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The effect of BMS-582949, a P38 mitogen-activated protein kinase (P38 MAPK) inhibitor on arterial inflammation: A multicenter FDG-PET trial

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ABSTRACT

Objectives: This study evaluated the effect of p38 mitogen-activated protein kinase (p38MAPK) inhibitor, BMS-582949, on atherosclerotic plaque inflammation, using ^{18}FDG-PET imaging. p38MAPK is an important element of inflammatory pathways in atherothrombosis and its inhibition may lead to reduced inflammation within atherosclerotic plaques.

Methods: Subjects with documented atherosclerosis (n = 72) on stable low-dose statin therapy and having at least one lesion with active atherosclerotic plaque inflammation in either aorta or carotid arteries were randomized to BMS-582949 (100 mg once daily), placebo, or atorvastatin (80 mg once daily), for 12 weeks. Arterial inflammation was assessed using ^{18}FDG-PET/CT imaging of the carotid arteries and aorta. Uptake of arterial ^{18}FDG was assessed as target-to-background ratio (TBR): 1) as a mean of all slices of the index vessel, and 2) within active slices of all vessels (AS: which includes only slices with significant inflammation (TBR $\geq$ 1.6) at the baseline).

Results: Treatment with BMS-582949 did not reduce arterial inflammation relative to placebo, (ΔTBR $_{index}$: 0.10 [95% CI: −0.11, 0.30], p = 0.34; ΔTBR $_{AS}$: −0.01 [−0.31, 0.28], p = 0.93) or hs-CRP (median %ΔCRP [IQR]: 33.83% [153.91] vs. 16.71% [133.45], p = 0.61). In contrast, relative to placebo, statin intensification was associated with significant reduction of hs-CRP (%ΔCRP [IQR]: −17.44% [54.68] vs. 16.71% [133.45], p = 0.04) and arterial inflammation in active slices (ΔTBR$_{AS}$ = −0.24 [95% CI: −0.46, −0.01], p = 0.04).

Conclusions: The findings of this study demonstrates that in stable atherosclerosis, 12 weeks of treatment with BMS-582949 did not reduce arterial inflammation or hs-CRP compared to placebo, whereas intensification of statin therapy significantly decreased arterial inflammation.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide [1]. Atherothrombosis is the primary cause of ischemic CVD and is caused by the accumulation of inflammatory cells, which culminates in the development of complex atherosclerotic plaques, precursors of acute coronary syndromes [2].

Abbreviations: ^{18}FDG, ^{18}F-fluorodeoxyglucose; hs-CRP, high sensitivity C-reactive peptide; MAPK, mitogen-activated protein kinase; PET, positron emission tomography; ROI, region of interest; SUV, standardized uptake value; TBR, target-to-background ratio.

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Currently, the mainstay for the preventive treatment of atherothrombosis is lipid lowering, mainly using statins, whereby anti-inflammatory effects are believed to contribute to their mechanism of action [3,4]. Statin usage in secondary prevention trials has been shown to produce about a 30% reduction in events, which leaves approximately 70% of the events unattenuated [5]. Novel treatments are therefore needed to address the residual risk.

Inflammation is a critical component in the pathogenesis of atherothrombosis [6] and represents an attractive therapeutic target [7]. Novel anti-inflammatory therapeutics have been developed targeting specific intracellular protein kinases to suppress key mediators of inflammation. One approach is targeted towards the inhibition of the p38 mitogen-activated protein kinases (P38 MAPKs) [8]. P38 MAPKs are members of a key signaling pathway responsible for the cellular response to various extracellular stresses, which function to orchestrate a broader cellular response [9]. Activation of P38 MAPKs is linked to increased production of inflammatory mediators such as proinflammatory cytokines, prostaglandins/prostacyclins and matrix metalloproteinases [9]. In humans, the inhibition of p38 MAPK has been demonstrated to improve nitric oxide mediated vasodilation accompanied by a reduction in systemic inflammation [10], and a decrease in neointima formation and systemic inflammatory markers, after percutaneous coronary intervention [11].

Quantification of inflammation in atherosclerotic plaques with ^{18}FDG-PET is based on the metabolic activity of plaque macrophages, which avidly take up ^{18}F-fluordeoxyglucose (^{18}FDG). ^{18}F-fluordeoxyglucose then becomes metabolically trapped and can be detected non-invasively with positron emission tomography (PET) [12,13]. This technique has been demonstrated as a reproducible imaging modality for the evaluation of inflammation in atherosclerotic plaques in both animal and human studies and allows for non-invasive efficacy assessment of therapeutic interventions [14–18].

