ARTICLE

Model-Informed Dosing of Venetoclax in Healthy Subjects: An Exposure–Response Analysis

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Venetoclax is an approved drug for the treatment of some hematological malignancies. Venetoclax can cause reduction in B-lymphocyte counts as an on-target effect. The purpose of this analysis is to quantify the relationship between venetoclax exposure and B-lymphocyte levels to inform dosing of venetoclax in healthy subjects. Data were pooled from 10 studies in healthy subjects with venetoclax doses ranging from 10 mg to 400 mg and food ranging from fasting to high-fat meals. Venetoclax pharmacokinetics (PK) was characterized in 203 subjects using a population approach, as implemented in NONMEM version 7.3 (Icon Development Solutions, Ellicott City, MD, USA). A semimechanistic pharmacodynamic (PD) model with a linear drug effect was fit to the B-lymphocyte data to determine the exposure-response relationship. The population PK and PD model described the observed data adequately. The 200 and 400 mg doses were shown to reduce the B-lymphocyte levels by 24% (15–35%) and 38% (25–54%), respectively. B-lymphocytes recovered to normal levels within an average of 48 (21–64) days and 59 (30–66) days, respectively, with 200 and 400 mg doses. Venetoclax can be safely administered in healthy subjects. The PK-PD model characterized the relationship between venetoclax exposure and reduction in B-lymphocytes and will help design future venetoclax studies in healthy subjects.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Venetoclax can cause reduction in B-lymphocyte counts as an on-target effect.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The study quantified the relationship between venetoclax exposure and B-lymphocytes levels in healthy subjects.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The venetoclax 200 and 400 mg doses were shown to reduce the B-lymphocytes levels by 24% (15–35%) and

38% (25–54%), respectively. B-lymphocytes recovered to normal levels within an average of 48 (21–64) days and 59 (30–66) days, respectively, with 200 and 400 mg doses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These results will inform safe dosing of venetoclax in healthy subjects to allow quick and robust assessment of its bioavailability and interactions with other drugs.

Venetoclax (ABT-199/GDC-0199) is a selective, potent B-cell lymphoma-2 (BCL-2) inhibitor, approved for the treatment of patients with chronic lymphocytic leukemia (CLL) and patients with acute myeloid leukemia who have comorbidities that prevent use of chemotherapy.[1–3] It is currently being evaluated in several other hematological malignancies.[4–7] BCL-2, overexpressed in several cancers, inhibits programmed cell death by protecting cells from a variety of proapoptotic stimuli. Venetoclax inhibits BCL-2 signaling which, in turn, induces apoptotic cell death in cells. BCL-2-mediated effects on lymphocytes and neutrophil progenitor cells lead to venetoclax-pharmacodynamic (PD) effects, such as reduction in B-lymphocytes and neutropenia.[8,9]

The clinical pharmacokinetics (PK) of venetoclax has been investigated in multiple studies.[10–14] Following

oral administration, the maximum plasma concentration (C_{max}) of venetoclax is reached 5–8 hours postdose, and the area under the curve (AUC) increases proportionally up to 800 mg.[15,16] Venetoclax is mainly metabolized by CYP3A, and it is also a P-glycoprotein and breast cancer resistance protein transporter substrate.[17–19] The mean terminal elimination half-life is 17 hours in healthy subjects and 35 hours in subjects with severe hepatic impairment.[20] Administration of food increases venetoclax exposures by threefold to fivefold as compared with fasting conditions.[21]

In studies in healthy subjects, venetoclax doses ranged from 10 mg to 400 mg. In some of these studies, a decrease in B-lymphocytes following venetoclax dosing was observed.[22] Hence, the objective of this PK-PD

analysis is to evaluate the effect of venetoclax exposures on B-lymphocytes to inform safe dosing of venetoclax in future studies in healthy subjects.

