Acalabrutinib, A Second-Generation Bruton's Tyrosine Kinase Inhibitor

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Contents

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Abstract

The Bruton's tyrosine kinase (BTK) is an essential in the B-cell receptor (BCR) signaling pathway which was identified as crucial in the pathogenesis of B-cell malignancies. Ibrutinib, a first-in-class BTK inhibitor, has been approved for the treatment of distinct B-cell malignancies. To overcome off-target side effects of and emerging resistances to ibrutinib, more selective second-generation BTK inhibitors were developed. Acalabrutinib is a novel second-generation BTK inhibitor and has shown promising safety and efficacy profiles in phase 1/2 clinical trials in patients with relapsed CLL and pretreated MCL. Recently, acalabrutinib was approved by the FDA for treatment of adult patients with MCL who received at least one prior therapy. However, clinical trials on a direct comparison between ibrutinib and acalabrutinib and on combination treatment options with other agents as CD20 antibodies are warranted.

Keywords

Acalabrutinib · Bruton's tyrosine kinase · Hematologic malignancies

1 Introduction

B-cell receptor (BCR) signaling pathway has been identified to play an important role in the pathogenesis and progression of B-cell malignancies (Bojarczuk et al. 2015). As Bruton's tyrosine kinase (BTK) is an essential kinase in the BCR signaling pathway, ibrutinib, a first-in-class BTK inhibitor, has been approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma and Waldenstrom's macroglobulinemia (WM) (Thompson and Burger 2017; Agency EM 2017; Martin et al. 2016; Kapoor et al. 2017; Noy et al. 2017). More specific second-generation BTK inhibitors were developed to overcome off-target side effects of and emerging resistances to ibrutinib (Wu et al. 2016). Herein, the mechanism of action, preclinical and clinical data, including toxicity profile and drug interactions of the novel second-generation BTK inhibitor, acalabrutinib (also known as ACP-196), are summarized.

2 Structure and Mechanism of Action

The molecular formula of acalabrutinib is $C_{26}H_{23}N_7O_2$, the chemical name 4-{8-Amino-3-[(2S)-1-(2-butynoyl)-2-pyrrolidinyl]imidazo[1,5-a]pyrazin-1-yl}-*N*-(2-pyridinyl)benzamide, and the molar mass 465.507 g/mol (AstraZeneca 2017). The chemical structure is shown in Fig. 1.

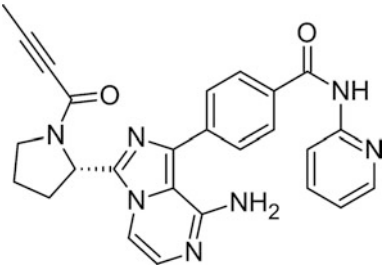

Fig. 1 Chemical structure of acalabrutinib. The figure was used in agreement with the Wikimedia Commons License

Acalabrutinib and its active metabolite, ACP-5862, bind covalently to a cysteine residue (Cys481) in the adenosine triphosphate- (ATP-) binding pocket of BTK via a reactive butynamide group thereby acting as an irreversible small-molecule inhibitor of BTK (Barf et al. 2017; Wu et al. 2016). Acalabrutinib was demonstrated to inhibit BTK with a half maximal inhibitory concentration (IC_{50}) of 5.1 ± 1.0 nM in the immobilized metal ion affinity-based fluorescence polarization (IMAP) assay (Barf et al. 2017; Byrd et al. 2016). In vitro, increasing concentrations of acalabrutinib led to a dose-dependent inhibition of the BCR signaling pathway in primary human CLL cells (Byrd et al. 2016).

