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Expert opinion on use of acalabrutinib for chronic lymphocytic leukemia treatment

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Abstract

Bruton's tyrosine kinase inhibitors (BTKis) have become one of the most vital drugs in the treatment of patients with chronic lymphocytic leukemia (CLL). BTKis are currently a well-established therapy for treatment-naïve, as well as relapsed or refractory, cases. BTKis have been shown to be crucial in the treatment of high-risk CLL patients bearing *TP53* aberrations or characterized by the unmutated status of the immunoglobulin heavy-chain variable region (*IGHV*) gene. Ibrutinib was the first-in-class BTK inhibitor; however, despite its therapeutic potential, it is also characterized by specific adverse events, including hypertension, increased bleeding risk, cardiac toxicity, and skin changes. Although the next generation of BTKis was shown to be more specific, this adverse event profile is regarded currently as class-specific. In this review, we discuss the current status of acalabrutinib, a second-generation BTKi.

Keywords: Bruton's tyrosine kinase inhibitor, ibrutinib, acalabrutinib, chronic lymphocytic leukemia

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Introduction

Chronic lymphocytic leukemia (CLL) is an indolent, mature lymphoproliferative malignancy characterized by a progressive accumulation of monoclonal and dysfunctional B lymphocytes. Most CLL patients are elderly, with a median age at diagnosis of 72 years [1–3]. Bruton's tyrosine kinase (BTK) inhibitors have become one of the most vital drugs in treating CLL patients. BTK inhibitors (BTKis) are currently a well-established therapy for treatment-naïve (TN), as well as relapsed or refractory (RR), cases. BTKis have been shown to be crucial in treating high-risk CLL patients bearing *TP53* aberrations or characterized by the unmutated status of the immunoglobulin heavy-chain variable region (*IGHV*) gene [1]. Ibrutinib was the first-in-class BTKi; however, despite its therapeutic potential, it is also characterized by a specific adverse event profile comprising *inter alia* increased bleeding risk and cardiac toxicity (mainly hypertension and atrial fibrillation). Although

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the next generation of BTKi was shown to be more specific, this adverse event (AE) profile is currently regarded as class-specific [4].

Currently, there are three covalent BTKis reimbursed in Poland. All of them (ibrutinib, acalabrutinib, and zanubrutinib) can be used for the treatment of TN as well as RR CLL patients. Ibrutinib, combined with venetoclax, may also be used to treat TN CLL [1]. This therapeutic option is currently (April 2024) reimbursed in Poland. In randomized clinical trials, the abovenamed BTKi showed remarkable activity in TN and RR CLL patients. In the RESONATE-2 trial, ibrutinib significantly improved response rates, overall survival (OS), and progression-free survival (PFS) compared to chlorambucil in TN CLL patients [5]. Moreover, after a median follow-up of eight years, median PFS in the ibrutinib arm was not reached [5]. The RESONATE phase III trial compared ibrutinib to ofatumumab in patients with RR CLL. With a median follow-up of 65.3 months, median PFS was significantly longer in the ibrutinib vs. the ofatumumab arm (44.1 vs. 8.0 months) [6]. The first registered second class BTKi acalabrutinib, with or without the addition of obinutuzumab, demonstrated remarkable efficacy in TN CLL in the ELEVETE-TN trial (Table I). After a median follow-up of 74.5 months, median PFS was not reached or was significantly longer with acalabrutinib monotherapy or acalabrutinib-obinutuzumab compared to obinutuzumab-chlorambucil [7, 8]. Acalabrutinib was also studied in two randomized clinical trials in the RR setting. In the ASCEND trial, patients were treated with acalabrutinib or a therapy chosen by the investigators (idelalisib-rituximab or bendamustine-rituximab). After a median follow-up of 46.5 months for acalabrutinib patients and 45.3 months for patients in the control arm, acalabrutinib showed significantly better PFS as opposed to the comparator arm (not reached vs. 16.8 months) [9]. The ELEVETE-RR trial was a head-to-head study comparing acalabrutinib and ibrutinib in high-risk RR CLL. This trial showed that although no significant differences were noted regarding PFS between both BTKis, patients treated with acalabrutinib experienced fewer cardiovascular events [10, 11].

