Cumulative review of hypertension in patients with chronic lymphocytic leukemia treated with acalabrutinib

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell malignancy predominantly affecting older adults.[1,2] Comorbid cardiovascular disease in patients with CLL/SLL is correlated with higher mortality,[3] with hypertension among the most commonly occurring.[1]

Bruton tyrosine kinase (BTK) inhibitors have been associated with cardiovascular toxicities, including hypertension.[4] Acalabrutinib is a second-generation BTK inhibitor that has less off-target kinase inhibition than ibrutinib and zanubrutinib.[5] In the phase III ELEVATE-RR study, hypertension was less frequent with acalabrutinib (9.4%) *versus* ibrutinib (23.2%).[6] To more comprehensively compare hypertension rates with acalabrutinib *versus* other comparators, we performed a cumulative analysis of hypertension incidence and prevalence in patients with CLL/SLL in the acalabrutinib clinical trial database. We also analyzed hypertension prevalence before treatment initiation from claims data to provide a background hypertension rate from an untreated CLL/SLL population.

Patients with CLL/SLL who were treated with acalabrutinib with or without obinutuzumab and enrolled in one of six clinical trials within the acalabrutinib clinical database were included (phase I-II clinical trials: 15-H-0016, CL-001, CL-003; phase III clinical trials: ELEVATE-RR, ELEVATE-TN, ASCEND; *clinicaltrials gov. Identifer: NCT02337829, NCT02029443, NCT02296918, NCT02477696, NCT02475681, NCT02970318; Online Supplementary Table S1)*. All patients had CLL/SLL requiring treatment and had treatment-naive (TN) or relapsed/refractory (R/R) disease. Details regarding study populations and acalabrutinib dosing were previously published.[6-12] Because phase I-II clinical trials were included, acalabrutinib was administered at total daily doses ranging from 100-400 mg; most patients in this analysis (>75%) received 100 mg twice daily. Treatment continued until progressive disease or toxicity. Comparator data included ibrutinib from ELEVATE-RR and other comparators, including obinutuzumab + chlorambucil from ELEVATE-TN and idelalisib + rituximab or bendamustine + rituximab from ASCEND; details on comparator dosing were also previously published.[6,11,12]

Data from patients with TN CLL/SLL from three fully adjudicated closed claims databases (Optum, MarketScan, IQVIA) were analyzed. The studies used in this analysis were conducted in accordance with the consensus ethical principles derived from international guidelines. Study protocols were approved by the institutional review boards. All patients provided written informed consent.

In the clinical database analysis, hypertension events and related preferred terms were defined using the “hypertension” narrow Standardized MedDRA Query per Medical Dictionary for Regulatory Activities (MedDRA) v25.1, which included new and worsening hypertension. New and worsening hypertension events were defined as treatment-emergent hypertension events among patients without and with past medical history (PMH) of hypertension, respectively. Hypertension prevalence was assessed at median treatment exposure, and exposure-adjusted incidence rate was measured in events/100 person-years per the following formula:

$$\text{exposure-adjusted incidence} = \frac{(N \times 100)}{(\Sigma_i\ t_i)}$$

in which N is the number of events in the treatment arm, t_i is the duration of the treatment-emergent period (in years) for the patient i, and Σ_i is the sum across all patients in the treatment arm.

To provide a background prevalence, hypertension prevalence based on ICD-9 and ICD-10 codes was assessed in patients from the claims databases within 6 months prior to CLL/SLL treatment initiation.

In total, 1,756 patients (TN CLL/SLL, N=660; R/R CLL/SLL, N=1,096) from the clinical trial database were included; 947 (53.9%) received acalabrutinib monotherapy, 223 (12.7%) received acalabrutinib + obinutuzumab, 264 (15.0%) received ibrutinib as a comparator (from ELEVATE-RR), and 322 (18.3%) received other comparators (obinutuzumab + chlorambucil in ELEVATE-TN; idelalisib + rituximab or bendamustine + rituximab in ASCEND). Demographics and baseline characteristics were similar between treatment groups. PMH of hypertension was documented in 54.2% of patients treated with acalabrutinib monotherapy, 65.9% treated with acalabrutinib + obinutuzumab, 48.5% treated with ibrutinib, and 59.9% treated with other comparators (*Online Supplementary Table S2*).

