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Short Communication

J Hematol. 2023;12(4):170-175

Local and Systemic Immunity During Five Vaccinations Against SARS-CoV-2 in Zanubrutinib-Treated Patients With Chronic Lymphocytic Leukemia

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Abstract

Background: Patients with chronic lymphocytic leukemia (CLL) are vulnerable to coronavirus disease 2019 (COVID-19) and are at risk of inferior response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, especially if treated with the first-generation Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib. We aimed to evaluate the impact of the third-generation BTKi, zanubrutinib, on systemic and mucosal response to SARS-CoV-2 vaccination.

Methods: Nine patients with CLL with ongoing zanubrutinib therapy were included and donated blood and saliva during SARS-CoV-2 vaccination, before vaccine doses 3 and 5 and 2 - 3 weeks after doses 3, 4, and 5. Ibrutinib-treated control patients (n = 7) and healthy aged-matched controls (n = 7) gave blood 2 - 3 weeks after vaccine dose 5. We quantified reactivity and neutralization capacity of SARS-CoV-2-specific IgG and IgA antibodies (Abs) in both serum and saliva, and reactivity of T cells activated with viral peptides.

Results: Both zanubrutinib- and ibrutinib-treated patients had significantly, up to 1,000-fold, lower total spike-specific Ab levels after dose 5 compared to healthy controls ($P < 0.01$). Spike-IgG levels in serum from zanubrutinib-treated patients correlated well to neutralization capacity ($r = 0.68$; $P < 0.0001$) and were thus functional. Mucosal immunity (specific IgA in serum and saliva) was practically absent in zanubrutinib-treated patients even after five vaccine doses, whereas healthy controls had significantly higher levels (tested in serum after vaccine dose 5) ($P < 0.05$). In contrast, T-cell reactivity against SARS-CoV-2 peptides was equally high in zanubrutinib- and ibrutinib-treated patients as in healthy control donors.

Conclusions: In our small cohort of zanubrutinib-treated CLL patients, we conclude that up to five doses of SARS-CoV-2 vaccination induced no detectable IgA mucosal immunity, which likely will impair the primary barrier defence against the infection. Systemic IgG responses were also impaired, whereas T-cell responses were normal. Further and larger studies are needed to evaluate the impact of these findings on disease protection.

Keywords: CLL; Zanubrutinib; SARS-CoV-2; Immunity; Vaccination

Manuscript submitted May 14, 2023, accepted July 14, 2023
Published online August 8, 2023

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doi: https://doi.org/10.14740/jh1140

Introduction

Immunocompromised patients with chronic lymphocytic leukemia (CLL) are vulnerable to coronavirus disease 2019 (COVID-19) and exhibit variable responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination [1, 2]. Antibody (Ab) titers are notably low in patients receiving the first-generation Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib [2, 3], and their vaccine-induced T-cell responses are weaker than in most other patient groups with immunodeficiency [4]. Zanubrutinib, a third-generation BTKi, offers improved progression-free survival compared to ibrutinib [5] and possesses increased selectivity to BTK with

Table 1. Clinical Characteristics at Start of Vaccination Against SARS-CoV-2 and Timepoints of Vaccination and Tests

Median age, years (range)	75 (52 - 83)
Male	56% (5/9)
Zanubrutinib as first-line treatment	67% (6/9)
Time (months) of zanubrutinib treatment before dose 1, median (range)	28 (3.5 - 33.5)
Time (months) between vaccine doses	
Dose 1-2 (n = 9)	1.4 (0.7 - 2.2)
Dose 2-3 (n = 9)	5 (4.1 - 6.2)
Dose 3-4 (n = 8)	3.9 (3.4 - 9.0)
Dose 4-5 (n = 7)	3.2 (3.0 - 6.5)
Type of vaccine[a]	
Dose 1 (n = 9)	C = 4, S = 2, V = 3
Dose 2 (n = 9)	C = 4, S = 2, V = 3
Dose 3 (n = 9)	C = 4, S = 5, V = 0
Dose 4 (n = 8)	C = 0, S = 8, V = 0
Dose 5 (n = 7)	C = 3, S = 4, V = 0
Time (days) since pretest to vaccination, median (range)	
Dose 3 (n = 9)	31 (10 - 73)
Dose 5 (n = 4)[b]	4 (0 - 8)
Time (days) since vaccination to post-test, median (range)	
Dose 3 (n = 9)	24 (15 - 36)
Dose 4 (n = 8)	32 (21 - 43)
Dose 5 (n = 7)	21 (17 - 53)