In order to determine the selectivity of acalabrutinib, inhibitory assays on kinases with a cysteine residue in the same position as BTK were performed. Herein, acalabrutinib showed almost no inhibitory activity on epidermal growth factor receptor (EGFR), IL2-inducible T-cell kinase (ITK) and tyrosine-protein kinase Tec (TEC) (Barf et al. 2017; Byrd et al. 2016; Patel et al. 2017). These findings indicated a higher selectivity of acalabrutinib over ibrutinib with reduced off-target side effects. In this regard, ibrutinib but not acalabrutinib treatment resulted in a reduced platelet–vessel wall interaction compared to healthy controls in a humanized mouse model of thrombosis. These results demonstrated that acalabrutinib did not inhibit platelet activity, probably due to its improved selectively (Byrd et al. 2016).

3 Preclinical Data

Preclinical in vivo data on single-agent activity of acalabrutinib were obtained from mouse and canine animal models.

Herman et al. demonstrated acalabrutinib to be a potent inhibitor of BTK in two murine models of human CLL: the human NSG (NOD-Scid-IL2Rgc^{null}) primary CLL xenograft model and the Eμ-TCL-1 adoptive transfer model. In both mouse models, acalabrutinib treatment had on-target effects including decreased activation of key signaling molecules such as BTK, phospholipase C-γ2 (PLCγ2), ribosomal

protein S6, and extracellular signal regulated kinase (ERK). Moreover, a significant inhibition of CLL cell proliferation, reduced tumor burden, and increased survival were observed (Herman et al. 2017).

In a model of spontaneously occurring canine lymphoma, a B-cell malignancy similar to human diffuse large B-cell lymphoma, Harrington et al. proved activity of acalabrutinib. In particular, upon treatment at dosages of 2.5–20 mg/kg every 12 or 24 h an overall response rate (ORR) of 25% and a median progression-free survival (PFS) of 22.5 days have been observed (Harrington et al. 2016).

These preclinical studies provided detailed insights into the mechanism of action of acalabrutinib and paved the way for subsequent clinical trials.

4 Clinical Data

The safety and efficacy of single-agent acalabrutinib was evaluated in phase 1/2 clinical trials in relapsed CLL and previously pretreated MCL.

In an uncontrolled multicenter study (NCT02029443) acalabrutinib was administered orally at a dose of 100–400 mg once daily (phase 1 dose escalation) and 100 mg twice daily (phase 2) to 61 patients with relapsed CLL (median of three previous therapies). Among the recruited patients, 75% had an unmutated immunoglobulin variable-region heavy-chain gene, 31% a chromosome 17p13.1 deletion, and 29% a chromosome 11q22.3 deletion. The median age was 62 (range 44–84) years. Compared to once-daily dosing, the twice-daily application improved the kinase occupancy allowing continues BTK inhibition without increasing toxic effects. The ORR was 95%, including 10% of patients with partial response (PR) with lymphocytosis and 85% with a PR, after a median follow-up of 14.3 months. Stable disease (SD) was observed in the remaining 5% of patients. In patients with a chromosome 17p13.1 deletion, the ORR was 100%. Only one patient, with a chromosome 17p13.1 deletion, experienced disease progression during therapy. Interestingly, at progression a C481S mutation in BTK (major clone) and a L845F mutation in PLCγ2 (minor clone) was found in this patient. Overall, acalabrutinib showed promising efficacy in relapsed CLL (Byrd et al. 2016). Based on these data, a subsequent phase 3 clinical trial comparing acalabrutinib versus ibrutinib in pretreated patients with high-risk CLL has been initiated (NCT02477696). Further clinical trials evaluating acalabrutinib in combination with other agents in CLL are ongoing (Table 1).