Data from a total of 24,025 patients were analyzed from the claims databases, 9,149 from Optum, 4,058 from MarketScan, and 10,818 from IQVIA.

Hypertension prevalence among the 24,025 patients with TN CLL/SLL prior to treatment initiation included in the three claims databases ranged from 47.3-66.1% (Figure 1A). In the clinical trial data, hypertension prevalence during treatment was 59.6% in the 947 patients treated with acalabrutinib monotherapy (median treatment exposure: 47.3 months) and 70.0% in the 223 patients treated with acalabrutinib + obinutuzumab (median treatment exposure: 59.4 months) (Figure 1B).

Among the 1,756 patients included in the clinical trial database, 270 (15.4%) experienced a treatment-emergent adverse event (new or worsening) of hypertension. Among

the 147 patients treated with acalabrutinib monotherapy who experienced hypertension, median age was 65 years, 66.0% were male, and 59.9% had hypertension at the time of acalabrutinib initiation (*Online Supplementary Table S3*). The exposure-adjusted incidence rate of hypertension (any grade) was 4.205 in the 947 patients treated with acalabrutinib monotherapy, 3.926 in the 223 patients treated with acalabrutinib + obinutuzumab, 8.590 in the 264 patients treated with ibrutinib, and 4.788 in patients treated with other comparators (Table 1). A similar trend was observed for the exposure-adjusted incidence rate of grade ≥3 hypertension. The exposure-adjusted incidence rate of new-onset hypertension (any grade) was 3.718 in the 434 patients treated with acalabrutinib monotherapy, 2.620 in the 76 patients treated with acalabrutinib + obinutuzumab, 9.056 in the 136 patients treated with ibrutinib, and 4.746 in the 129 patients treated with other comparators (Figure 2). The exposure-adjusted incidence rate of new-onset grade ≥3 hypertension was low with acalabrutinib monotherapy (0.504) and acalabrutinib + obinutuzumab (0.291); the rate with ibrutinib was 2.145. In patients with a PMH of hypertension, the exposure-adjusted incidence rate of worsening hypertension was similar among most treatment groups, but was relatively higher with ibrutinib (Figure 2). Among patients with new-onset hypertension, 2.7% (N=4) treated with acalabrutinib monotherapy and 0 treated with acalabrutinib + obinutuzumab required new concomitant antihypertensives. Among patients with worsening hypertension, 6.8% (N=10) treated with acalabrutinib monotherapy and 5.1% (N=2) treated with acalabrutinib + obinutuzumab required new concomitant antihypertensives. No patients discontinued acalabrutinib treatment due to hypertension; four patients (2.7%) with worsening hypertension in the acalabrutinib monotherapy group had their dose temporarily withheld, and one patient (2.6%) with worsening hypertension in the acalabrutinib + obinutuzumab group had their dose reduced.

The exposure-adjusted incidence rates of the most common hypertension preferred terms are provided in Table 1. In a subgroup analysis of patients from ELEVATE-RR, the exposure-adjusted incidence rate of any-grade hypertension in patients treated with acalabrutinib (3.053) was 2.8-fold lower than that reported in patients treated with ibrutinib (8.590) and similarly lower for grade ≥3 events (1.200 *vs.* 3.146).

Based on our analysis of patients with CLL/SLL from large claims databases, hypertension is common, with hypertension prevalence prior to treatment initiation for