Zanubrutinib is another second-generation covalent BTK inhibitor that has shown high effectiveness in TN and RR CLL patients. In the SEQUOIA trial, the efficacy of a zanubrutinib regimen was compared to that of a bendamustine-rituximab regimen in previously untreated CLL patients. The estimated 42-month PFS rate reached 82.4% in the zanubrutinib group and 50.0% in the control group [12, 13]. As patients with aberration in *TP53* are refractory to bendamustine-rituximab, the SEQUOIA study included a nonrandomized cohort of 'high-risk' CLL patients with del(17p) treated with zanubrutinib monotherapy (Arm C). In this cohort, the estimated 18-month PFS and OS rates were 88.6% and 95.5%, respectively [14]. The ALPINE phase III trial compared head-to-head zanubrutinib to ibrutinib treatment in RR CLL patients. Zanubrutinib was superior regarding PFS and overall response rate (ORR) [15]. As stated above, all of the mentioned covalent BTKis enable durable responses in previously untreated and treated patients.

Taking into account the subtle differences between these compounds in terms of efficacy, in this review we discuss in more detail the current status of a second-generation BTK inhibitor, acalabrutinib, regarding adverse event profile and safety management.

Mechanism of adverse events during BTKi therapy

BTKis are generally better tolerated than chemotherapy-based regimens. However, these oral agents are associated with a unique AE profile that includes varying rates of rash, diarrhea, musculoskeletal events, fatigue, bruising/bleeding, infections, cytopenia, and cardiovascular events, particularly atrial fibrillation. Although these AEs are not usually life-threatening, they can distress patients and even lead to treatment discontinuation [16–18]. Mediated by both on-target inhibition of BTK and variable off-target inhibition of other kinases, the toxicity profile of BTKis is closely linked to their pattern of kinase binding. Some of these AEs are thought to result from off-target inhibition of protein kinases and show a trend for decreased incidence with more selective second-generation BTK inhibitors compared to ibrutinib.

Ibrutinib irreversibly binds other kinases including interleukin-2-inducible T-cell kinase (ITK), tyrosine-protein kinase (TEC), and endothelial growth factor receptor (EGFR) [17, 19–23]. These off-target effects influence the AE profile associated with ibrutinib therapy [17]. Rash and diarrhea are attributable to the impact on epidermal growth factor receptor (EGFR), bleeding is possibly related to the effects on BTK and TEC, while the development of atrial fibrillation is caused by the impact of ibrutinib on C-terminal Src kinase (CSK) [24].

Safety profile of acalabrutinib vs. ibrutinib therapy

Acalabrutinib demonstrates reduced off-target activity, rapid absorption, and a short pharmacokinetic half-life [19, 25, 26]. An advantage of a short half-life is that there is no lasting impact on noncovalently bound enzymes [19]. The selectivity of acalabrutinib is thought to be associated with the lower intrinsic reactivity of its butynamide group that binds to C481 in BTK. Off-target kinases such as EGFR, ITK, ERB-B2 receptor tyrosine kinase and B lymphocyte kinase are not inhibited by acalabrutinib [22, 23, 25, 27]. Other important off-target kinases, particularly the TEC family, are inhibited by acalabrutinib *in vitro* only at high nanomolar concentrations [22, 23]. The impact

Table I. Key efficacy and safety data of randomized phase III clinical trials of acalabrutinib in treatment-naïve and relapse-refractory patients with chronic lymphocytic leukemia

Study name	Treatment arms	Median duration of treatment	Median duration of follow-up	Efficacy analysis		Safety analysis
				Median PFS	ORR	Most common AEs reported with A in ≥20% patients (any grade)
ACE-CL-007 Phase III (6 years follow-up)	A+O (n = 178) A (n = 179) O+Clb (n=177)	–	74.5 months	A+O – NR A – NR O+Clb – 27.8 months	A+O – 96% A – 90% O+Clb – 83%	A+O arm Diarrhea (43.8%) Headache (40.4%) Arthralgia (36%) Neutropenia (34.3%) Fatigue (30.9%)
ACE-CL-007 Phase III (6 years follow-up)	A+O (n = 178) A (n = 179) O+Clb (n = 177)	–	74.5 months	A+O – NR A – NR O+Clb – 27.8 months	A+O – 96% A – 90% O+Clb – 83%	A arm Diarrhea (42.5%) Headache (39.1%) Arthralgia (27.4%) Cough (25.1%) Fatigue (24%)
ASCEND (ACE-CL-309) Phase III	A (n = 155) IdR/BR (n = 155); [IdR (n = 119) BR (n = 36)]	46.5 months	46.5 months	Investigator--assessed PFS: Acalabrutinib NR vs. IdR/BR – 16.8 months	Acalabrutinib – 83% vs. IdR/BR – 84%	Neutropenia: 24% Headache: 23% Diarrhea: 21% URTI: 20%
ELEVATE-RR (ACE-CL-006) Phase III	A (n = 268) I (n = 265)	38.3 months	40.9 months	Non-inferiority on IRC-assessed PFS: acalabrutinib – 38.4 months vs. ibrutinib – 38.4 months	–	Diarrhea: 37% Headache: 35% Cough: 29% URTI: 27% Neutropenia: 21%