[a]C: Comirnaty® (BNT162b2, Pfizer BioNTech); S: Spikevax® (mRNA-1273, Moderna); V: Vaxzevria® (AZD22, Astra Zeneca). [b]Missing test for two patients and one patient did not receive dose 5 due to SARS-CoV-2 infection.

fewer off-target effects [6], including on interleukin-2-inducible T-cell kinase (ITK). This suggests that zanubrutinib's immunological imprint on the outcome of vaccination might differ from earlier generations of BTKi. We here examined systemic and mucosal immunity during repeated (up to 5) SARS-CoV-2 vaccinations in a cohort of patients with CLL on long-term zanubrutinib therapy. Results were compared with patients on first-generation BTKi therapy (ibrutinib) and healthy age-matched donors that were tested after vaccine dose 5.

Materials and Methods

Patients with CLL receiving zanubrutinib in the clinical trials BGB-3111-304 [7] and BGB-3111-305 [5] at one single site (Karolinska University Hospital) without a history of previous COVID-19 tested negative for anti-nucleocapsid Abs, who had received at least two vaccine doses against SARS-CoV-2, were included. Patients who developed COVID-19 during the study period were withdrawn from further analyses from that time point. The study was approved by the Swedish Ethical Review Authority [8]. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Zanubrutinib-treated patients donated blood and saliva samples before vaccine doses 3 and 5 and 2 - 3 weeks after doses 3, 4, and 5. Ibrutinib-treated control patients (n = 7) (median age 67 years, range 67 - 82) and healthy aged-matched controls (n = 7) (median age 71 years, range 64 - 88) gave blood after dose 5. Quantitative measurements of antibodies against the spike-receptor-binding domain (RBD) and the nucleocapsid were performed on serum samples (Elecsys®, Roche Diagnostics), and further analyses of anti-spike IgA, IgG, and ACE inhibition capacity were performed on both serum and saliva samples (V-PLEX, Meso Scale Diagnostics). Peripheral blood mononuclear cells (PBMCs) were used for T-cell response analysis using an activation-induced marker (AIM) assay as described [4]. A complete description of all methods, mainly as described earlier [9], is provided in the Supplementary Material 1 (www.thejh.org).

Results

Patient characteristics and vaccination details are shown in Table 1. Nine zanubrutinib-treated patients with a median age of 75 years (range 52 - 83) were included. Six received zanubrutinib as first-line treatment and three as salvage therapy > 2.5 years since their last treatment. The median time from zanu-

