Journal of Developing Drugs
ISSN: 2329-6631

Wang, J Dev Drugs 2016, 5:3
DOI: 10.4172/2329-6631.1000e149

Editorial Open Access

Ivabradine for the Management of Chronic Stable Angina: Should it be considered?

Amy Zhe Wang*

Department of Pharmacy, Long Island University, New York, USA

***Corresponding author:** Amy Z Wang, Department of Pharmacy, Long Island University, New York, USA, Tel: 718-780-5583; E-mail: amy.wang@liu.edu

Received date: Nov 01, 2016; **Accepted date:** Nov 02, 2016; **Published date:** Nov 05, 2016

Editorial

Angina, or chest pain, often occurs when oxygen demand of the heart exceeds oxygen supply. The imbalance between oxygen supply and demand may be due to blockage in the coronary arteries, arterial vasospasm, or myocardial dysfunction [1]. Chronic stable angina (CSA) is described as having chest pain due to exertion (such as exercise or stress), or chest pain that is relieved by rest or administration of nitroglycerin [2]. Conventional therapies for CSA includes negative inotropes, such as beta blockers (BB) and calcium channel blockers (CCB), or vasodilators, such as nitroglycerin (NTG). Unfortunately, BBs and CCBs have been associated with adverse effects such as fatigue and severe bradycardia, while use of NTG may lead to severe hypotension and headache [1]. Ivabradine is a new class of medication, and works by blocking the If current in the sinoatrial node to slow down heart rate. By lowering the heart rate, it decreases workload and oxygen demand for the heart [3]. In the European Union, ivabradine was approved for the management of symptoms on CSA in patients with history of coronary artery disease (CAD), or for the management of heart failure (HF). Prior to initiating ivabradine for the management of CSA, patients must have heart rates of at least 70 beats per minute, and either cannot tolerate beta blocker therapy, or whose symptoms are not adequately controlled by beta blocker therapy alone [4]. In the United States, ivabradine is only approved for the management of HF, but not for CSA [3].

Efficacy of ivabradine for the relief of angina symptoms was investigated in the 3 main trials, which compared ivabradine to either placebo, amlodipine, or atenolol. Patients 18 years of age or older, with a history of CAD, minimum of 3 months history of stable, effort induced angina, and positive exercise tolerance test [ETT] were eligible for inclusion. When ivabradine 2.5 mg, 5 mg, and 10 mg twice daily were compared to placebo during ETT, all doses of ivabradine significantly increased time to 1-mm ST-segment depression, time to onset of angina symptoms, and time to limiting angina from baseline at peak and trough drug levels. Ivabradine also significantly reduced frequency of angina attacks from 4.14+5.59 attacks per week to 0.95+2.24 attacks per week ($p<0.001$). Short-acting NTG use also decreased from 2.28+3.74 units per week to 0.50+1.14 units per week ($p<0.001$) [5]. When ivabradine 7.5 mg and 10 mg twice daily were compared to amlodipine 10 mg daily or atenolol 100 mg daily during ETT, all doses of ivabradine was non-inferior to amlodipine or atenolol in increasing total exercise duration, time to 1-mm ST-segment depression, and time to onset of angina symptoms from baseline at trough drug level. Ivabradine was also non-inferior to atenolol in extending time to limiting angina. When ivabradine was compared to atenolol at peak drug level, all doses of ivabradine was non-inferior to atenolol 100 mg once daily in increasing all exercise parameters, except for time to 1-mm ST-segment depression. Ivabradine, amlodipine, and atenolol decreased frequency of angina symptoms and NTG use from baseline. No significant difference was found in changes in frequency of angina symptoms or NTG use between ivabradine and amlodipine. Differences between ivabradine and atenolol was not directly compared. Bradycardia and visual disturbances were the most common adverse effects for ivabradine patients. Higher percentage of amlodpine patients experienced peripheral edema [6,7].

As ivabradine was effective in reduce angina symptoms, two clinical trials were conducted to investigate the impact of ivabradine on mortality and hospitalization outcomes. SIGNIFY was a randomized, double-blind, placebo-controlled, event-driven study to investigate ivabradine for the management of stable CAD. Patients with a history of stable CAD without HF were randomized to receive ivabradine 7.5 mg twice daily or matching placebo (patients 75 years of age or older received 5 mg twice daily). Doses were adjusted at follow up visits based on heart rate. Ivabradine patients experienced similar rates of primary endpoint (composite of death due to cardiovascular [CV] causes or nonfatal myocardial infarction [MI]) when compared to patients who received placebo (ivabradine 6.8% vs. placebo 6.4; hazard ratio [HR]: 1.08; 95% confidence interval [CI]: 0.96-1.20; $p=0.20$). Additionally, ivabradine did not decrease risks of death due to any cause (ivabradine 5.1% vs. placebo 4.8%; HR: 1.06; 95% CI: 0.94-1.21; $p=0.35$), death due to CV causes (ivabradine 3.4 vs placebo 3.2%; HR: 1.1; 95% CI: 0.94-1.28; $p=0.25$), or hospitalization for HF (ivabradine 2.3% vs. placebo 1.9%; HR: 1.20; 95% CI: 0.99-1.46; $p=0.07$). In patients with activity limiting angina at baseline (Canadian Cardiovascular Society [CCS] class II or higher), ivabradine was associated with significantly higher risks of primary outcome (ivabradine 7.6%, vs placebo 6.5%; HR: 1.18; 95% CI: 1.03 to 1.35; $p=0.02$). No significant difference was found between ivabradine and placebo in patients without activity-limiting angina at baseline (CCS class I) ($p=0.25$). In the CCS class II or higher groups, more ivabradine patients experienced improvements in CCS angina symptoms than the placebo patients (ivabradine 24%, placebo 18.8%, $p=0.01$). Taking ivabradine was associated with higher risks of symptomatic or asymptomatic bradycardia, atrial fibrillation, and visual disturbances ($p<0.001$ for all) [8].

