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The PACMAN-AMI trial: game over for the "vulnerable plaque"?

Rocco Vergallo [1]* **and Carlo Patrono** [2]

[1]Department of Cardiovascular Medicine, Interventional Cardiology Unit, Fondazione Policlinico Universitario A. Gemelli—IRCCS, Catholic University of the Sacred Heart, Largo A. Gemelli, 8, 00168 Rome, Italy; and [2]Department of Pharmacology, Catholic University of the Sacred Heart, Rome, Italy

Comment on the article 'Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial', published in *JAMA*, doi:10.1001/jama.2022.5218.

Key Points

- The PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) trial is an investigator-initiated, multicentre, double-blind, randomized clinical trial aiming to determine the effects of 1-year treatment with the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor alirocumab in addition to statin therapy on coronary atherosclerosis assessed by serial multimodality intracoronary imaging in patients with acute myocardial infarction (AMI).[1] The primary hypothesis was that, when compared with placebo, treatment with alirocumab would determine a greater reduction in percent atheroma volume (PAV) in non-infarct-related arteries (IRAs), as measured by serial intravascular ultrasound (IVUS). At nine European centres, 300 patients (mostly statin-naïve) with AMI undergoing percutaneous coronary intervention (PCI) of the IRA and successful multimodality intracoronary imaging of two non-IRAs were randomized to receive biweekly subcutaneous alirocumab 150 mg ($n = 148$) or placebo ($n = 152$), initiated <24 h after urgent PCI of the culprit lesion, and continued for 52 weeks in addition to rosuvastatin 20 mg, without dose adjustment in either treatment.
- Patients underwent multimodality invasive imaging with IVUS, near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT) in the proximal segments of two non-IRAs during the index procedure and after 52 weeks. The primary endpoint was the change in PAV assessed by IVUS. The two powered secondary endpoints were: (i) the change in the maximum lipid core burden index (LCBI) within 4 mm assessed by NIRS and (ii) the change in minimal fibrous cap thickness measured by OCT imaging.
- Out of 300 randomized patients (mean age, 59 years; 19% females), 265 (88%) underwent serial IVUS imaging in 537 arteries. At Week 52, the mean change in PAV was −2.13% with alirocumab vs. −0.92% with placebo [difference, −1.21; 95% confidence interval (CI), −1.78 to −0.65%; $P < 0.001$]. When compared with placebo, patients randomized to alirocumab showed a significantly greater reduction in maximum LCBI within 4 mm (difference, −41.24; 95% CI, −70.71 to −11.77; $P = 0.006$), and a significantly greater increase in minimal fibrous cap thickness (difference, 29.65 μm; 95% CI, 11.75–47.55; $P = 0.001$).
- At Week 52, LDL cholesterol (LDL-C) level was 23.6 ± 23.8 mg/dL in the alirocumab group and 74.4 ± 30.5 mg/dL in the placebo group ($P = 0.001$), representing 85 and 51% reduction vs. baseline, respectively. Patients in the alirocumab group also showed significantly greater decreases in triglycerides, lipoprotein(a), and apolipoprotein B, without significant difference in high-sensitivity C-reactive protein levels.

Comment

Acute coronary syndromes (ACS) typically develop from the rupture or superficial erosion of an atherosclerotic plaque causing subocclusive or occlusive thrombosis of a coronary artery, and these events generally follow the disruption of a delicate balance between instability and healing capacity.[2] During the past three decades, the advancement of intravascular imaging techniques enabled the *in vivo* identification of atherosclerotic plaque phenotypes at higher risk of causing ACS.[3,4] Plaques with large atheroma burden, characterized by a large lipid pool and a thin fibrous cap (i.e. thin-cap fibroatheroma) infiltrated by macrophages represent the rupture-prone phenotype.[3,4] Previous IVUS and OCT studies showed that statin treatment can slow or halt the progression, or cause the regression of atherosclerotic

