with venetoclax monotherapy. In combination therapy with rituximab, the high uMRD rates observed in blood even at low exposures of venetoclax may have contributed to the lack of statistical significance for the relationship between venetoclax exposure and uMRD rates in blood. One drawback of the logistic regression analysis is that it ignores the time of achieving uMRD and censoring in the data. However, a sensitivity analysis that excluded the fixed duration regimen study (MURANO/NCT02005471) did not result in different findings. Time-to-event models may be investigated to address this concern.

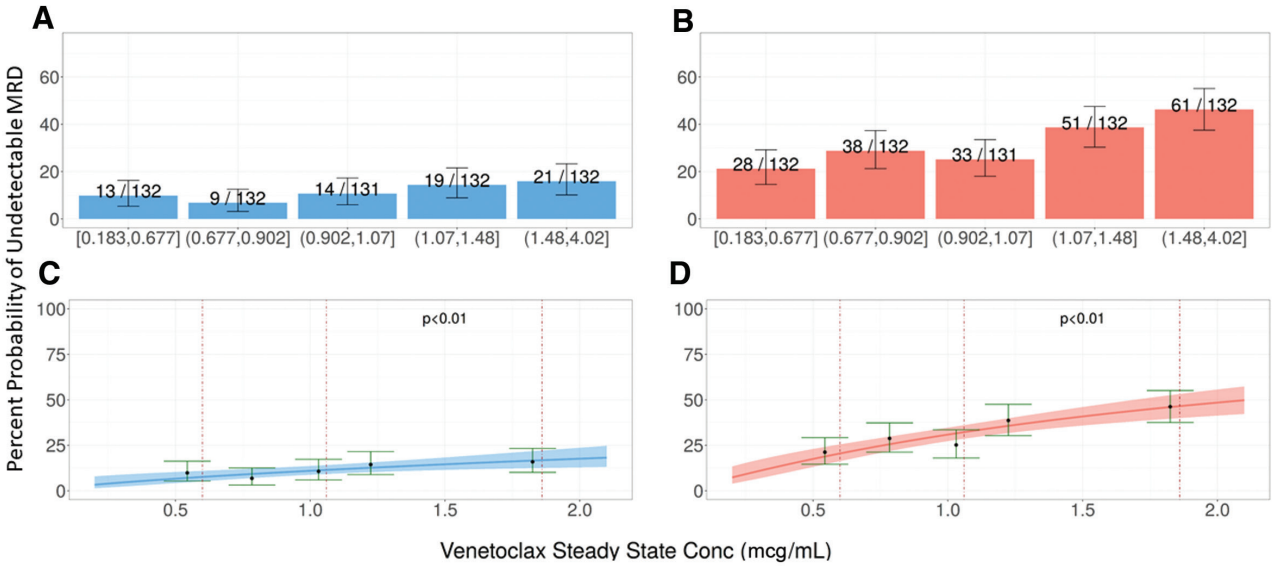

Figure 1. uMRD rates increase with venetoclax exposure during venetoclax monotherapy. (A,B) show the observed percent uMRD rates in bone marrow (A) and blood (B) vs venetoclax exposure quintiles. (C,D) show observed and model-predicted uMRD rates vs venetoclax exposures. The blue and red solid lines and bands indicate medians and 95% confidence intervals of the predicted uMRD rates in bone marrow (C) and blood (D), respectively. The dark-green dots and error bars denote the binned medians and 95% binomial confidence intervals of the observed uMRD rates. The brown vertical dashed-dotted lines indicate median exposures at 200 mg, 400 mg, and 800 mg doses of venetoclax in C and D. uMRD = undetectable minimum residual disease.