METHODS

The PK data included in the current analyses were pooled from 10 healthy subjects' studies (**Table 1**). These were clinical pharmacology studies ranging from bioavailability and food effect studies to drug–drug interaction studies. All studies were approved for each site by the appropriate institutional review board and were conducted in accordance with the principles described in the Declaration of Helsinki (1946) up to and including the Seoul revision (2008). All subjects provided written informed consent prior to participation.

Healthy female subjects between 21 and 65 years of age with a body mass index of 18.6–30.1 kg/m^2 were enrolled in the studies. Male subjects were excluded due to findings in 4-week dog toxicology studies suggesting that male fertility may be compromised by treatment with venetoclax based on testicular toxicity (germ cell loss). In all the studies, venetoclax was administered orally 1–4 times separated by a minimum of a 7-day washout period. The doses ranged from 10 mg to 400 mg. Venetoclax was administered either after 10-hour overnight fast or within 30 minutes after completion of a low, moderate, or high-fat breakfast.

Venetoclax concentrations were collected serially up to 96 hours after dosing and determined using liquid–liquid extraction and liquid chromatography with tandem mass spectrometric detection.[23] Total and B-lymphocytes were also quantified at baseline and after dosing. Three of the 10 studies did not have B-lymphocytes quantified and were, therefore, not included for PD modeling.

PK model

The population PKs of venetoclax was characterized using a nonlinear mixed effects approach and was implemented in NONMEM version 7.3 (Icon Development Solutions, Ellicott City, MD, USA) using data combined from all studies listed in **Table 1**. The NONMEM code for the PK and PD models is included as a **Supplemental Material**. The starting model used was adapted from the population PK model used previously to characterize venetoclax PKs in patients with CLL, patients with non-Hodgkin's lymphoma (NHL), and healthy subjects (**Figure 1a**).[24] Briefly, the structural model was a two-compartment PK model with first-order absorption and elimination, and interindividual variability modeled exponentially on apparent clearance, apparent central volume of distribution, and bio-availability. A combined residual error model was used to describe the intraindividual variability observed with venetoclax. The statistical significance of the included covariates was tested by backward elimination and a covariate was retained if $P < 0.01$. The model was evaluated using goodness-of-fit plots.

PD model

The PK parameters of individual subjects obtained as *post hoc* empirical Bayesian estimates from the PK models were fixed prior to the PD modeling. A semimechanistic model adapted from the model developed by Friberg *et al.*[25] was used to describe the dynamics of B-lymphocytes. A schematic of the model is shown in **Figure 1b**.

Briefly, B-lymphocytes were assumed to proliferate in a compartment (for example, the bone marrow), followed by sequential transit compartments, where their maturation occurs before entering circulation. A feedback mechanism incorporated as the ratio of the number of circulating cells at baseline and the number of circulating cells at time *t* allows for adequate description of the rebound of lymphocytes after reaching a nadir. The feedback is quantified by an exponent γ. More details regarding the model are provided in Friberg *et al.*[25] The median of observed B-lymphocyte counts prior to venetoclax administration was used as the baseline, with an associated interindividual variability. The model was fit to log-transformed B-lymphocyte counts to ensure stability, and an additive residual error model was used. The developed model was evaluated using goodness-of-fit plots.

Table 1 Studies included in the exposure-response analysis

| Study	Purpose of study	Dose (mg)	Food	Number of subjects	References
I	PK in Chinese subjects	100	Low fat	12	Cheung *et al.*[10]
II	Effect of venetoclax on warfarin PK	400	Moderate fat	3	Salem *et al.*[22]
III	Effect of ritonavir on venetoclax PK	10	Low fat	20	Freise *et al.*[11]
IV	Effect of venetoclax on digoxin PK	100	Moderate fat	10	Chiney *et al.*[12]
V	Effect of azithromycin on venetoclax PK	100	Moderate fat	12	Agarwal *et al.*[13]
VI	BA and food effect	20	Fasting	12	Not published
VII	BA and food effect	100/200	Fasting and high fat	83	Not published
VIII	BA	50	Moderate fat	15	Salem *et al.*[21]
IX	BA and food effect	100	Fasting, low and high fat	24	Salem *et al.*[21]
X	Effect of rifampin on venetoclax PK	200	Moderate fat	12	Agarwal *et al.*[14]

BA, bio-availability; PK, pharmacokinetic.