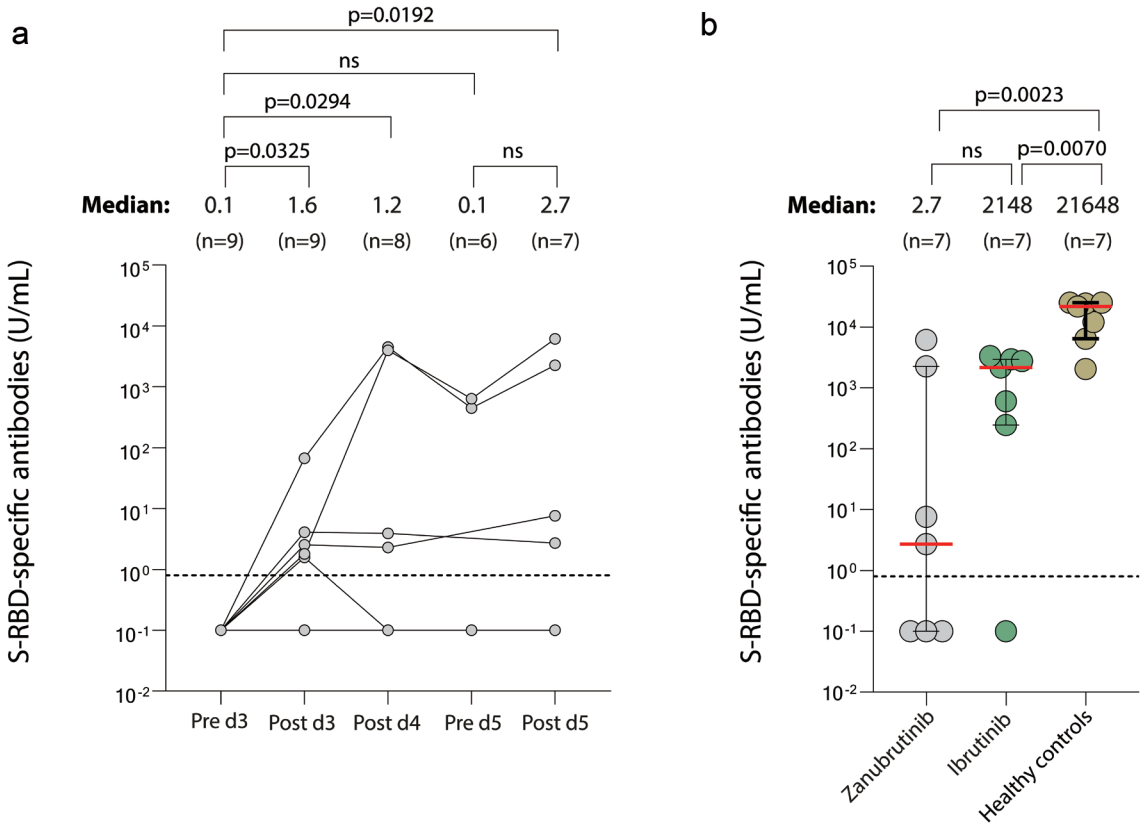

Figure 1. Serological immunity in zanubrutinib- and ibrutinib-treated patients with CLL after SARS-CoV-2 vaccination. Levels of SARS-CoV-2 Abs against spike-receptor-binding domain (RBD) were quantified in serum samples from zanubrutinib treated patients pre- and post-vaccine dose 3, post-dose 4, and pre- and post-dose 5 (a), and in addition post-dose 5 in PBMC from seven ibrutinib-treated patients and seven age- and gender-matched healthy donors (b). The median level of reactivity and number of samples are indicated above each time point. Dashed line represents positive threshold of 0.8 U/mL and the upper limit of detection is 25,000 U/mL. Error bars represent the median (red line) and interquartile range where applicable. Non-parametric Kruskal-Wallis test was used to assess differences between all-time points and Mann-Whitney test for comparison between patient groups and healthy controls. CLL: chronic lymphocytic leukemia; PBMC: peripheral blood mononuclear cell.

brutinib initiation to the first vaccination was 28 months (range 4 - 34). All had stable partial remission during the vaccination period. One patient experienced a SARS-CoV-2 breakthrough infection before dose 4 and 1 before dose 5 and was subsequently excluded from further analyses.

All zanubrutinib-treated patients (9/9) were seronegative prior to dose 3 (total spike-Ab < 0.8 U/mL). When compared to baseline, significant increases of total titers were noted after vaccine doses 3, 4, and 5 ($P < 0.05$), albeit 44% (4/9) were still seronegative after dose 3, 50% (4/8) after dose 4 and 43% (3/7) after dose 5 (Fig. 1a). Similar results were found for serum tested against both anti-wt- (Wuhan ancestral strain) and anti-Omicron spike IgG (data not shown). Total Ab levels after dose 5 were significantly lower in the zanubrutinib cohort than in age-matched healthy donors (median 2.7 U/mL vs. 21,648 U/mL; $P < 0.01$; Fig. 1b), with comparable results for anti-spike IgG against wt and Omicron ($P < 0.01$ and $P < 0.05$). Also, the anti-spike total Ab levels in the ibrutinib-treated cohort were significantly lower compared to healthy donors (median 2,148 U/mL; range 0 - 3,331; Fig. 1b). Two zanubrutinib-treated patients mounted Ab levels in parity with the healthy controls, but no individual factors (for example, age, gender, duration of zanubrutinib treatment, or type of vaccine) that might explain this were deviant compared to the other patients (data not shown).