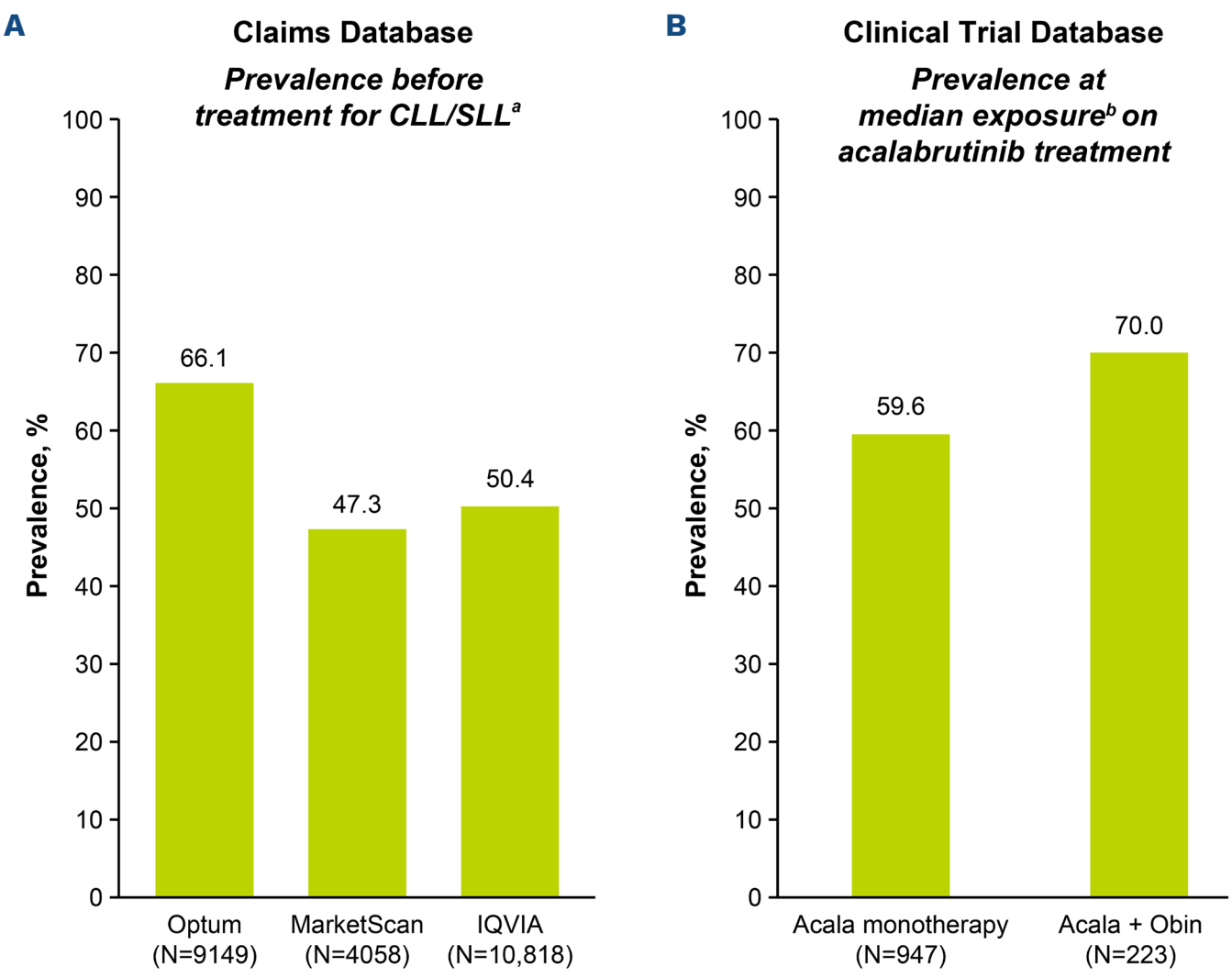

Figure 1. Hypertension prevalence in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. (A) Prevalence of hypertension in patients before the start of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treatment in the claims database. (B) Prevalence of hypertension in patients treated with acalabrutinib (acala) in the clinical trial database. [a]Proportion of CLL/SLL patients with hypertension diagnosis who were within 6 months of initiating treatment for CLL/SLL. [b]Median treatment exposure of 47.3 months for acala monotherapy and 59.4 months for acala + obinutuzumab (obin).

CLL/SLL ranging from 47.3-66.1%. In patients treated with acalabrutinib from the clinical trial database, on-treatment hypertension prevalence was 59.6%. Similarly, previous clinical trial data analyses have shown that a number of patients with CLL/SLL develop new or worsening hypertension during an observation period regardless of treatment.[13] In the CLL12 study, a study of early intervention in patients with asymptomatic CLL, the event rate of new or worsening hypertension in patients assigned to the placebo arm was 8.3% at a median follow-up of 69.3 months.[13] In the ELEVATE-TN study, among patients with TN CLL treated with acalabrutinib monotherapy, 8.9% experienced hypertension at a median follow-up of 58.2 months.[14]