RESULTS

A total of 203 healthy female subjects were included in the analyses. Of these, 12 were Chinese subjects. The median age was 40 years (range 21–65 years).

PK model

A two-compartment population PK model with a lag in absorption and first order elimination adequately described the concentration-time profiles of venetoclax in the healthy subjects for doses ranging from 10 mg to
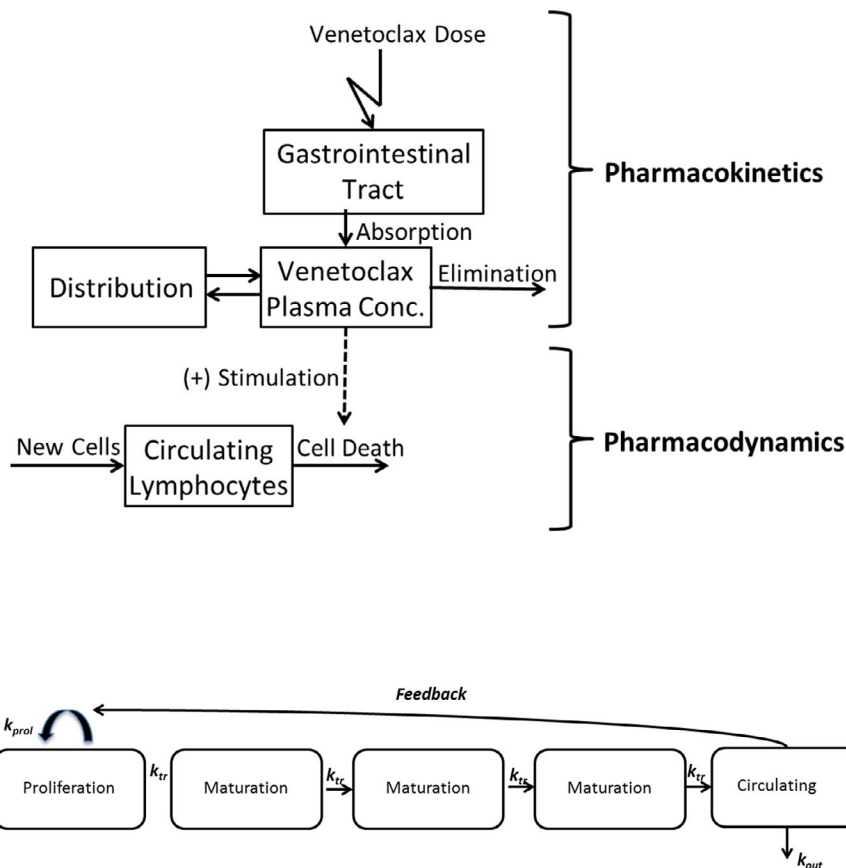
Figure 1 Schematic of the integrated pharmacokinetic pharmacodynamic model and of the lymphocytes dynamics model. Conc., concentration. K_{prol}, proliferation rate constant; k_{tr}, transit rate constant; k_{out}, elimination rate constant.

Table 2 Parameter estimates of the population PK and PD models

| Parameter (units)	Estimate	95% confidence interval	Parameter (units)	Estimate	95% confidence interval
PK model					
CL/F (L/day)	449	392–506	Low fat on F1	1	
V2 (L)	99	82–116	Fasting on F1	0.29	0.28–0.29
Q (L/day)	130	116–144	Moderate/high-fat on F1	1.47	1.43–1.51
V3 (L)	147	135–159	Azithromycin on F1	0.65	0.61–0.70
KA (1/day)	3.83	3.48–4.18	Chinese on F1	1.53	0.81–2.47
ALAG (day)	0.04	0.0399–0.0401	Rifampin on F1	4.91	2.38–7.44
Rifampin on CL	2.67	1.59–3.75	Dose nonlinearity on F1	−0.178	Fixed
PD model					
$t_{1/2}$ (days)	37.5	34.0–41.0	k_{in}, proliferation (and transit maturation) rate (day^{-1})	0.1	0.02–0.61
Feedback exponent	0.1	0.09–0.11	Slope of drug effect	20.9	18.4–23.7