The serum inhibition of angiotensin-converting enzyme 2 (ACE-2) binding to wt spike strongly correlated with the level of wt spike-specific IgG for all tested sera ($r = 0.82$; $P < 0.0001$) and for sera from zanubrutinib-treated patients when tested separately ($r = 0.68$; $P < 0.0001$). Saliva analysis showed a low but significant increase of IgG against wt spike in zanubrutinib-treated patients ($P < 0.05$), which strongly correlated with spike-specific serum IgG ($r = 0.77$; $P < 0.0001$). In contrast to IgG, anti-spike IgA levels remained unchanged in serum or saliva in zanubrutinib-treated patients (data not shown). However, healthy donors tested after dose 5 exhibited elevated serum IgA levels (saliva was not available) against both wt- and Omicron spike compared to patients (both $P < 0.05$).

Additionally, we measured SARS-CoV-2-specific T-cell responses. There was no significant change in wt- or Omicron-specific $CD4^+$ T-cell frequencies after three or more vaccine doses (Fig. 2a), but a significant increase of Omicron-specific $CD8^+$ T cells after dose 3 ($P < 0.05$), with a similar trend for wt-

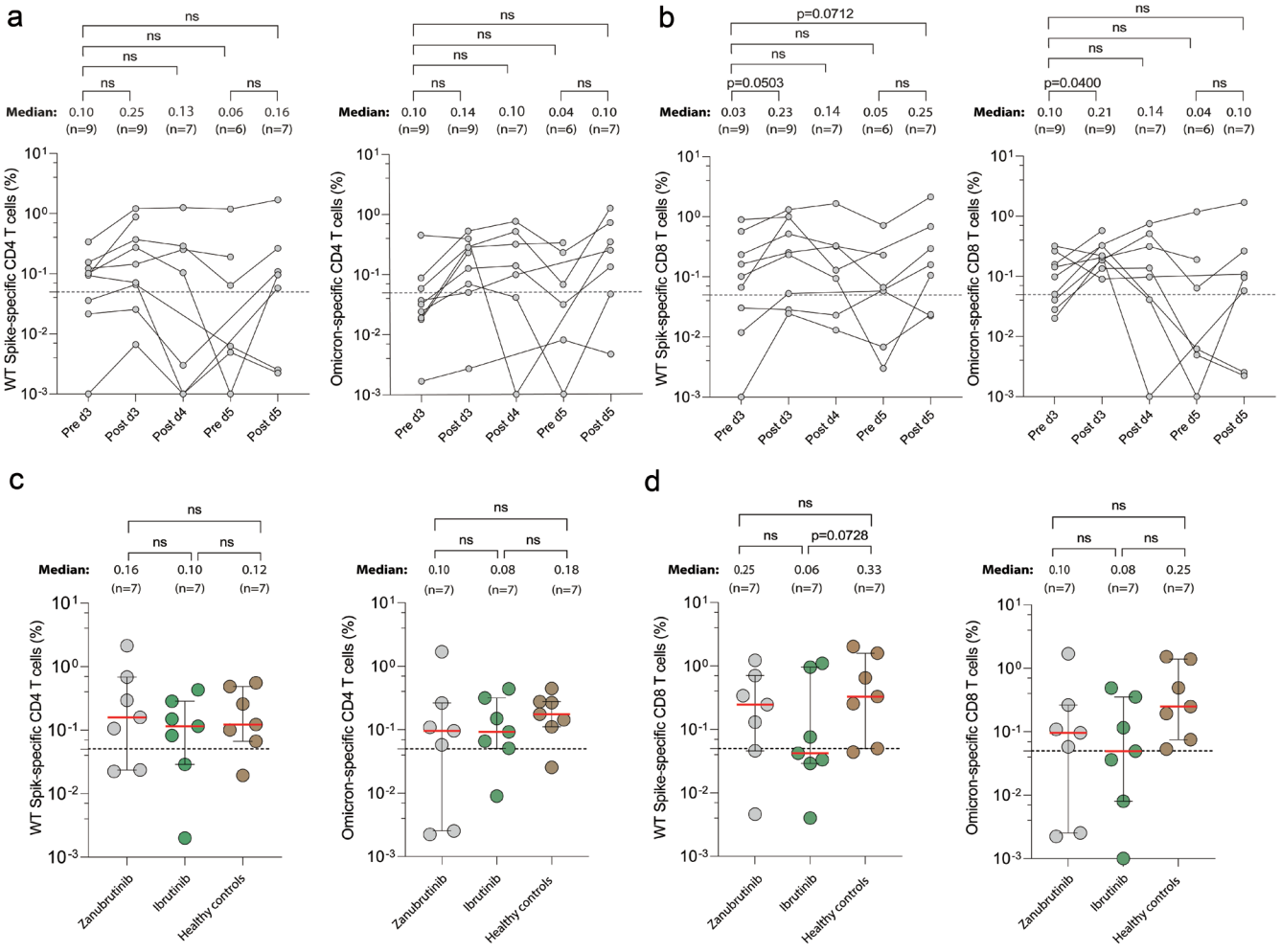

Figure 2. SARS-CoV-2 specific T-cell responses in zanubrutinib- and ibrutinib-treated patients with CLL after SARS-CoV-2 vaccination. Antigen specific $CD4^+$ ($CD69^+CD154^+$) and $CD8^+$ ($CD69^+CD137^+$) memory T cells were measured after SARS-CoV-2 wild-type and Omicron BA.1 peptide stimulation in PBMC samples from zanubrutinib-treated patients pre- and post-vaccine dose 3, post-dose 4, and pre- and post-dose 5 (a, b), and in addition post-dose 5 in PBMC from seven ibrutinib-treated patients and seven age- and gender-matched healthy donors (c, d). The median level of reactivity and number of samples are indicated above each time point. Omicron-specific $CD8^+$ T cells increased significantly ($P < 0.05$) after dose 3, and there was a similar trend for wt-specific $CD8^+$ T cells ($P = 0.050$). No significant differences were noticed between the different groups of patients, or between patients and healthy controls, post-dose 5. Background is subtracted using DMSO negative control of AIM^+ $CD4^+/CD8^+$ among all patients. A positive response was defined with a cut-off level of 0.05% (dashed lines). Error bars represent the median (red line) and interquartile range where applicable. Non-parametric Kruskal-Wallis test was used to assess differences between all-time points and Mann-Whitney test for comparison between CLL patients and healthy controls. ns: $P > 0.05$, not statistically significant. CLL: chronic lymphocytic leukemia; PBMC: peripheral blood mononuclear cell.

specific $CD8^+$ T cells ($P = 0.050$, Fig. 2b). Doses 4 and 5 did not result in additional increases. In contrast to the serology results, spike-specific T-cell responses after vaccine dose 5 were similar between zanubrutinib-treated patients and healthy controls for both $CD4^+$ (Fig. 2c) and $CD8^+$ (Fig. 2d) T cells, with comparable levels observed in the ibrutinib cohort (Fig. 2c, d).

Discussion

Patients with CLL remain at risk of severe COVID-19 even during the Omicron era [10, 11] and often display limited responsiveness to vaccination against SARS-CoV-2, with the lowest seroconversion rates if receiving CD20 monoclonal Ab-containing therapy or BTKi [2]. Even though multiple vaccinations may lead to seroconversion in more patients, some continue to remain seronegative or to have very low Ab titers [12]. Limited information is available on the impact on serological response under a strong BTK inhibitor such as zanubrutinib. Recently, a seroconversion rate of 77% was reported after three vaccine doses in zanubrutinib-treated patients with CLL or Waldenstrom's macroglobulinemia using an alternative antibody detection method (even though the levels were not specified in U/mL) [13]. In the zanubrutinib-treated pa-

