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Acalabrutinib

Updated: July 31, 2018.

OVERVIEW

Introduction

Acalabrutinib is an oral inhibitor of Bruton's tyrosine kinase that is used in the therapy of B cell malignancies including refractory mantle cell lymphoma. Acalabrutinib has not been associated with serum enzyme elevations during therapy or with cases of idiosyncratic acute liver injury, but has been linked to cases of reactivation of hepatitis B.

Background

Acalabrutinib (a kal" a broo' ti nib) is an orally available, small molecule inhibitor of Bruton's tyrosine kinase (BTK), which is an essential component in the B cell receptor signaling pathway. Inhibition of this pathway prevents B cell activation, differentiation and proliferation. Deficiency of BTK is the cause of X linked (Bruton's) agammaglobulinemia, and B cell receptor signaling through BTK has been shown to be critical for proliferation and survival of malignant B lymphocytes in mantle cell lymphoma and CLL. Unlike ibrutinib, another BTK inhibitor, acalabrutinib has a high degree of specificity for BTK and has little or no activity against EGFR and other tyrosine kinases. Acalabrutinib was approved for use in the United States as therapy for refractory mantle cell lymphoma in 2017 and is under evaluation in other malignancies such as CLL, pancreatic and non-small cell lung cancer. Acalabrutinib is available in capsules of 100 mg under the brand name Calquence. The recommended dose is 100 mg once daily. Side effects are common, but usually mild-to-moderate in severity; they include myelosuppression, fatigue, diarrhea, nausea, vomiting, anorexia, constipation, peripheral edema, dyspnea, headache, arthralgia, myalgia, rash and fever. Uncommon, but potentially serious side effects include severe bone marrow suppression, infections, bleeding, tumor lysis syndrome and renal toxicity.

Hepatotoxicity

In two open label clinical trials of acalabrutinib in patients with CLL and mantle cell lymphoma, serum aminotransferase elevations occurred in 19% to 23% of patients during therapy and rose to above 5 times ULN in 2% to 3%. These elevations were transient and resolved spontaneously. Among the 610 patients treated with acalabrutinib in these trials, there were no instances of clinically apparent liver injury attributed to its use, but there was a single instance of acute liver failure and death due to reactivation of hepatitis B. Similar cases of reactivation have been reported with ibrutinib, another small molecule inhibitor of Bruton's tyrosine kinase. Experience with acalabrutinib has been limited and the frequency of clinically apparent liver injury and reactivation of hepatitis B are not known.

Likelihood score: D (possible rare cause of clinically apparent liver injury and suspected cause of reactivation of hepatitis B).

Mechanism of Injury

The mechanism by which acalabrutinib might cause liver injury is known known. Acalabrutinib is metabolized in the liver largely by the CYP 3A4 and is susceptible to drug-drug interactions with inhibitors or inducers of this enzyme reactivity. Reactivation of hepatitis B from acalabrutinib is probably the result of profound B cell suppression, which leads to increases in viral replication, which can result in severe hepatitis with immune reconstitution.

Outcome and Management

Liver injury due to acalabrutinib is generally mild and asymptomatic. Reactivation of hepatitis B, however, can result in severe hepatitis and even acute hepatic failure. Patients who are to receive B cell inhibitors such as acalabrutinib, ibrutinib, rituximab and usteokinumab should be screened for hepatitis B markers, including HBsAg and anti-HBc before starting chemotherapy, and those who are positive given prophylaxis against reactivation using oral antiviral agent with activity against HBV such as tenofovir and entecavir or monitored carefully for changes in HBV DNA levels during therapy. If HBV DNA levels increase significantly (by 10-fold or greater; at least one log increase in HBV DNA), initiation of antiviral therapy is appropriate. Therapy should be continued for at least six months after immunosuppressive therapy has been completed.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Acalabrutinib – Calquence®

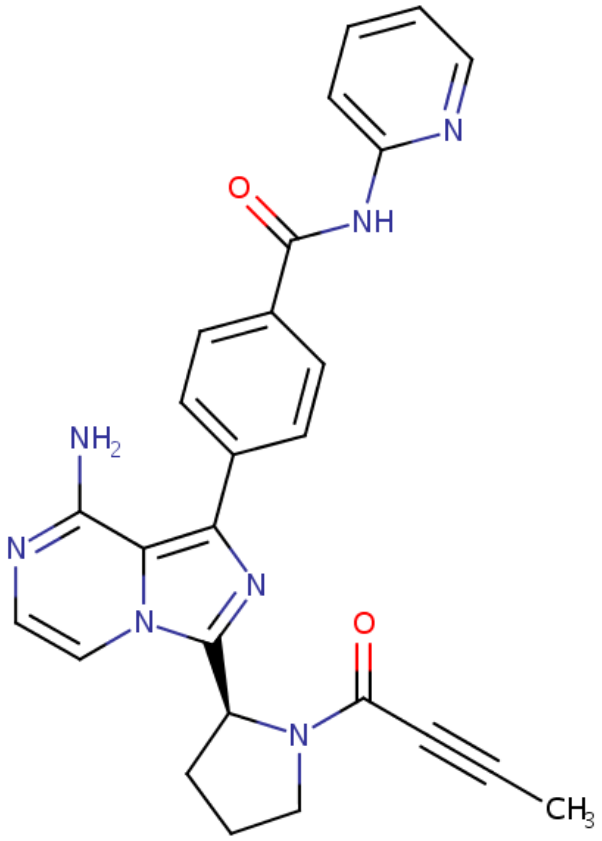
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Acalabrutinib	1420477-60-6	C26-H23-N7-O2	