Our results suggest *de novo* hypertension (9.056) is more frequent than worsening hypertension (8.109) in patients treated with ibrutinib. These findings may have implications for clinical practice, as increased surveillance for *de novo* hypertension development should be implemented in the management of patients receiving ibrutinib, particularly as hypertension management may differ based on whether the patient has pre-existing hypertension or develops *de novo* hypertension.[15]

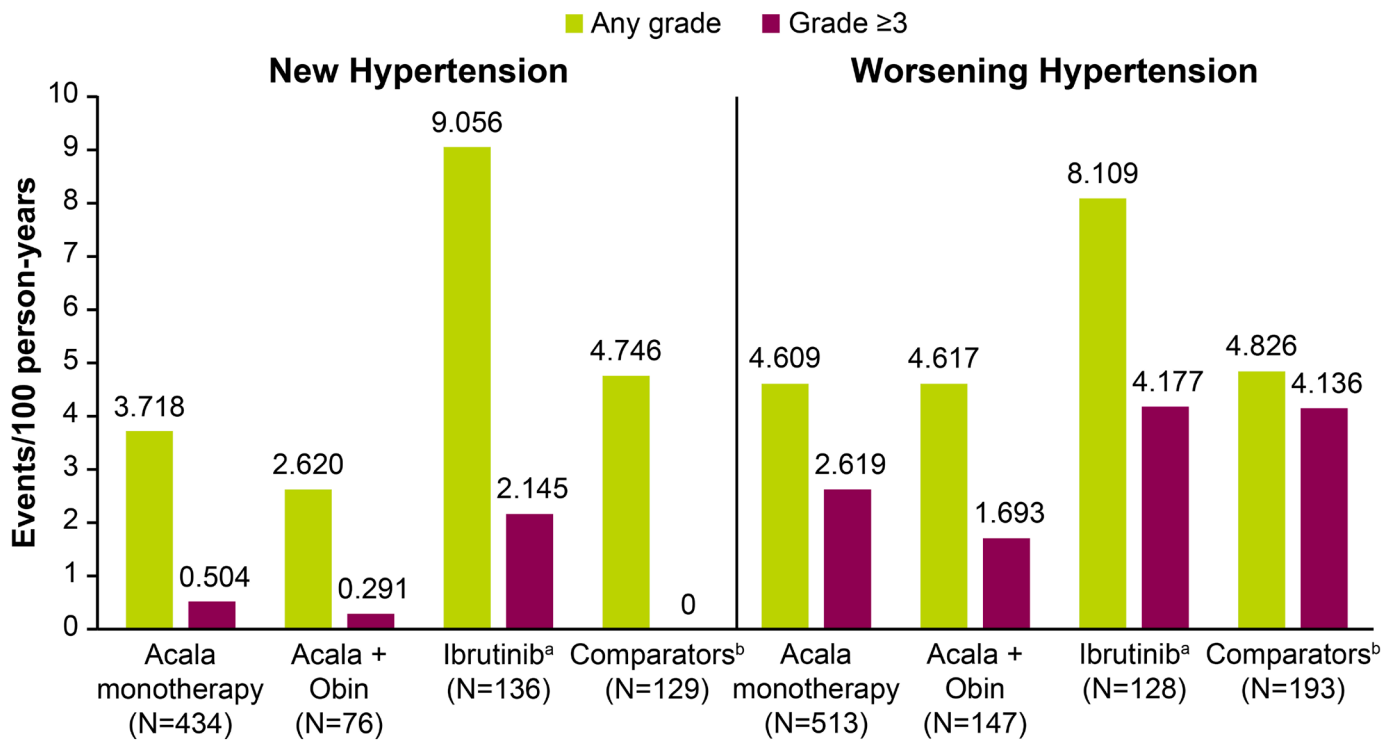

Figure 2. Exposure-adjusted incidence rate of new and worsening hypertension in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma according to treatment. Exposure-adjusted incidence rate of new and worsening hypertension in the subset of patients without and with prior history of hypertension, respectively. [a]Patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) from ELEVATE-RR. [b]Patients with CLL treated with obinutuzumab (obin) + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND). Acala: acalabrutinib; Obin: obinutuzumab.

Table 1. Exposure-adjusted incidence rates of "hypertension" standardized MedDRA query (narrow) by preferred terms.