ALAG, absorption lag time; CL, clearance; CL/F, apparent clearance; F1, bio-availability; KA, absorption rate; PD, pharmacodynamic; PK, pharmacokinetic; Q, intercompartmental clearance; $t_{1/2}$, half-life of circulating B cells; V2/F, apparent central volume of distribution; V3, peripheral volume of distribution.

400 mg. Bio-availability had a nonlinear relationship with venetoclax dose, as observed earlier.[26] The estimated PK parameters, the effect of the covariates, and their associated variability for the PK model are listed in **Table 2**. Food (47% higher bio-availability with a moderate/high-fat meal and 71% lower bio-availability under fasting conditions, relative to a low-fat meal), coadministration of azithromycin (35% lower bio-availability) or rifampin (167% higher clearance and 391% higher bioavailability), and Chinese ethnicity (53% higher bio-availability) were significant covariates. The plot of predicted and observed concentrations shows that most values were close to the line of identity (**Figure 2a**), indicating that the model adequately described the observations over the entire venetoclax plasma concentration range. In addition, prediction-corrected visual predictive check (**Figure S1**) reveals that the model can adequately describe the central tendency and variability in the PK data.

PD model
The semimechanistic PD models with a linear drug effect adequately described the exposure–response relationship between venetoclax exposures and the change in B-lymphocyte counts. A maximum effect (E_{max}) drug-effect model was not supported by the data. **Table 2** provides the parameter estimates. The goodness-of-fit plots showed that the model was able to describe the observed data well across its range (**Figure 2a**). The conditional weighted residual plots showed no bias with model-based population predictions (**Figure 2b**).
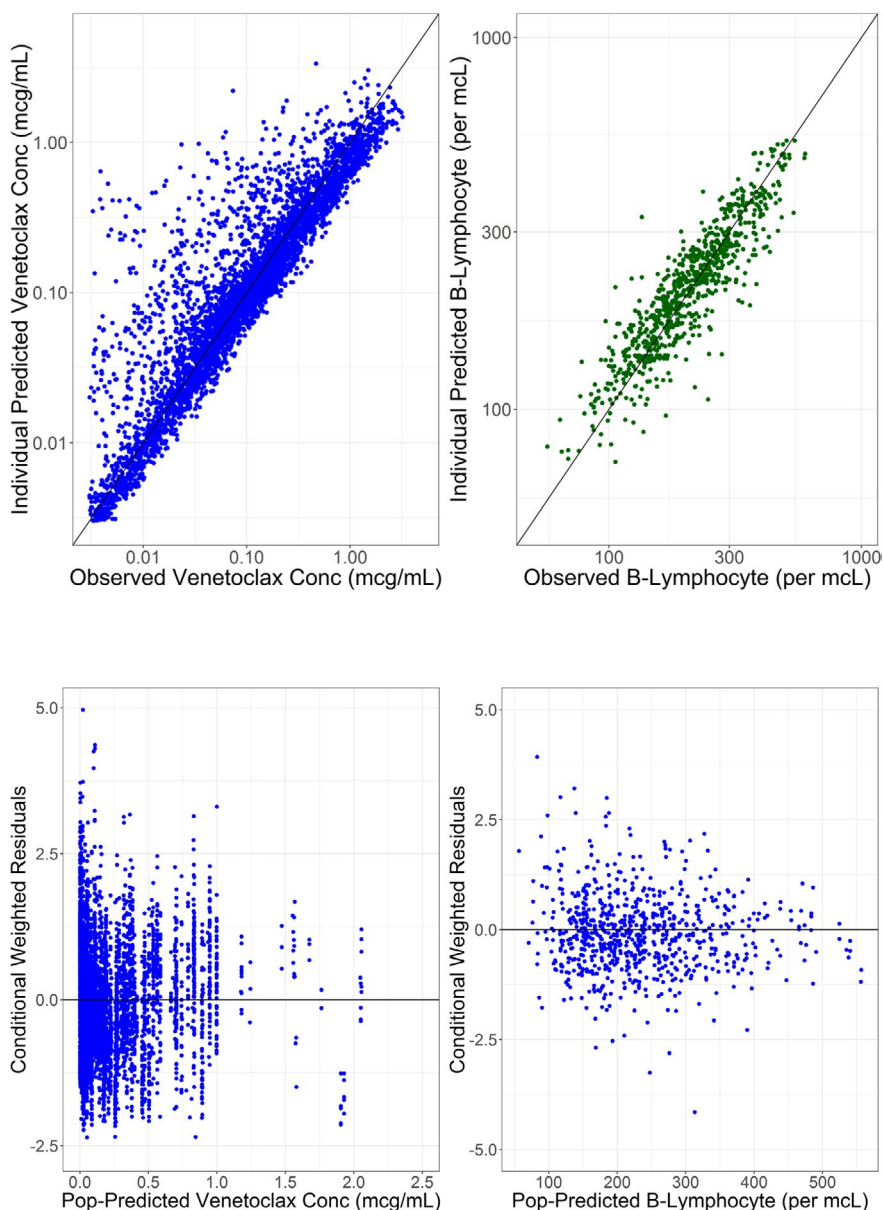
Figure 2 Observed vs. model-predicted venetoclax concentrations and B-lymphocyte counts and conditional weighted residual plots. Conc., concentration; Pop, population.