A – acalabrutinib; A+O – acalabrutinib+obinutuzumab; BR – bendamustine-rituximab; IdR – idelalisib-rituximab; I – ibrutinib; IRC – independent review committee; NR – not reached; O+Clb – obinutuzumab-chlorambucil; ORR – overall response rate; PFS – progression-free survival; URTI – upper respiratory tract infections

of this selectivity of acalabrutinib on safety profile has been confirmed in clinical trials.

Awan et al. showed that acalabrutinib was well-tolerated and effective in ibrutinib-intolerant CLL patients (n = 33) [17]. In this cohort, there were two cases of treatment-emergent atrial fibrillation (AF), but both patients continued therapy. Importantly, only three patients discontinued therapy with acalabrutinib due to adverse events (AEs) [17]. Similar results were revealed in a phase II study of acalabrutinib in a group of 60 ibrutinib-intolerant patients with RR CLL who discontinued therapy due to severe AEs (grade 3/4) (ACE-CL-208; NCT02717611) [28]. At a median follow-up of 23 months, 62% of patients remained on acalabrutinib; the ORR was 77% [28]. These findings supported the real-world use of acalabrutinib following ibrutinib intolerance. After five months of follow-up, ORR was 62%, and discontinuation rate due to AEs similar to those reported by Awan et al. [17, 29].

The ELEVATE-RR study compared head-to-head acalabrutinib to ibrutinib in patients with RR CLL/SLL with high-risk cytogenetic features (deletion of chromosome 17p or deletion of chromosome 11q), providing a direct comparison between these two agents [10, 11]. At the data cut-off for the final analysis, the median follow-up was 40.9 months (range = 0.0–59.1). Median progression-free survival was 38.4 months (95% CI = 33.0–38.6 months) in the acalabrutinib group vs. 38.4 months (95% CI = 33.0–41.6 months) in the ibrutinib group (HR = 1.00, 95% CI = 0.79–1.27) thus meeting the noninferiority criterion. Among common AEs, incidences of any-grade diarrhea, arthralgia, urinary tract infection, back pain, muscle spasms, and dyspepsia were higher with ibrutinib, with 1.5-fold to 4.1-fold higher exposure-adjusted incidence rates [10]. Incidences of headache and cough were observed more often in the acalabrutinib arm, with 1.6- and 1.2-fold higher exposure-adjusted incidence rates, respectively. Overall, incidences of

cardiac events and infections were similar between arms. The incidences of any-grade atrial fibrillation/flutter, hypertension, and bleeding were higher with ibrutinib, as were exposure-adjusted incidence rates (2.0-, 2.8-, and 1.6-fold, respectively). Rate of discontinuation because of AEs was lower for acalabrutinib (hazard ratio, 0.62; 95% confidence interval, 0.41–0.93). AE burden score was higher for overall ibrutinib vs. acalabrutinib and atrial fibrillation/flutter, hypertension, and bleeding [10]. Worthy of mention are the recently published observations from five acalabrutinib clinical trials, where the incidence of sudden deaths (SDs) and both fatal and non-fatal ventricular arrhythmias (VAs) were examined in this analysis. Acalabrutinib was administered to 1,299 patients (exposure, 4,568.4 patient-years). VAs or SDs were experienced by 16 patients (1.2%) (event rate: 0.350/100 patient-years). Eleven (0.8%) individuals experienced non-fatal VAs, with nine (0.7%) of them experiencing merely premature ventricular contractions. There were five patients (0.4%) who experienced SD and fatal VAs (event rate: 0.109/100 patient-years; median time to event: 46.2 months) [30]. This data underscores that acalabrutinib poses a minimal risk of inducing AF or fatal VA.