Hypertension, events/100 person-years	Acalabrutinib monotherapy N=947		Acalabrutinib + obinutuzumab N=223		Ibrutinib[a] N=264		Comparators[b] N=322	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
"Hypertension" SMQ (narrow)	4.205	1.659	3.926	1.208	8.590	3.146	4.788	2.210
Blood pressure increased	0.114	0.029	0	0	0.363	0.242	0	0
Blood pressure systolic increased	0	0	0	0	0.121	0	0	0
Essential hypertension	0.029	0.029	0	0	0	0	0	0
Hypertension	4.005	1.573	3.826	1.208	8.469	3.025	4.788	2.210
Hypertensive crisis	0.029	0	0.101	0	0	0	0	0
Hypertensive heart disease	0	0	0.101	0	0	0	0	0
Malignant hypertension	0.029	0.029	0	0	0	0	0	0

[a]Patients with relapsed/refractory chronic lymphocytic leukemia (CLL) from ELEVATE-RR. [b]Patients with CLL treated with obinutuzumab + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND). MedDRA: Medical Dictionary for Regulatory Activities; SMQ: standardized MedDRA query.

Our results are consistent with previously reported safety data in patients treated with acalabrutinib. In an analysis of ELEVATE-RR, exposure-adjusted incidence rate (events per 100 person-months) of hypertension as a selected event of clinical interest (as defined by MedDRA v23.0) was 3 times higher with ibrutinib (1.2) than with acalabrutinib (0.4) for any-grade events and four times higher with ibrutinib (0.4) than with acalabrutinib (0.1) for grade ≥3 events.[16]

A limitation of this analysis is that the six clinical studies were not designed to detect differences in hypertension rates between treatment groups; therefore, no statistical comparisons were performed. The analysis was also not designed to provide statistically valid cross-trial comparisons. In addition, a small number of patients treated with acalabrutinib monotherapy did not receive the 100 mg twice-daily dosing because some included studies started before the dose was standardized. Another limitation is that the reporting of hypertension prevalence rates prior to treatment provided by claims databases is dependent on ICD-9 and ICD-10 codes used to define hypertension, and therefore may be influenced by possible cases of errors or omission in coding. However, the purpose of using these claims data was to provide a background rate of hypertension in patients with CLL/SLL prior to treatment initiation, not to provide comparisons with clinical trial data. Lastly, our analysis does not explore the mechanisms behind BTK inhibitor-induced hypertension, which are not well understood.

In summary, exposure-adjusted incidence rates of new or worsening hypertension in patients with CLL/SLL receiving treatment with acalabrutinib monotherapy and acalabrutinib + obinutuzumab in this analysis were low overall. Our analysis suggests that acalabrutinib monotherapy does not worsen pre-existing hypertension or increase the risk of new-onset hypertension in patients with CLL/SLL.

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Disclosures

AF has served on an advisory board for AbbVie, AstraZeneca, BeiGene, Genentech, and Janssen; has received research support to her institution from AbbVie, AstraZeneca, BeiGene, Eli-Lilly, and GenMab. GF has served on an advisory board for and was paid for lectures by AstraZeneca, BeiGene, AbbVie, Janssen, Lilly, and Takeda. YM, JR, NB, VM, KN, PM, DP are employees and stock shareholders of AstraZeneca. KP has provided consulting/advisory work for AbbVie, Adaptive, ADC, AstraZeneca, BeiGene, BMS, Caribou, Fate Therapeutics, Genentech/Roche, Janssen/Pharmacyclics, Kite, Lily/Loxo, Merck, MorphoSys, Sana, and Xencor; has received research funding (to institution) from AbbVie, Adaptive, Adicet, AstraZeneca, BMS, Caribou, Century, CRISPR, Fate Therapeutics, Genentech/Roche, Janssen/Pharmacyclics, Kite, Lily/Loxo, Merck, Nurix, Sana, and Xencor.

Contributions

Study design by AF, YM, JR and NB. AF, GF and KP were the main study investigators. AF, GF and KP enrolled patients. YM, NB and VM collected and assembled data. Data analysis was performed by AF, YM, JR, NB and PM. Data interpretation, manuscript preparation, manuscript review and revisions were performed by all authors. All authors approved the final version of the manuscript.

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Data-sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at please embed the hyperlink in the entire URL; it should read https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/ AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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