Recently, the dual αβ subtype, p38 MAPK inhibitor, losmapimod (7.5 mg once daily for 12 weeks), was associated with a modest reduction in arterial inflammation in stable atherosclerosis subjects, as measured by ^{18}FDG-PET/CT [19]. Furthermore, a significant reduction of inflammation in visceral fat and a persistent reduction in high sensitivity C-reactive peptide (hsCRP) was observed. In contrast to losmapimod, BMS-582949 is a novel highly selective p38α MAPK inhibitor [20]. In the current study, we sought to evaluate the effect of BMS-582949 on arterial inflammation in subjects with stable atherosclerosis, and to compare this potential anti-inflammatory action to the effect of statin intensification (using high-dose atorvastatin in subjects already on low-dose statins at baseline).

2. Methods

This 12 week, randomized, partially double-blinded study (double-blind for BMS-582949 and placebo, open label administration of atorvastatin 80 mg) was conducted at 17 US Centers in compliance with the principles of the Declaration of Helsinki and according to Good Clinical Practice guidelines (www.clinicaltrails.gov, NCT00570752). The protocol was reviewed and approved by each center's institutional review board and all participants provided written informed consent prior to any study procedures.

The predefined study objective was to determine whether 12 weeks of treatment with BMS-582949 results in a significant reduction of ^{18}FDG uptake signal from baseline in the carotid arteries and thoracic aorta compared to placebo. The vessel used for the primary per-protocol endpoint is the index vessel (the vessel with highest ^{18}FDG uptake at baseline). The index vessel was then evaluated for the change of FDG uptake in a 12 week period, which is defined in more detail below (see image analysis).

2.1. Study population

Men and woman 18–75 years old were included if there was a documented history of atherosclerosis defined as: 1) carotid artery disease (defined as > 50% stenosis) documented on angiography, MRA, CTA or carotid ultrasound ± a history of stroke or TIA ≥ 3 months prior to randomization; 2) coronary artery disease documented by angiogram (2 or more vessels with >50% stenosis) or MDCT ± history of acute coronary syndrome (ACS) event [ST elevation myocardial infarction (STEMI), non-STEMI, or unstable angina] documented by ECG, cardiac enzymes, or angiogram ≥ 3 months prior to randomization; 3) symptomatic peripheral artery disease documented by angiography, MRA, CTA or ankle brachial index < 0.74. Additional inclusion criteria included low-density lipoprotein cholesterol (LDL-C) between 70 and 130 mg/dL. Subjects were on a stable low-to moderate-dose statin and the permitted statin drugs/doses were atorvastatin ≤20 mg, simvastatin ≤40 mg, rosuvastatin ≤10 mg, pravastatin ≤40 mg, fluvastatin ≤80 mg or lovastatin ≤40 mg for at least 6 weeks prior to screening. A Body Mass Index (BMI) of 20–35 kg/m^2 was inclusive.

Exclusion criteria included intolerance to statins or presence of chronic inflammatory diseases. A complete list of exclusion criteria is provided in the supplement. After initial screening, subjects underwent baseline FDG-PET imaging. The subjects with average maximum target-to-background ratio (TBR) ≥1.6 in at least one vessel (either the aorta, right or left carotid artery), were eligible for randomization. Subjects were randomized 1:1:1 to either placebo + background therapy (low-to moderate-dose statin therapy; current prescribed medication), BMS-582949 (Bristol-Myers Squibb, Princeton, NJ; 100 mg/day) while continuing background therapy (low-to moderate-dose statin therapy and current prescribed medication) or Atorvastatin 80 mg/day (Pfizer, New York, NY) while low-to moderate-dose statin therapy was discontinued and subjects were randomized to 80 mg atorvastatin alone in a non-blinded fashion (statin intensification) (Fig. 1).

2.2. ^{18}FDG-PET and contrast-enhanced CT imaging

^{18}FDG-PET imaging of the carotid arteries and ascending thoracic aorta was performed using reproducible and validated methods [21,22]. ^{18}FDG was administered intravenously (10 mCi) after at least a 4 h fast and image acquisition was performed 2 h later. An attenuation correction scan was obtained using a voltage of 140 kVp. PET imaging was performed covering the neck and chest, with 15 min per bed position. Reconstruction of attenuation-corrected images was performed using an Ordered Subset Expectation Maximation (OSEM) algorithm. All subjects had a blood sugar concentration of <200 mg/dL at the time of imaging. Contrast-enhanced CT imaging was performed once (at baseline or at week 4) to provide anatomical information for image analysis. CT parameters included: a tube voltage of 120 kVp, tube current of ~750 mAs, slice section thickness of 0.75 mm and a pitch of 0.2–0.4, following injection of I.V. contrast.

2.3. ^{18}FDG-PET image analysis

Images were blinded to subject identifiers and temporal