In another phase 2 open-label, single-arm clinical trial (ACE-LY-004, NCT02213926) acalabrutinib was administered at a dosage of 100 mg twice daily until progression. 124 patients with relapsed/refractory MCL (median of two previous treatments, including 18% of patients with prior stem cell transplant) were included. Previous BTK treatment was defined as an exclusion criterion. The median age was 68 (range 42–90) years. 44 and 17% of patients had intermediate or high risk with regard to MCL International Prognostic Index (MIPI), respectively. At a median follow-up of 15.2 months, the ORR was 80%, with a 40% complete

Table 1 Acalabratunib trials in hematologic malignancies[a]

Phase	Agents	Diseases	NCT No	Status
1	Acalabrutinib + ACP-319	CLL	NCT02157324	Active, not recruiting
1	Acalabrutinib	B-cell malignancies	NCT03198650	Recruiting
1b	Acalabrutinib + Dexamethasone vs. Acalabrutinib	MM	NCT02211014	Active, not recruiting
1b	Acalabrutinib + Bendamustine + Rituximab	MCL	NCT02717624	Active, not recruiting
1b	Acalabrutinib + Obinutuzumab + Venetoclax and Acalabrutinib + Rituximab + Venetoclax	CLL, SLL, PLL	NCT02296918	Active, not recruiting
1b	Acalabrutinib	DLBCL	NCT02112526	Unknown
1/2	Acalabrutinib + Vistusertib	B-cell malignancies	NCT03205046	Recruiting
1/2	Acalabrutinib	CLL, Richters syndrome, SLL, PLL	NCT02029443	Active, not recruiting
1/2	Acalabrutinib + AZD6738 vs. AZD6738	CLL	NCT03328273	Not yet recruiting
1/2	Acalabrutinib + ACP-319	B-cell malignancies	NCT02328014	Recruiting
1b/2	Acalabrutinib + Pembrolizumab	Hematologic malignancies	NCT02362035	Active, not recruiting
1b/2	Acalabrutinib + Rituximab vs. Acalabrutinib	FL	NCT02180711	Active, not recruiting
2	Acalabrutinib	WM	NCT02180724	Active, not recruiting
2	Acalabrutinib	MCL	NCT02213926	Active, not recruiting
2	Acalabrutinib	CLL	NCT02717611	Active, not recruiting

(continued)

Table 1 (continued)

Phase	Agents	Diseases	NCT No	Status
2	Acalabrutinib	CLL, SLL	NCT02337829	Recruiting
3	Acalabrutinib + Bendamustine + Rituximab vs. Placebo + Bendamustine + Rituximab	MCL	NCT02972840	Recruiting
3	Acalabrutinib vs. Rituximab + Idelalisib or Rituximab + Bendamustine	CLL	NCT02970318	Recruiting
3	Acalabrutinib vs. Ibrutinib	CLL	NCT02477696	Recruiting
3	Acalabrutinib + Obinutuzumab vs. Acalabrutinib vs. Obinutuzumab + Chlorambucil	CLL	NCT02475681	Active, not recruiting

[a]As registered at ClinicalTrials.gov (2017)

CLL chronic lymphocytic leukemia, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *MCL* mantel cell lymphoma, *MM* multiple myeloma, *PLL* prolymphocytic leukemia, *SLL* small lymphocytic leukemia, *vs*. versus, *WM* Waldenstrom's macroglobulinemia

response (CR) and 40% PR rate (AstraZeneca 2017b). These data demonstrated the potential impact of acalabrutinib in treatment of relapsed/refractory MCL and led to an accelerated Food and Drug Administration (FDA) approval of Calquence® (acalabrutinib) for treatment of adult patients with MCL who received at least one prior therapy (FDA 2017).

5 Toxicity

Side effects of acalabrutinib were reported in the two previously described phase 1/2 clinical trials.

The most common non-hematological side effects described in the acalabrutinib/relapsed CLL trial (NCT02029443) were headache (43%), diarrhea (39%), weight gain (26%), pyrexia (23%), upper respiratory tract infection (23%), hypertension (20%) and nausea (20%). Severe (grade $\geq$ 3) diarrhea, weight gain, pyrexia, fatigue, hypertension, and arthralgia were rare (2–7%). Grade 1–2 petechiae were reported in 16% of patients, grade $\geq$ 3 anemia and neutropenia in 2% of patients, respectively. Overall, no dose-limiting toxicities in the phase 1 part of the trial and no cases of atrial fibrillation (common during ibrutinib treatment) were observed (Byrd et al. 2016).

