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LETTERS TO THE EDITOR

FDG-PET Imaging for Oxidized LDL in Stable Atherosclerotic Disease: A Phase II Study of Safety, Tolerability, and Anti-Inflammatory Activity

Previous reports have demonstrated that oxidized low-density lipoprotein (oxLDL) is a key mediator in atherogenesis (1). oxLDL increases endothelial cell adhesion molecules, recruitment of inflammatory cells into the vessel wall, and formation of foam cells, all hallmarks of atherosclerosis (1). In preclinical models, antibodies to oxLDL decreased atherosclerotic burden (2). Accordingly, available data have suggested that oxLDL antibody therapy may attenuate atherosclerotic inflammation and stabilize plaques.

Positron emission tomography (PET) imaging with ^{18}F-fluorodeoxyglucose (FDG) is used to quantify arterial inflammation. PET imaging measures of FDG uptake are reproducible, correlate with macrophage infiltration, are predictive of future clinical cardiovascular events, and are modifiable by antiatherosclerotic interventions (3). As such, this imaging approach has been widely adopted for noninvasive assessment of plaque inflammation in response to interventions.

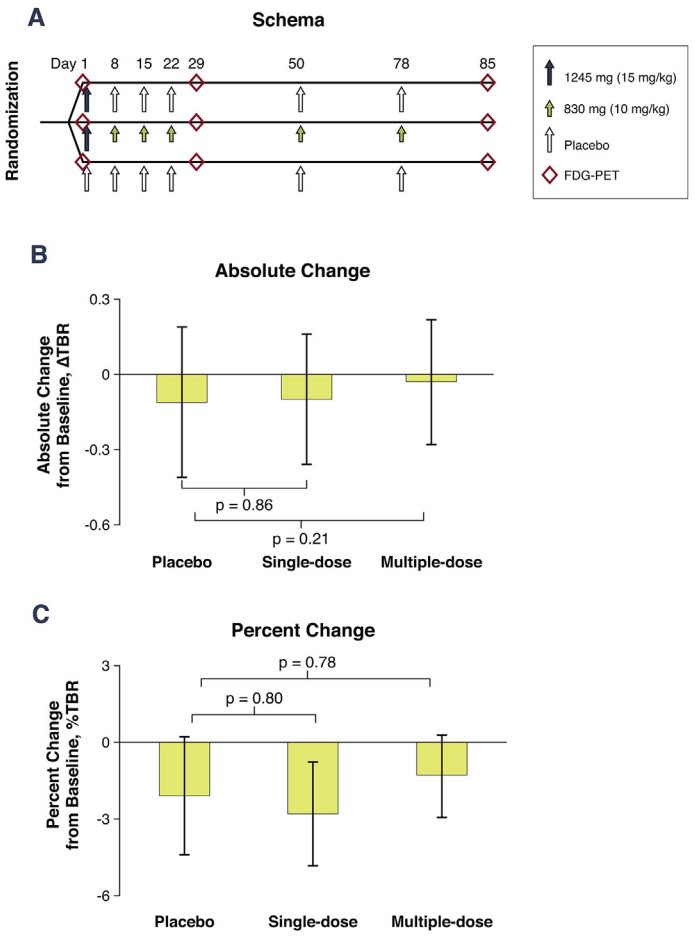
The GLACIER (Goal of Oxidized LDL and Activated Macrophage Inhibition by Exposure to a Recombinant Antibody) trial is the first multicenter, randomized, double-blind study evaluating an anti-oxLDL targeted monoclonal antibody in patients with stable inflammatory vascular lesions. We tested the hypothesis that selective inhibition of oxLDL by MLDL1278A, a recombinant immunoglobulin G1 antibody targeting a malondialdehyde-modified epitope of ApoB-100, reduces atherosclerotic inflammation (as assessed with FDG-PET). The study population consisted of 147 participants (83% male; mean age 63.0 ± 9.0 years) with atherosclerosis and evidence of carotid or aortic plaque inflammation, measured by FDG-PET/computed tomography (CT). Patients were randomized 1:1:1 to receive MLDL1278A in: 1) a single intravenous (IV) infusion, followed by placebo to maintain blinding; 2) multiple IV infusions; or 3) multiple placebo IV infusions (**Figure 1A**). Patients remained on standard-of-care therapy, including background statins, and underwent serial FDG-PET/CT scans. Serum biomarkers were obtained concurrently with imaging.

Arterial FDG uptake was assessed as target-to-background ratio (TBR). The artery with the highest TBR at baseline was identified as the index vessel. A focal measure of arterial FDG activity, most diseased segment (MDS)-TBR, defined as 3 contiguous segments centered on the arterial slice demonstrating the highest FDG uptake at baseline, was determined. The primary outcome variable was change in index vessel MDS-TBR measured by FDG-PET/CT from baseline to week 12. Secondary outcomes were: 1) change in index vessel MDS-TBR from baseline to week 4; 2) incidence of adverse events; and 3) presence of antitherapeutic antibodies to MLDL1278A.

Baseline demographics were comparable among groups for the 117 patients with evaluable week 12 FDG-PET images included in the primary analyses. Although high serum concentrations of MLDL1278A were achieved throughout the study for both treatment groups, treatment did not significantly reduce arterial inflammation (primary endpoint of index vessel MDS-TBR) versus placebo (**Figures 1B and 1C**). MLDL1278A was well tolerated, and there was no evidence of immunogenicity. Notably, a nominal increase in the levels of tumor necrosis factor alpha ($p = 0.03$) and interleukin 6 ($p = 0.04$) occurred at 4 weeks in the multiple-dose group. No significant decreases in lipid parameters or high-sensitivity C-reactive protein level were observed in either group. Further, none of the secondary outcomes were different between groups.

The hypothesized mechanism of action of MLDL1278A involves immune complex formation with oxLDL within plaques, resulting in inhibition of inflammatory macrophages. It is possible that MLDL1278A binding may be restricted to oxLDL-rich inflamed plaques, which may have been less common in this population with stable cardiovascular disease on background statins. Indeed, statin therapy has been shown to reduce lipoprotein oxidation biomarker levels. Accordingly, it is plausible that a larger number of patients may be required to detect an incremental effect of MLDL1278A on plaque burden and progression. Further, it is possible that a follow-up period of 3 months and lack of coronary artery assessment may be inadequate to assess potential anti-inflammatory effects of MLDL1278A.

FIGURE 1 Schema and Primary Endpoint Analysis of Index Vessel MDS-TBR



(A) Treatment schematic. No significant **(B)** absolute or **(C)** percent change from baseline across groups. *Whiskers indicate standard error. FDG = ^{18}F-fluorodeoxyglucose; MDS = most diseased segment; PET = positron emission tomography; TBR = target-to-background ratio.

However, it should be noted that other prospective FDG-PET/CT studies examining arterial wall inflammation have observed significant treatment effects as early as 1 to 4 months (3), and recent studies have demonstrated that changes in FDG activity in large arteries mirror those in the coronary circulation.

Although MLDL1278A did not reduce either imaging or circulating markers of inflammation in this study, this finding is not necessarily generalizable to other antibody-based approaches targeting oxLDL, which may target other oxLDL epitopes and have distinct in vitro effects. Future therapeutic approaches, such as vaccination against oxLDL or administration of immunoglobulin M class anti-oxidized phospholipid, warrant investigation as well.

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