As ivabradine was not shown to improve outcomes in patients without HF in the SIGNIFY trial, it was investigated again in the BEAUTIFUL trial, which was a randomized, double-blind, placebo-controlled, parallel-group study. Patients with a history of stable CAD, and ejection fraction lower than 40% were randomized to ivabradine 5 mg bid or matching placebo. Dose was adjusted at subsequent visits based on heart rate. No significant difference was found between ivabradine and placebo in the primary endpoint, which was a composite of death due to CV causes, hospital admissions for acute MI, or hospital admissions for new-onset or worsening HF (ivabradine 15.4% vs placebo 15.3%; HR 1.0; 95% CI: 0.91-1.10; $p=0.94$). Ivabradine did not significantly decrease risks of all cause death

(ivabradine 10.4% vs placebo 10.1%; HR: 1.04; 95% CI: 0.92-1.16; p=0.55), death due to CV causes (ivabradine 8.6% vs placebo 8%; HR: 1.07; 95% CI: 0.94-1.22; p=0.32), or hospital admissions for HF (ivabradine 7.8% vs placebo 7.9%; HR: 0.99; 95% CI: 0.86-1.13; p=0.85). In the subgroup of patients with heart rates of 70 beats per minute or higher at baseline, ivabradine was associated with reduced risks of hospital admissions due to MI (3.1% vs 4.9%; HR: 0.64; 95% CI: 0.49-0.84; p=0.001), hospital admission due to MI or unstable angina (5.3% vs 6.8%; HR: 0.78; 95% CI: 0.62-0.97; p=0.023), and coronary revascularization (2.8% vs 4%; HR: 0.70; 95% CI: 0.52-0.93; p=0.016). Higher percent of ivabradine patients experienced bradycardia (13% vs 2%) and visual disturbances (0.5% vs 0.2%) [9].

In patients with CSA, ivabradine has been shown to improve exercise tolerance and was non-inferior to atenolol and amlodipine. Additionally, it decreases frequency of angina symptoms and short acting NTG use [5-7] However, its role in the management of CSA may be limited, as it has not been shown to improve mortality or hospitalization outcomes [8,9]. In the BEAUTIFUL trial, a subgroup of patients with baseline heart rate of 70 beats per minute or higher experienced lower occurrence rates of hospitalization due to MI, hospitalization due to MI or unstable angina, and coronary revascularization [9]. Efficacy of ivabradine on CV mortality, MI, and hospitalization in this subgroup of CSA patients should be explored in future studies. As ivabradine is an off-labelled use for management of CSA in the United States and has not been shown to improve survival, it may only be considered for CSA patients, whose symptoms are not well controlled on, or for patients who cannot tolerate convention therapies such as BBs and CCBs [3,4] Clinicians must ensure that the patient's heart rate is 70 beats per minute or higher prior to prescribing ivabradine. While on ivabradine, patients need to have their vital signs, heart rhythm, and vision monitored closely.

References

1. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. (2013) ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34: 2949-3003.
2. Fihn SD, Gardin JM, Abrams J (2012) ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 60: e44-e164.
3. Ivabradine (Corlanor®) package insert. Amgen Inc, Thousand Oaks, California, USA.
4. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004187/human_med_001911.jsp&mid=WC0b01ac058001d124.
5. Borer JS, Fox K, Jaillon P (2003) Antianginal and Antiischemic Effects of Ivabradine, an If Inhibitor, in Stable Angina: A Randomized, Double-Blind, Multicentered, Placebo-Controlled Trial. Circulation 107: 817-823.
6. Ruzyllo W, Tendera M, Ford I, Fox KM (2007) Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris a 3-month randomised, double-blind, multicentre, noninferiority trial. Drugs 67: 393-405.
7. Tardif JC, Ford I, Tendera M (2005) Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 26: 2529-2536.
8. Fox K, Ford I, Steg PG (2014) Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. N Engl J Med 371: 1091-1019.
9. Fox K, Ford I, Steg PG (2008) Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 372: 807-886.