In the acalabrutinib/pretreated MCL study (ACE-LY-004, NCT02213926) anemia (46%), thrombocytopenia (44%), headache (39%), neutropenia (36%), diarrhea (31%), fatigue (28%), myalgia (21%), bruising (21%), nausea (19%), and rash (18%) were common side effects. Grade $\geq$ 3 non-hematological events included diarrhea, headache, abdominal pain as well as vomiting and were also rare (2–3%). Grade $\geq$ 3 anemia, thrombocytopenia and neutropenia were observed in 10, 12, and 15% of patients, respectively. Dose-adjustment and treatment discontinuation was reported in 2 and 7% of patients (AstraZeneca 2017a, b).

6 Drug Interactions

Acalabrutinib is predominantly metabolized by CYP3A enzymes in the liver. Therefore, plasma concentrations and side effects were elevated when administered in combination with moderate and strong CYP3A inhibitors such as itraconazole, erythromycin, fluconazole, or diltiazem. On the other hand, co-administration of CYP3A inducers, like rifampicin, resulted in reduced plasma concentration. Furthermore, solubility of acalabrutinib was affected by the pH. Thus, co-administration with antacida and proton pump inhibitors decreased absorption. In combination with CYP3A inhibitors, CYP3A inducers or gastric acid-reducing agents dose adjustments and/or separate dosing are recommended (AstraZeneca 2017).

7 Biomarkers

So far, no predictive or prognostic biomarkers were reported for acalabrutinib.

8 Summary and Perspective

Acalabrutinib is a novel second-generation BTK inhibitor with improved selectivity compared to the first-in-class BTK inhibitor ibrutinib. Acalabrutinib showed promising safety and efficacy profiles in phase 1/2 clinical trials in patients with relapsed CLL and pretreated MCL. In contrast to ibrutinib, so far no cases of atrial fibrillation have been reported during treatment with acalabrutinib. Recently, acalabrutinib was approved by the FDA for treatment of adult patients with MCL who received at least one prior therapy. However, clinical trials and a direct comparison between ibrutinib and acalabrutinib are warranted to reveal the superiority and possible resistance mechanisms of acalabrutinib. Currently, several phase 1, 2, and 3 clinical trials on acalabrutinib single-agent activity and combinations with other agents in hematologic malignancies (Table 1) and solid tumors (Table 2) are ongoing. As indicated in preclinical studies, combinations of acalabrutinib with other agents as CD20 antibodies, phosphoinositide 3 (PI3) kinase and BCL-2 inhibitors will likely increase rates and duration of response (Patel et al. 2017; Niemann et al. 2017; Golay et al. 2017; Deng et al. 2017) Finally, additional selective BTK inhibitors, as ONO/GS-4059, CC-292, BGB-3111, are currently

Table 2 Acalabrutinib trials in solid tumors[a]

Phase	Agents	Diseases	NCT No	Status
1b/2	Acalabrutinib	Glioblastoma multiforme	NCT02586857	Recruiting
2	Acalabrutinib + Pembrolizumab versus Acalabrutinib	Ovarian cancer	NCT02537444	Active, not recruiting
2	Acalabrutinib + Pembrolizumab versus Pembrolizumab	Non-small lung cancer	NCT02448303	Active, not recruiting
2	Acalabrutinib + Pembrolizumab	Head and neck squamous cell carcinoma	NCT02454179	Active, not recruiting
2	Acalabrutinib + Pembrolizumab	Metastatic urothelial carcinoma	NCT02351739	Active, not recruiting
2	Acalabrutinib + Pembrolizumab versus Acalabrutinib	Metastatic pancreatic cancer	NCT02362048	Active, not recruiting
2	Acalabrutinib + Nab-paclitaxel	Metastatic pancreatic cancer	NCT02570711	Terminated
2	Acalabrutinib + Methotrexate versus Methotrexate + Placebo	Rheumatoid arthritis	NCT02387762	Completed

[a]As registered at ClinicalTrials.gov. (2017)

tested in B-cell malignancy models and early phase clinical trials (Thompson and Burger 2017; Robak and Robak 2017; Vidal-Crespo et al. 2017; Wu et al. 2017; Walter et al. 2016).