Simulations of the model indicated a rapid decrease in B-lymphocytes proportional to the exposure of venetoclax. The decrease in B-lymphocytes ranged from 14% (9–23%) for 100 mg venetoclax to 38% (25–54%) for 400 mg venetoclax doses (**Figure 3**). B-lymphocytes recovered to 90% of baseline levels within an average of 48 (21–64) days and 59 (30–66) days, respectively, with 200 and 400 mg single doses (**Figure 4**). Simulations were also carried out for three 200 mg doses of venetoclax every week (7-day washout) or every other week (14-day washout) under moderate/high-fat food conditions. The decrease in B-lymphocytes was 51% (36–67%) and 46% (33–61%) for 200 mg every week and every other week, respectively. In both these situations, the recovery of B-lymphocytes to 90% of baseline levels was within 2 months. The median time courses of B-lymphocytes under different treatment regimens (**Figure 5**) also show the decrease and subsequent recovery of B-lymphocytes for different venetoclax dosing regimens.

DISCUSSION

This is the first assessment of the PD effects of venetoclax in healthy subjects and its relationship with its exposures. Previous studies have evaluated the venetoclax exposure response relationships in subjects with CLL, NHL, multiple myeloma, or acute myeloid leukemia.[27–32]

In a study to assess effect of venetoclax on the PKs of warfarin in healthy female subjects, the study was terminated due to the decrease observed in B-lymphocytes.[22] New studies in healthy subjects are needed to address questions of drug–drug interactions and bio-availability. Understanding the impact of venetoclax exposures on B-lymphocytes in healthy subjects will ensure safe dosing of venetoclax in healthy subjects.

The final population PK model has some differences from the model used previously to characterize venetoclax PKs in patients with CLL, patients with NHL, and healthy subjects.[24] The data set consisted of only healthy subjects with no CYP3A modulators or rituximab. Therefore, these previously reported covariates on apparent clearance were removed. In addition, CLL/small lymphocytic lymphoma/NHL (vs. healthy) and female sex (vs. male) covariates on apparent central volume of distribution were also excluded. Because our data set consisted of rich PK data at multiple timepoints for all the subjects, the model fit better by adding a lag in absorption and including the food effect on lag time. For the food effect on bio-availability, a low-fat meal was assigned as the reference category. In addition, Chinese ethnicity and coadministration with azithromycin and rifampin were identified as new covariates. Because rifampin inhibits transporters as well as induces CYP3A, it was found to increase both venetoclax bio-availability and clearance in this analysis. This analysis characterized fully the impact of various factors, such as food conditions, concomitant medications, and ethnicity on venetoclax exposures, which, in turn, impacted the change in B-lymphocyte counts.