The use of acalabrutinib in the setting of previous exposure of patients to BTKi and BCL2 antagonists has so far not been reported, and the data is limited. However, it is possible to exert some effectiveness when used following BCL2 antagonist treatment and a reason for BTKi discontinuation (progression vs. intolerance) [31].

Matching-adjusted indirect comparison (MAIC) of safety and efficacy of acalabrutinib and zanubrutinib

Currently, there are no head-to-head clinical trials between acalabrutinib and zanubrutinib comparing efficacy and safety. A matching-adjusted indirect comparison (MAIC) is an established method for indirectly comparing the treatment effects of different therapies. MAIC uses weighting of individual patient-level data from trials of one treatment to match the aggregated baseline data population of trials from another treatment. Recently, MAIC analysis was performed comparing the efficacy and safety of both second-generation covalent BTKis in patients with TN and RR CLL. Previously untreated CLL population for MAIC analysis included patients treated in phase III clinical trials i.e. ELEVATE-TN and SEQUOIA. A comparison of acalabrutinib +/– obinutuzumab and zanubrutinib therapy did not imply superior safety and efficacy of one drug over the other [32]. In a population of RR CLL patients, an anchored comparison of ELEVATE-RR and ALPINE could not be used due to significant population differences in del(17p) and del(11q) mutations and in patient characteristics [33]. Therefore, an unanchored MAIC was used to compare the efficacy and safety of second-generation BTKi treatment between ASCEND and ALPINE, as the patient characteristics of these studies were more comparable. In the MAIC, the PFS for acalabrutinib and zanubrutinib monotherapy were similar in RR CLL patients after matching patient baseline characteristics. The safety profiles of both BTKi were comparable; however, the risk of any grade hemorrhage (OR 0.54; 95% CI 0.34–0.87) and hypertension (OR 0.18; 95% CI 0.086–0.37) was lower with acalabrutinib compared to zanubrutinib [33]. Moreover, the risk of a serious AE was lower with acalabrutinib compared to zanubrutinib (OR 0.61; 95% CI 0.39–0.97). However, these findings should be confirmed in further head-to-head clinical trials.

Management before and during therapy with BTKi

Before initiating BTKi therapy, it is crucial to carefully consider each patient's clinical history. Baseline medical history must be taken, including recent surgery/plans for surgery; history of cardiac arrhythmias; hypertension; infections (including the history of hepatitis B virus infection); and current medications, including prescription, over-the-counter medicines, and, importantly, herbs and supplements. BTKi is not recommended for patients with severe or uncontrolled congestive heart failure (left ventricular ejection fraction [LVEF] <30%), a history of ventricular arrhythmia, severe, uncontrolled hypertension, and/or a family history of sudden cardiac death [34]. In patients with established cardiovascular disease, such as well-controlled AF, hypertension, heart failure, or valvular heart disease, or who are at risk for developing poorly controlled hypertension or atrial fibrillation, a second-generation BTKi should be preferred over ibrutinib [35]. The pretreatment workup for all patients with a higher risk of cardiac AEs should include a comprehensive patient history and targeted cardiovascular examination, including an electrocardiogram (ECG) and a blood pressure measurement to identify cardiac AEs, including AF and hypertension early, and to implement appropriate management [34].

Patients with a higher bleeding risk might also benefit from acalabrutinib. However, acalabrutinib is associated with a higher risk of headaches and cough. Therefore, patients with a history of migraine or chronic cough who do not have a significant cardiovascular or bleeding risk may experience less debilitating side effects with ibrutinib [34]. Other side effects, including cardiac AEs, should be considered and discussed with the patient. In patients with no significant comorbidities, initiating treatment with any available BTKi in the first-line setting may be most appropriate. BTKi therapy also seems to be the preferred treatment option in cases of underlying mild or moderate kidney disease due to the increased risk of tumor lysis syndrome in venetoclax-based regimens. If ibrutinib is not

well tolerated, consideration can be made to switch to a second-generation BTKi [36].

Although some AEs may occur at a lower frequency with second-generation BTKis, they can still occur. To maximize safety long-term, paying careful attention to patient-reported signs and symptoms observed during therapy is crucial. Continuous monitoring and management of AEs and potential drug interactions over the course of therapy are pivotal for maintaining patient quality of life and optimizing patient outcomes. Long-term AE monitoring and polypharmacy considerations require the involvement of multiple healthcare team members [34, 36, 37].