References

Agency EM (2017) Ibrutinib [monograph on the internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003791/human_med_001801.jsp&mid=WC0b01ac058001d124

AstraZeneca (2017a) Prescribing information of CALQUENCE (acalabrutinib) [monograph on the internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf

AstraZeneca (2017b) S FDA approves AstraZeneca's Calquence (acalabrutinib) for adult patients with previously-treated mantle cell lymphoma [monograph on the internet]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2017/us-fda-approves-astrazenecas-calquence-acalabrutinib-for-adult-patients-with-previously-treated-mantle-cell-lymphoma-24102017.html

Barf T, Covey T, Izumi R, van de Kar B, Gulrajani M, van Lith B, van Hoek M, de Zwart E, Mittag D, Demont D, Verkaik S, Krantz F, Pearson PG, Ulrich R, Kaptein A (2017) Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther 363:240–252

Bojarczuk K, Bobrowicz M, Dwojak M, Miazek N, Zapala P, Bunes A, Siernicka M, Rozanska M, Winiarska M (2015) B-cell receptor signaling in the pathogenesis of lymphoid malignancies. Blood Cells Mol Dis 55:255–265

Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, Chaves J, Wierda WG, Awan FT, Brown JR, Hillmen P, Stephens DM, Ghia P, Barrientos JC, Pagel JM, Woyach J, Johnson D, Huang J, Wang X, Kaptein A, Lannutti BJ, Covey T, Fardis M, McGreivy J, Hamdy A, Rothbaum W, Izumi R, Diacovo TG, Johnson AJ, Furman RR (2016) Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 374:323–332

ClinicalTrials.gov (2017) Acalabrutinib (ACP-196) clinical trials [monograph on the internet]. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=acalabrutinib&cntry1=&state1=&Search=Search

Deng J, Isik E, Fernandes SM, Brown JR, Letai A, Davids MS (2017) Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia. Leukemia 31:2075–2084

FDA (2017) FDA grants accelerated approval to acalabrutinib for mantle cell lymphoma [monograph on the internet]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm583106.htm

Golay J, Ubiali G, Introna M (2017) The specific Bruton tyrosine kinase inhibitor acalabrutinib (ACP-196) shows favorable in vitro activity against chronic lymphocytic leukemia B cells with CD20 antibodies. Haematologica 102:e400–e403

Harrington BK, Gardner HL, Izumi R, Hamdy A, Rothbaum W, Coombes KR, Covey T, Kaptein A, Gulrajani M, Van Lith B, Krejsa C, Coss CC, Russell DS, Zhang X, Urie BK, London CA, Byrd JC, Johnson AJ, Kisseberth WC (2016) Preclinical evaluation of the novel BTK inhibitor acalabrutinib in canine models of B-cell non-hodgkin lymphoma. PLoS ONE 11:e0159607

Herman SEM, Montraveta A, Niemann CU, Mora-Jensen H, Gulrajani M, Krantz F, Mantel R, Smith LL, McClanahan F, Harrington BK, Colomer D, Covey T, Byrd JC, Izumi R, Kaptein A, Ulrich R, Johnson AJ, Lannutti BJ, Wiestner A, Woyach JA (2017) The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib demonstrates potent on-target effects and efficacy in two mouse models of chronic lymphocytic Leukemia. Clin Cancer Res 23:2831–2841