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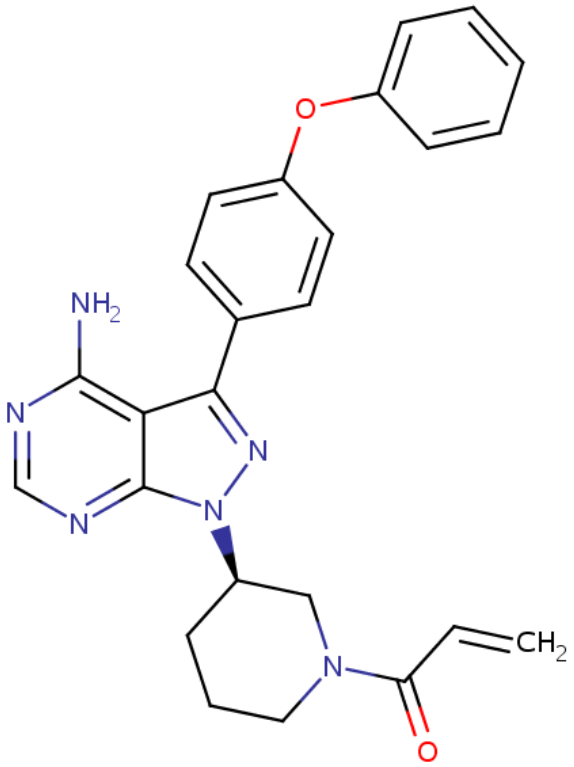
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ibrutinib	936563-96-1	C25-H24-N6-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 31 July 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of tyrosine kinase receptor inhibitors).

DeLeve LD. Kinase inhibitors. Gefitinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents, does not discuss acalabrutinib or ibrutinib).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

Ponader S, Burger JA. Bruton's tyrosine kinase: from X-linked agammaglobulinemia toward targeted therapy for B-cell malignancies. J Clin Oncol 2014; 32: 1830-9. PubMed PMID: 24778403.

(History of discovery of X-linked agammaglobulinemia, identification of BTK as its cause, elucidation of role of BTK in the pathway of B cell activation, and development of BTK inhibitors including ibrutinib).

de Jésus Ngoma P, Kabamba B, Dahlqvist G, Sempoux C, Lanthier N, Shindano T, Van Den Neste E, et al. Occult HBV reactivation induced by ibrutinib treatment: a case report. Acta Gastroenterol Belg 2015; 78: 424-6. PubMed PMID: 26712054.

(80 year old man with CLL and anti-HBc without HBsAg in serum [HBV DNA 420 IU/mL] developed reactivation of hepatitis B 5 months after starting ibrutinib [HBsAg positive, HBV DNA 23 million IU/mL, ALT rising to 103 U/L], improving on entecavir therapy with decline in HBV DNA and ALT levels, but HBsAg remained positive).

Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, Chaves J, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 2016; 374: 323-32. PubMed PMID: 26641137.

(Among 61 patients with relapsed CLL treated with acalabrutinib [100 to 400 mg daily], the overall response rate was 95% and common adverse events included headache [43%], diarrhea [39%], fever [23%], fatigue [21%], hypertension [20%], nausea [20%] and weight loss [26%]; no mention of ALT elevations or hepatotoxicity).

Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. J Hematol Oncol 2016; 9: 21. PubMed PMID: 26957112.

(Review of the mechanism of action, preclinical evaluation and status of clinical studies of acalabrutinib mentions its specificity for BTK and lack of effect on EGFR and other tyrosine kinases).

Herishanu Y, Katchman H, Polliack A. Severe hepatitis B virus reactivation related to ibrutinib monotherapy. Ann Hematol 2017; 96: 689-90. PubMed PMID: 28058492.

(79 year old man with CLL and anti-HBc without HBsAg in serum developed reactivation of hepatitis B 12 months after starting ibrutinib [HBsAg positive, HBV DNA 1.9 million IU/mL, ALT 987 U/L, direct bilirubin 14.2 mg/dL], resolving with tenofovir therapy and later tolerated restarting ibrutinib).

Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, Damaj G, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet 2018; 391 (10121): 659-67. PubMed PMID: 29241979.

(Among 124 patients with relapsed or refractory mantle cell lymphoma treated with acalabrutinib, 81% had an objective response which was complete in 40% and the most common side effects were headache, diarrhea, fatigue and myalgia; no mention of ALT elevations or hepatotoxicity).

Markham A, Dhillon S. Acalabrutinib: first global approval. Drugs 2018; 78: 139-45. PubMed PMID: 29209955.

(Review of the history of development, mechanism of action, clinical efficacy and safety of acalabrutinib, mentions that reactivation of hepatitis B occurred in one of 610 subjects treated with acalabrutinib, but does not mention ALT elevations or hepatotoxicity).