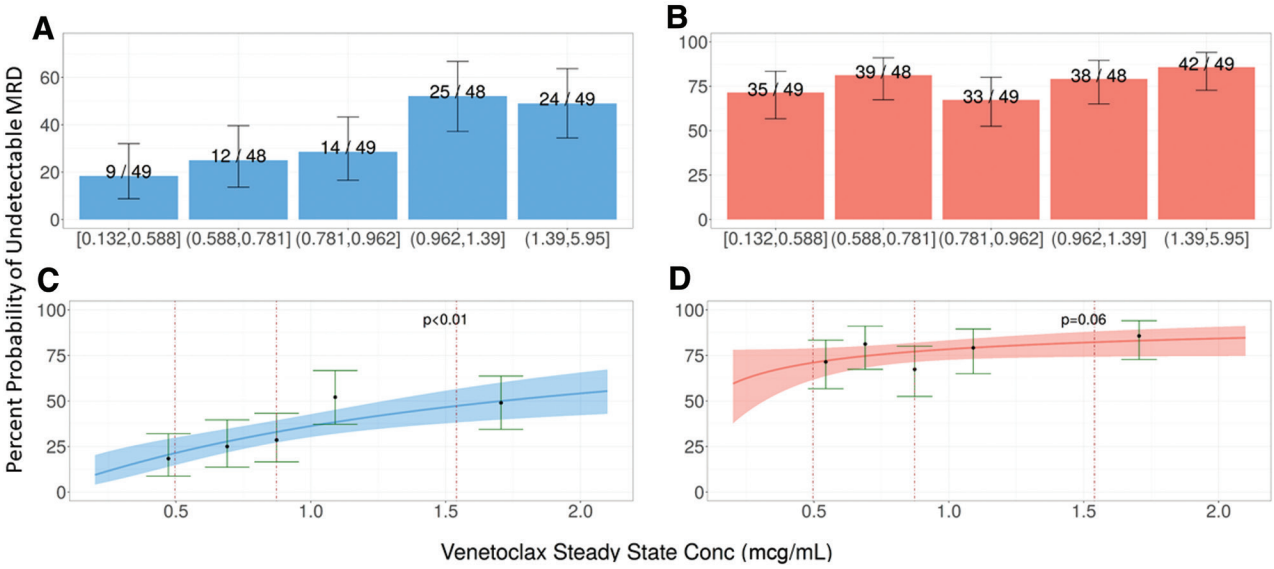

Figure 2. Increasing uMRD rates in bone marrow and lack of relationship of uMRD rates in blood with venetoclax exposure for venetoclax + rituximab combination therapy. (A,B) show the observed percent uMRD rates in bone marrow (A) and blood (B) vs venetoclax exposure quintiles. (C,D) show observed and model-predicted uMRD rates vs venetoclax exposures. The blue and red solid lines and bands indicate medians and 95% confidence intervals of the predicted uMRD rates in bone marrow (C) and blood (D), respectively. The dark-green dots and error bars denote the binned medians and 95% binomial confidence intervals of the observed uMRD rates. The brown vertical dashed-dotted lines indicate median exposures at 200 mg, 400 mg, and 800 mg doses of venetoclax in C and D. uMRD = undetectable minimum residual disease.

It is important to note that in the early monotherapy studies (NCT01328626, NCT01889186), neither blood nor bone marrow specimens for MRD assessments were required to be systematically collected from all patients, whereas bone marrow collections were required in the first combination study (NCT01682616). Venice I (NCT02756611) had mandatory peripheral blood collections for all patients at protocol designated times. Thus, blood MRD assessments in the monotherapy and combination studies were obtained for 70% and 90% of patients, respectively, and bone marrow MRD assessments in the monotherapy and combination studies were obtained for 37% and 49% of patients, respectively. This represents a limitation of the current analyses.

While number of therapies identified as a significant covariate was expected, it was surprising that other covariates that were screened including prior BCRi therapy and chromosomal abnormalities such as 17p deletion were not identified as impacting uMRD rates, although statistical power to detect such associations was low. One potential reason for this may be the correlation between covariates with poor prognosis (such as 17p deletion and prior BCRi therapy) with increased lines of prior treatment. However, this is not an altogether new finding as previous exposure-response analyses also failed to indicate 17p deletion as a significant covariate.[13]

In conclusion, venetoclax at the approved 400 mg dose results in substantial uMRD rates in the blood and bone marrow. The analyses demonstrate a concentration-dependent, and hence, dose-dependent effect of venetoclax on uMRD rates in the blood and bone marrow. These conclusions need to be confirmed in future prospective studies.

ACKNOWLEDGMENTS

We thank Neha Thakre, PhD, an employee of Abbvie, for her contributions during manuscript revisions. Medical writing support was provided by Stormy Koeniger, PhD, an employee of AbbVie.

AUTHOR CONTRIBUTIONS

SG, RM, AAS, and AHS participated in research design. SG, RM, AAS, APK, SS, JFS, BC, TL, SYK, AWR, JAW, SM, and AHS participated in the writing/review of the manuscript. SG, RM, AAS, APK, SS, JFS, BC, SYK, AWR, JAW, SM, and AHS participated in the performance of the research. SG and AAS participated in data analysis.

DATA AVAILABILITY

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this article for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/, then select "Home." Clinical Trials: NCT01328626 (https://clinicaltrials.gov/ct2/show/NCT01328626); NCT01889186 (https://clinicaltrials.gov/ct2/show/NCT01889186); NCT02141282 (https://clinicaltrials.gov/ct2/show/NCT02141282); VENICE I/NCT02756611 (https://clinicaltrials.gov/ct2/show/NCT02756611); NCT01682616 (https://clinicaltrials.gov/ct2/show/NCT01682616); MURANO/NCT02005471 (https://clinicaltrials.gov/ct2/show/NCT02005471).

DISCLOSURES

RM, BC, SM, and AHS are AbbVie employees and may hold stock or options. SG, AAS, and SYK were employed at AbbVie when this work was conducted and may hold AbbVie stock or options. TL is a Genentech employee and may own stock. APK receives research funding from Janssen, AbbVie, Roche/Genentech, Astra Zeneca, and BMS and is a member of advisory boards for Janssen, AbbVie, Roche/Genentech, and BMS. APK also receives speaker fees from AbbVie. SS receives honoraria for consultancy, speaker honoraria, research grants, and travel support from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffman La-Roche, Janssen, and Novartis and is an advisory board member for AbbVie, Amgen, AstraZeneca, Celgene, Gilead, Glaxo-Smith Kline, Hoffman La-Roche, Janssen, and Novartis. JFS receives research funding from AbbVie, Celgene, Janssen, and Roche, provides expert testimony for Celgene and Roche, is on the speakers'

bureau for AbbVie, Celgene, and Roche, and is an advisory board member for AbbVie, Astra Zeneca, Celgene, Genentech, Gilead, Janssen, Mei Pharma, Morphosys, Roche, Sunesis, and Takeda. AWR is an employee of the Walter and Eliza Hall Institute which has received venetoclax-related milestone and royalty payments in which he shares. AWR received research funding from Abbvie and holds a patent related to venetoclax. JAW is a consultant for AbbVie, Pharmacyclics, Janssen, Astra Zeneca, Beigene, and Arqule.

ETHICS STATEMENT

The studies reported herein were conducted in accordance with the International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Approval was granted by institutional review boards and independent ethics committees at participating institutions. All participants provided written consent prior to participation or study-related procedures. All individual participants signed informed consent regarding publishing their data.

SOURCES OF FUNDING

Venetoclax is being developed in a collaboration between AbbVie and Genentech. AbbVie and Genentech provided financial support for this study and participated in the design, study conduct, analysis, and interpretation of data, as well as the writing, review, and approval of this article.

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