tients included in the present study, the median Ab level after five vaccine doses as determined by the standardized Elecsys® assay was only 2.7 U/mL, which was 1,000-fold lower than in age-matched healthy donors, and 43% of tested patients were still seronegative. There was considerable inter-individual response variation, and enlarged studies are needed to explore if there may be a relation to factors such as type of vaccine, age, or duration of zanubrutinib therapy. The serum neutralization capacity correlated very well to serum IgG levels, suggesting functionality of the Abs but also lower protection in individuals with low responses. The numerically higher Ab levels found in our cohort of ibrutinib-treated patients should be viewed with caution; enlarged studies of both BTKi are warranted. Local virus-specific IgA in mucosa probably plays a key role in protection against SARS-CoV-2 infection [14, 15], as it has a dimeric form with enhanced neutralizing capacity [16]. The fact that spike-specific IgA failed to increase either in serum or saliva after repeated subcutaneous vaccination in zanubrutinib-treated patients is, therefore, worrisome.

The extent to which seronegative patients with CLL can mount sufficient T-cell responses is currently unclear [2, 12]. The present study showed that seronegative patients with CLL on long-term zanubrutinib treatment could generate T-cell responses comparable to healthy individuals (tested after dose 5 only, thus, time kinetics could not be compared). This aligns with findings in patients with primary immunodeficiency (PID) who developed T-cell responses upon mRNA vaccination despite lacking B cells [4]. There are conflicting reports on whether additional vaccinations may boost T-cell responses. For instance, a fourth dose did so in older healthy individuals [17] as well as in patients with HIV [17], whereas a plateau was reached after the second dose in another report on healthy individuals [18]. Our small cohort size precluded definitive conclusions about T-cell kinetics, although we found a significant boost in $CD8^+$ T-cell reactivity after dose 3, with no further increase after doses 4 and 5. Also in the three-dose zanubrutinib vaccine report by Nguyen et al, T-cell reactivities were increased by a third dose [13]. A third-dose boost was also reported in other subsets of patients with CLL [19, 20], whereas in lymphoma patients, a Th1, but not $CD8^+$ T cell response, was reported by dose 3 [21].

The major limitations of our study are the small number of included patients and inter-individual data variation, limiting generalized conclusions from the observations. The risk of applying multiple analyses on small materials should also be kept in mind. Another limitation was the absence of saliva and longitudinally sampled serum from healthy donors. Finally, using exact cell counting techniques would have improved the flow cytometry analyses. Nevertheless, to our knowledge, this is the first study of systemic and mucosal vaccine responses in patients with ongoing third-generation BTKi therapy.

In summary, our study on a limited number of patients suggested that many but not all zanubrutinib-treated patients demonstrated a very low ability to generate spike-specific Abs in serum and almost no spike-specific Abs in saliva. Importantly, however, their capacity to generate spike-specific T cells was normal, reaching levels similar to age-matched healthy donors when tested after five vaccine doses. Further research is needed to understand how this impaired vaccine immunity affects the risk of severe SARS-CoV-2 infection and whether differences exist between various BTKi types.

Supplementary Material

Suppl 1. Complete description of all methods.

Acknowledgments

We thank all patients and controls who donated blood for this study and A. Fahlen, K. Heimersson, and L. Relander for technical assistance.

Financial Disclosure

This study was supported by grants from the SciLifeLab National COVID-19 Research Program, the Swedish Research Council, Region Stockholm, the Swedish Cancer Society, the Cancer Society in Stockholm, the Cancer and Allergy Foundation, the Swedish Blood Cancer Foundation, Beigene Ltd, Center for Innovative Medicine (CIMED) and Karolinska Institutet.

Conflict of Interest

The authors declare no competing financial interests. MB is a consultant for Oxford Immunotech. AO and MP received research funding from Beigene LDT.

Informed Consent

Written informed consent was obtained before sampling.

Author Contributions

HMIS, MA, AO, GB, MSC, HGL, HM, and MB contributed to the conceptualization, funding acquisition, and discussion of data. JW, DW, YG, KH, SN, PC, MA, and SM performed experiments and analyzed data. MA, MP, HMIS, LH, and AO recruited study participants, conducted the management of participants during the study, and analyzed data. MA, HMIS, KH, DW, MSC, AO, HGL, and MB wrote the original draft of the manuscript. All authors reviewed and edited revisions of the manuscript and had final responsibility for the decision to submit for publication.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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