Kapoor P, Ansell SM, Fonseca R, Chanan-Khan A, Kyle RA, Kumar SK, Mikhael JR, Witzig TE, Mauermann M, Dispenzieri A, Ailawadhi S, Stewart AK, Lacy MQ, Thompson CA, Buadi FK, Dingli D, Morice WG, Go RS, Jevremovic D, Sher T, King RL, Braggio E, Novak A, Roy V, Ketterling RP, Greipp PT, Grogan M, Micallef IN, Bergsagel PL, Colgan JP, Leung N, Gonsalves WI, Lin Y, Inwards DJ, Hayman SR, Nowakowski GS, Johnston PB, Russell SJ, Markovic SN, Zeldenrust SR, Hwa YL, Lust JA, Porrata LF, Habermann TM, Rajkumar SV, Gertz MA, Reeder CB (2017) Diagnosis and Management of Waldenstrom Macroglobulinemia: mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines 2016. JAMA Oncol 3:1257–1265

Martin P, Maddocks K, Leonard JP, Ruan J, Goy A, Wagner-Johnston N, Rule S, Advani R, Iberri D, Phillips T, Spurgeon S, Kozin E, Noto K, Chen Z, Jurczak W, Auer R, Chmielowska E, Stilgenbauer S, Bloehdorn J, Portell C, Williams ME, Dreyling M, Barr PM, Chen-Kiang S, DiLiberto M, Furman RR, Blum KA (2016) Postibrutinib outcomes in patients with mantle cell lymphoma. Blood 127:1559–1663

Niemann CU, Mora-Jensen HI, Dadashian EL, Krantz F, Covey T, Chen SS, Chiorazzi N, Izumi R, Ulrich R, Lannutti BJ, Wiestner A, Herman SEM (2017) Combined BTK and PI3Kdelta inhibition with acalabrutinib and ACP-319 improves survival and tumor control in CLL mouse model. Clin Cancer Res 23:5814–5823

Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, Collins GP, Ma S, Coleman M, Peles S, Smith S, Barrientos JC, Smith A, Munneke B, Dimery I, Beaupre DM, Chen R (2017) Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood 129:2224–2232

Patel VK, Lamothe B, Ayres ML, Gay J, Cheung J, Balakrishnan K, Ivan C, Morse J, Nelson M, Keating MJ, Wierda WG, Marszalek JR, Gandhi V (2017) Pharmacodynamics and proteomic analysis of acalabrutinib therapy: Similarity of on-target effects to ibrutinib and rationale for combination therapy. Leukemia

Robak P, Robak T (2017) Novel synthetic drugs currently in clinical development for chronic lymphocytic leukemia. Expert Opin Investig Drugs 26:1249–1265

Thompson PA, Burger JA (2017) Bruton's tyrosine kinase inhibitors: first and second generation agents for patients with Chronic Lymphocytic Leukemia (CLL). Expert Opin Investig Drugs 1–12

Vidal-Crespo A, Rodriguez V, Matas-Cespedes A, Lee E, Rivas-Delgado A, Gine E, Navarro A, Bea S, Campo E, Lopez-Guillermo A, Lopez-Guerra M, Roue G, Colomer D, Perez-Galan P (2017) The Bruton tyrosine kinase inhibitor CC-292 shows activity in mantle cell lymphoma and synergizes with lenalidomide and NIK inhibitors depending on nuclear factor-kappaB mutational status. Haematologica 102:e447–e451

Walter HS, Rule SA, Dyer MJ, Karlin L, Jones C, Cazin B, Quittet P, Shah N, Hutchinson CV, Honda H, Duffy K, Birkett J, Jamieson V, Courtenay-Luck N, Yoshizawa T, Sharpe J, Ohno T, Abe S, Nishimura A, Cartron G, Morschhauser F, Fegan C, Salles G (2016) A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. Blood 127:411–419

Wu J, Liu C, Tsui ST, Liu D (2016a) Second-generation inhibitors of Bruton tyrosine kinase. J Hematol Oncol 9:80

Wu J, Zhang M, Liu D (2016b) Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. J Hematol Oncol 9:21

Wu J, Zhang M, Liu D (2017) Bruton tyrosine kinase inhibitor ONO/GS-4059: from bench to bedside. Oncotarget 8:7201–7207