B-cells play an important role in humoral immune response, which causes destruction of extracellular micro-organisms and prevents the start and spread of intracellular infections.[33] Reduction in B lymphocytes is associated with immune cytopenias, splenomegaly, granulomatous disease, and lymphadenopathy.[34] B-cell counts lower than 50 cells/µL are associated with increased risk of infections and mortality as well as poor vaccine responses.[35] Our exposure–response analyses show that the decrease in B-lymphocytes ranged from 14% for 100 mg venetoclax to 38% for 400 mg venetoclax under moderate/high-fat meal conditions. To avoid the B-cell count from falling below 50 cells/µL, healthy subjects enrolled in venetoclax studies should have a B-lymphocytes baseline of ≥150 cells/µL. With the baseline B-lymphocytes values of ≥150 cells/µL, we can administer up to 400 mg under fasting or low or moderate fat conditions, or 200 mg under high-fat conditions. Simulations of repeated doses of 200 mg venetoclax under high-fat meal
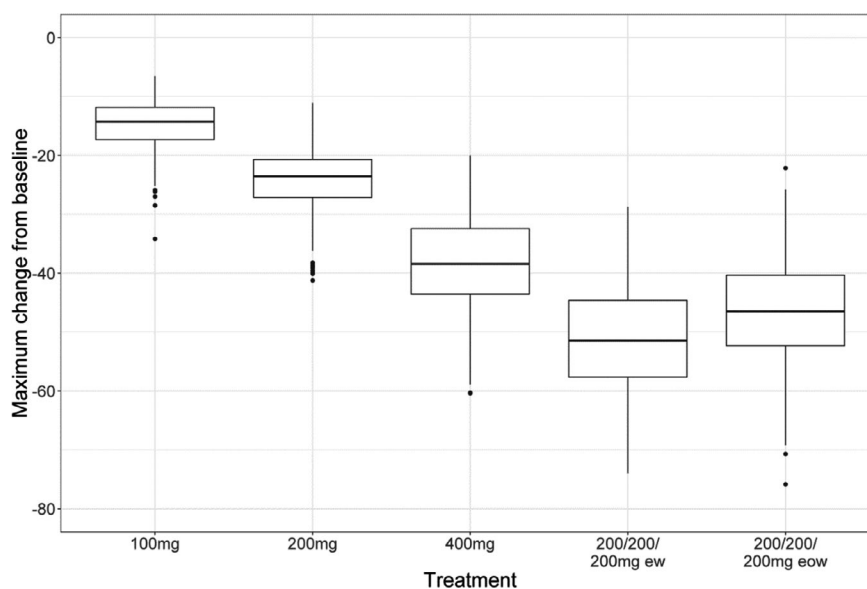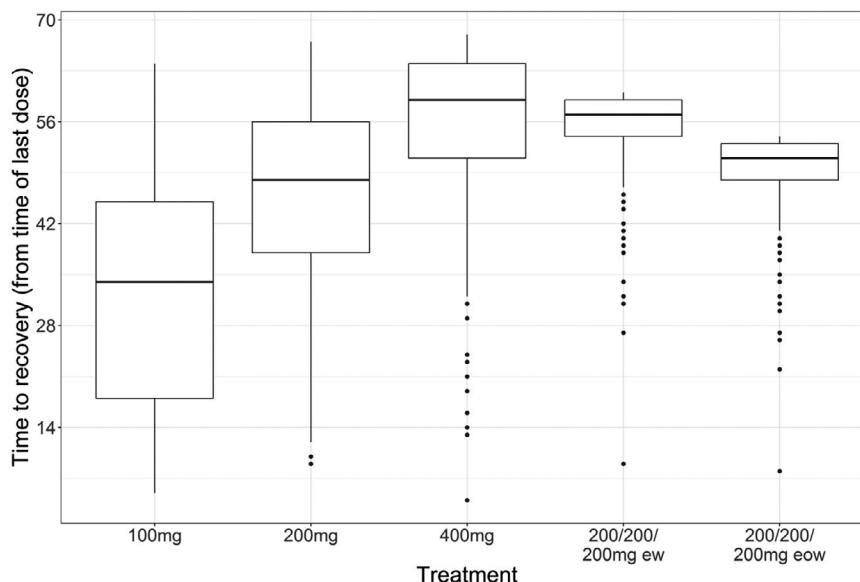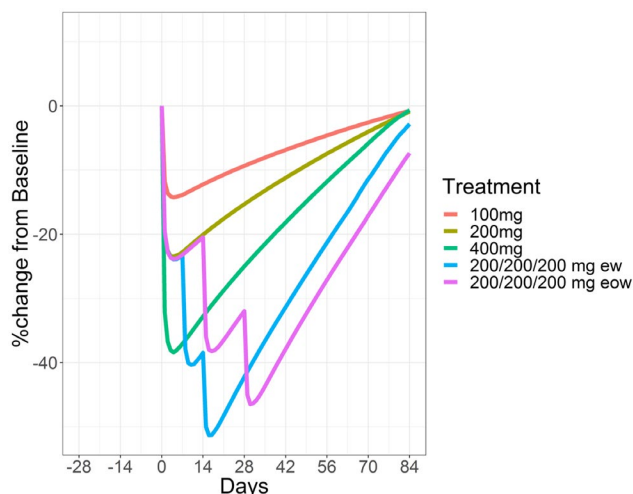

