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Ticagrelor

Updated: July 10, 2014.

OVERVIEW

Introduction

Ticagrelor is an oral antiplatelet drug that is used with low dose aspirin to decrease the risk of myocardial infarction and stroke in patients with acute coronary syndromes. Ticagrelor has been linked to rare instances of hypersensitivity reactions accompanied by mild liver injury.

Background

Ticagrelor (tye ka' grel or) is a non-thienopyridine, reversible inhibitor of adenosine diphosphate (ADP) receptors (P2Y 12) on platelets and is used to decrease the risk of recurrent coronary thromboses in patients who undergo interventions during an acute coronary syndrome. Activated platelets release ADP which binds to ADP platelet receptors, causing activation of intracellular glycoprotein IIb/IIIA complex which triggers platelet adherence and aggregation. The aggregation of platelets plays an important role in the growth of atheromatous plaques, which can lead to coronary, cerebral and peripheral arterial occlusions. In clinical trials, ticagrelor therapy during acute coronary events (unstable angina and myocardial infarction) has been shown to decrease the frequency of recurrence of myocardial infarction and stent thrombosis. Ticagrelor was approved for use in the United States in 2011 and has been used in limited numbers of patients for a limited time only. Current indications are reduction of recurrent cardiovascular events in patients with acute coronary syndromes. Ticagrelor is available in 90 mg tablets under the commercial name Brilinta. The usual maintenance dose is 90 mg twice daily in combination with daily low dose aspirin (<100 mg). Side effects are not common, but can include bleeding (12%), dyspnea (14%), headaches, nausea, diarrhea, hypotension and hypersensitivity reactions.

Hepatotoxicity

In several large clinical trials, ticagrelor was not associated with serum enzyme elevations during therapy and no instances of clinically apparent liver injury were reported. While there have been isolated reports of transient and mild serum enzyme elevations during ticagrelor therapy, these have been short lived and asymptomatic. In addition, since marketing and release, there have been no reports of clinically apparent liver injury or jaundice associated with ticagrelor therapy and hepatotoxicity is not mentioned in the product label. Thus, significant liver injury due to ticagrelor must be very rare, if it occurs at all.

Mechanism of Injury

Ticagrelor, unlike clopidogrel, does not require metabolic activation for its antiplatelet effects. Ticagrelor is metabolized in the liver predominantly via CYP 3A4 and it should be used with caution in patients taking CYP

3A4 inhibitors (such as ketaconazole, clarithromycin, atazanavir and nefazodone), which can increase serum levels, or CYP 3A4 inducers (such as rifampin, dexamethasone and phenytoin) which can decrease drug levels.

Outcome and Management

There is little evidence that ticagrelor can cause liver injury or has any cross sensitivity to other antiplatelet agents, so that switching from clopidogrel or prasugrel after clinically apparent liver injury is probably safe.

Drug Class: Antithrombotic Agents, Antiplatelet Agents

Other Drugs in the Subclass, Antiplatelet Agents: Aspirin, Cangrelor, Clopidogrel, Dipyridamole, Prasugrel, Ticlopidine, Vorapaxar

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ticagrelor – Brilinta®

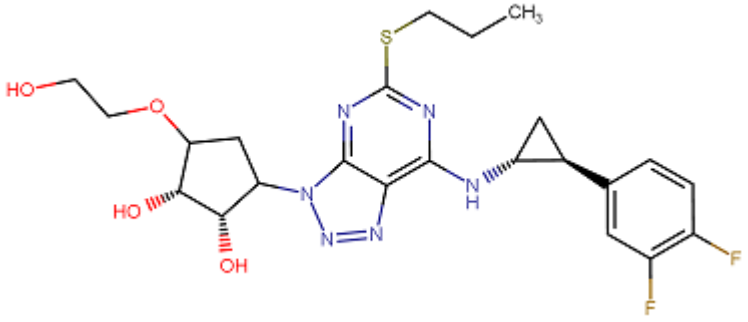
DRUG CLASS

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ticagrelor	274693-27-5	C23-H28-F2-N6-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 10 July 2014

Zimmerman HJ. Platelet aggregation inhibitors. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 641-3.

(Textbook of hepatotoxicity published in 1999; ticlopidine, but not clopidogrel, prasugrel or ticagrelor is discussed).

De Marzio DH, Navarro VJ. Antiplatelet agents. Hepatotoxicity of cardiovascular and antidiabetic drugs: antihypertensives. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 527-8.

(Review of hepatotoxicity of antiplatelet drugs discusses ticlopidine, clopidogrel and prasugrel, but does not mention ticagrelor).

Weitz JI. Blood coagulation and anticoagulant, fibrinolytic, and antiplatelet drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 849-76.

(Textbook of pharmacology and therapeutics).

Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006; 27: 1038-47. PubMed PMID: 16476694.

(Among 200 patients with atherosclerosis treated with one of 4 doses of ticagrelor or clopidogrel for 28 days, inhibition of platelet aggregation was greater with higher doses of ticagrelor and the most common adverse events were bleeding, dyspnea, dizziness and headache; "no notable time- or treatment-related changes in any ... clinical chemistry parameters ... were observed").

Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007; 50: 1844-51. PubMed PMID: 17980250.

(Among 990 patients with an acute coronary syndrome treated with one of 2 doses of ticagrelor or clopidogrel for 4-12 weeks, bleeding episodes were similar in the three groups [9.8% and 8.0% vs 8.1%]; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network(DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to antiplatelet agents).

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, et al.; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57. PubMed PMID: 19717846.

(Among 18,624 patients with acute coronary syndrome treated with ticagrelor or clopidogrel, deaths from vascular cases within 12 months were less with ticagrelor [9.8% vs 11.7%], while major bleeding rates were similar [11.6% vs 11.2%]; no mention of hepatotoxicity or ALT elevations).

Mohammad RA, Goldberg T, Dorsch MP, Cheng JW. Antiplatelet therapy after placement of a drug-eluting stent: a review of efficacy and safety studies. Clin Ther 2010; 32: 2265-81. PubMed PMID: 21353100.

(Systematic review of studies of antiplatelet therapy after coronary stenting discussed bleeding complications only, no mention of ALT elevations or hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were due to antiplatelet medications).

Anderson SD, Shah NK, Yim J, Epstein BJ. Efficacy and safety of ticagrelor: a reversible P2Y12 receptor antagonist. Ann Pharmacother 2010; 44: 524-37. PubMed PMID: 20124464.

(Systematic review of efficacy and safety of ticagrelor is associated with "no significant changes in laboratory values", with the exception of uric acid).

Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011; 57: 672-84. PubMed PMID: 21194870.

(Subgroup analysis of 1261 patients who underwent coronary artery bypass grafting and were treated with ticagrelor or clopidogrel; no discussion of ALT elevations or hepatotoxicity).

James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, Katus H, et al.; PLATO Study Group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ 2011; 342: d3527. PubMed PMID: 21685437.

(Among 5216 patients with acute coronary syndrome treated with ticagrelor or clopidogrel with a planned noninvasive treatment, cardiovascular death was lower with ticagrelor [12% vs 14.3%], while major bleeding episodes were greater [11.9% vs 10.3%]; no mention of ALT elevations or other adverse events).

Butler K, Teng R. Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with mild hepatic impairment. J Clin Pharmacol 2011; 51: 978-87. PubMed PMID: 20926753.

(Pharmacokinetic study in 20 volunteers, 10 with compensated cirrhosis, found minimally higher exposure after a single dose of ticagrelor in patients with liver disease, but not enough to recommend dose adjustment; no side effects or worsening of liver chemistry results).

Ticagrelor (Brilinta)--better than clopidogrel(Plavix)? Med Lett Drugs Ther 2011; 53 (1372): 69-70. PubMed PMID: 21897348.

(Concise review of the pharmacology, efficacy and safety of ticagrelor shortly after its approval in the US mentions side effects of bleeding, dyspnea, bradyarrhythmias and increases in uric acid and creatinine [effects probably related to stimulation of adenosine receptors]; no mention of ALT elevations or hepatotoxicity).

Antithrombotic drugs. Treat Guidel Med Lett 2011; 9 (110): 61-6. PubMed PMID: 21941228.

(Guidelines on use of antiplatelet agents including aspirin, clopidogrel, prasugrel and ticagrelor mentions that ticagrelor was found to be more effective than clopidogrel in one study without an increased rate of bleeding; no mention of other side effects, ALT elevations or hepatotoxicity).

Li H, Butler K, Yang L, Yang Z, Teng R. Pharmacokinetics and tolerability of single and multiple doses of ticagrelor in healthy Chinese subjects: an open-label, sequential, two-cohort, single-centre study. Clin Drug Investig 2012; 32: 87-97. PubMed PMID: 22168538.

(In a pharmacokinetic study of ticagrelor in 26 healthy volunteers, two patients developed asymptomatic serum ALT elevations [1.25 and 3 times ULN] without change in bilirubin or alkaline phosphatase within 3 days of starting ticagrelor and lasting for 10 days after stopping).

Htun WW, Steinhubl SR. Ticagrelor: the first novel reversible P2Y(12) inhibitor. Expert Opin Pharmacother 2013; 14: 237-45. PubMed PMID: 23268703.

(Review of pharmacology, efficacy and safety of ticagrelor in comparison to other antiplatelet agents; no mention of hepatotoxicity or ALT elevations during therapy).

DiNicolantonio JJ, Serebruany VL. Comparing the safety of ticagrelor versus clopidogrel: insights from the FDA reports. Ther Adv Cardiovasc Dis 2013; 7: 5-9. PubMed PMID: 23393061.

(The FDA analysis of trials of ticagrelor reported that patients with preexisting liver disease were more likely to have serious adverse events on ticagrelor than clopidogrel, including death [3.1% vs 0.9%] and major bleeds [11.2% vs 8.7%], the reasons for which were not clear).

Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J 2014; 35 (31): 2083-93. PubMed PMID: 24727884.

(Retrospective analysis of data from the PLATO trial of ticagrelor vs clopidogrel in 18,624 patients with acute coronary syndrome found similar rates of bleeding with both agents; no mention of ALT elevations or hepatotoxicity).