Unregistered acalabrutinib-based combinations tested in clinical trials

Although acalabrutinib monotherapy or acalabrutinib combined with obinutuzumab combination are approved for the treatment of CLL, clinical trials combining this BTKi with other agents have been performed. A triplet combination of acalabrutinib, venetoclax, and obinutuzumab was tested in a single-arm, open-label phase 2 trial [38]. Following enrollment, 37 patients with CLL received at least one dose of each trial medication. The patients' median age was 63 years. The median follow-up was 27.6 months. Of the 37 subjects, 14 (38%) had complete remission at cycle 16, day 1, with no detectable minimal residual disease (MRD) in the bone marrow. Neutropenia was the most frequent grade 3 or 4 hematological adverse event (16 [43%] of 37 patients). Hyperglycemia and hypophosphatemia were the most frequent grade 3–4 non-hematological adverse effects, with three and three [8%] cases, respectively. Nine patients (24%) experienced serious AEs, with neutropenia accounting for the highest frequency in three (8%) patients. There have been no deaths on the study [38]. This treatment combination was also tested in the CLL2-BAAG trial [39]. This phase II trial tested obinutuzumab, acalabrutinib, and venetoclax after an optional debulking with bendamustine in relapsed or refractory CLL. Of the 45 enrolled patients, 21 (47%) were treated with targeted agents. After receiving triple therapy for six months, 34 (76%) patients had an undetectable MRD in peripheral blood. After 13.8 months, two Richter transformations (4%) were noted. However, no progressions or deaths occurred in this observation period [39]. The above-mentioned clinical trials did not meet their prespecified primary outcome points [38, 39]. So far, no clinical benefit of acalabrutinib-based therapy escalation may be observed; the triplet therapies cannot be recommended for clinical use.

Considering the continued therapy with acalabrutinib and increased risk of toxicity and refractoriness development, a time-limited acalabrutinib-venetoclax combination efficacy and safety is being addressed in the ongoing MAJIC phase III trial [40, 41]. This randomized trial compares venetoclax-obinutuzumab to the BTK inhibitor acalabrutinib as first-line treatment for SLL/CLL. The duration of therapy in both treatment arms will be guided by minimal residual disease and disease response. All patients will eventually stop treatment after a maximum of two years [40].

Conclusions

Acalabrutinib is an effective therapeutic option in monotherapy in TN and RR CLL patients, especially those harboring del(17p) or *TP53* mutation. It shows also a clear benefit in patients with unmutated *IGHV* and poses an effective clinical option in this patient group. In patients with established cardiovascular disease, such as well-controlled AF, hypertension, heart failure, or valvular heart disease, or who are at risk for developing poorly controlled hypertension or atrial fibrillation, acalabrutinib should be the preferred choice over ibrutinib. Acalabrutinib may also be regarded as an effective BTKi alternative in the setting of ibrutinib intolerance.

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Authors' contributions
All authors wrote, reviewed and agreed to the final version of the manuscript.

Conflict of interest
BP served as a consultant for Abbvie, Roche, and Sandoz and received honoraria and research funding from Abbvie, AstraZeneca, BeiGene Amgen, Gilead, Celgene, and Janssen. EIJ served as a consultant for Abbvie and AstraZeneca and received honoraria and research funding from Abbvie, AstraZeneca, BeiGene, Roche, Sandoz and Janssen. KJ served as a consultant and received honoraria and research funding from AstraZeneca, Janssen, AbbVie, BeiGene, and Roche. KG served as a consultant for Abbvie, Roche, BeiGene, AstraZeneca, Gilead, Johnson & Johnson, Amgen, Novartis, Sanofi, BMS, Pfizer, Takeda and GSK, and received honoraria and research funding from Abbvie, BMS, Roche, BeiGene, AstraZeneca, Sanofi, Pfizer, Johnson & Johnson, Amgen, GSK, Karyopharm, and Novartis. TW served as a consultant for Janssen, Abbvie, BeiGene, AstraZeneca, Gilead, Janssen, Roche, and Takeda and received honoraria and research funding from Janssen, Abbvie, BeiGene, BMS, AstraZeneca, Roche, Sanofi, and Takeda. TR served as a consultant for Janssen, Abbvie, BeiGene, AstraZeneca, Gilead, and Octapharma and received honoraria and research funding from Janssen, Abbvie,

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