Figure 3 Percentage decrease in B-lymphocyte counts. ew, every week; eow, every other week.

Figure 4 Time for B-lymphocytes to get back to at least 90% baseline. ew, every week; eow, every other week.

Figure 5 Time course of B-lymphocytes in healthy subjects with different venetoclax dosing regimens. ew, every week; eow, every other week.

conditions with 7-day or 14-day washouts showed 51% and 46% changes from baseline, respectively. Prolonging the washout between periods in future studies beyond 1 week is not deemed necessary.

When B-cells are severely depleted from the secondary lymphoid tissue for an extended time, cognate T-cell help gets hampered, which, in turn, impairs response secretion of cytokines and activation of B-cells.[36] However, timely restoration of the B-cell compartment may be sufficient for a normal humoral immune response.[37] Treatment with rituximab in patients with rheumatoid arthritis has shown rapid reduction in B cells from circulation within 1–28 weeks post-infusion, and the B-cell counts returned to normal levels within 8 weeks to 18 months in most patients.[38] Humoral response to the influenza vaccine has been shown to be severely hampered in patients with rheumatoid arthritis receiving rituximab due to depletion of B-cells as compared with healthy controls.[39] Venetoclax, similar to rituximab, causes rapid depletion in B-cells. However, as shown in our simulations/observed data, the B-cell count raise back to the baselines within 2–3 months, and, therefore, is unlikely to impact the humoral response as seen with rituximab.

CONCLUSIONS

Based on the exposure–response analyses described here, the decrease in B-lymphocytes ranged from 14% (9–23%) for 100 mg venetoclax to 38% (25–54%) for 400 mg venetoclax doses and the simulations of repeated doses of 200 mg venetoclax under high-fat meal conditions with 7-day or 14-day washouts showed 51% (36–67%) and 46% (33–61%) changes from baseline, respectively. The B-cell count recovered to 90% of baseline within 2 months even at the 400 mg dose of venetoclax and, therefore, is unlikely to impact the humoral response. To avoid the B-cell count from falling below 50 cells/µL, healthy female subjects enrolled in venetoclax studies should have a B-lymphocytes baseline of ≥150 cells/µL. Dosing of venetoclax in healthy volunteers rather than oncology patients saves both time and resources and can thereby accelerate drug development.

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