* Corresponding author. Tel: +39 0630154462, Email: rocco.vergallo@policlinicogemelli.it, rocco.vergallo@unicatt.it

plaques, by reducing lipid content and thickening the overlying fibrous cap.[5] Mounting evidence suggests that the combination of a PCSK9 inhibitor with statin therapy might have an additive favourable effect on atherosclerotic plaque burden and phenotype.[6] The PACMAN-AMI trial indeed found that early PCSK9 inhibition produced incremental benefits on coronary plaque evolution, composition, and phenotype beyond the beneficial effects of statin therapy.[1]

This trial is unique in providing a comprehensive phenotypic and morphometric characterization of coronary atherosclerosis by using two imaging catheters (i.e. IVUS-NIRS and OCT) in multiple non-IRAs, at two time points, and this represents the main strength of the trial. The difference in PAV reduction observed in patients treated with alirocumab when compared with placebo (i.e. −1.21%), which may appear small at first glance, is actually larger than measured in previous trials,[6] and exceeds the difference in atheroma volume that has been reported to have an impact on cardiovascular outcomes.[7] The absolute reduction in PAV in the alirocumab group (i.e. 2.3%), which is more than two times greater than that found in similar trials,[6] may be due to the fact that the vast majority of patients (∼90%) enrolled in the PACMAN-AMI were statin-naïve, and the observed additive effect on plaques may therefore be explained by the concomitant initiation of statin and PCSK9 inhibitor. Other important findings of the study are the significantly greater reduction in lipid burden by NIRS and increase in OCT-measured minimal fibrous cap thickness (both hallmarks of 'vulnerable plaque') in the alirocumab group. While these observations are of potential clinical interest, it is important to interpret them with respect to the overall data provided by the authors. In particular, while repeated measurements of all the study endpoints with their relative between-group and across time points differences were provided, no data were reported about the number and phenotype of the analysed plaques. While PAV can be measured for all types of lesions, lipid burden and fibrous cap thickness can be assessed only if a fibroatheroma is present, and this crucial information is missing in the present report.

There are a number of additional points that need to be considered when analysing the results of the trial. First, while acknowledging the complexity of conducting an imaging study with these characteristics, the sample size ($n = 300$) was relatively small, and a non-trivial proportion of patients (12%) did not undergo an assessment at 52 weeks. The study was therefore largely underpowered for the assessment of clinical outcomes. Furthermore, women (19%) and diabetic patients (10%) were under-represented in the study population. Finally, all patients enrolled in the study were treated with rosuvastatin 20 mg. Although this represents a high-intensity lipid-lowering regimen, there is considerable individual variation in the achieved LDL-C reduction,[8] and a substantial proportion of patients with AMI usually need higher intensity regimens (e.g. rosuvastatin 40 mg, or atorvastatin 80 mg) to achieve LDL-C target levels, in particular during the first months after the acute event. In fact, the mean LDL-C level achieved in the placebo group after 52 weeks of statin therapy indicates that the vast majority of patients had not reached the target level recommended by current guidelines (i.e. <55 mg/dL).[9] This finding reinforces the importance of early achievement of LDL-C target soon after AMI, and a missing analysis of the data is whether the extent of individual PAV changes correlated with the achieved LDL-C level.

Despite these limitations, the PACMAN-AMI trial represents one of the most relevant studies of the natural history of coronary atherosclerosis in the current era of intensive secondary prevention, possibly providing the missing link between further lipid-lowering with PCSK9 inhibitors after AMI and incremental reduction in major adverse cardiovascular events observed in large clinical trials.[10]

Conflict of interest: R.V. reports personal fees from Abbott Vascular and Terumo, outside the submitted work. C.P. reports personal fees from Acticor Biotech, personal fees from Amgen, personal fees from Bayer, personal fees from Eli Lilly, personal fees from Tremeau, personal fees from Zambon, grants from AIFA (Italian Drug Agency), grants from the European Commission, other from Scientific Advisory Board of the International Aspirin Foundation, outside the submitted work.

References

1. Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, *et al.* Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA*; https://doi.org/10.1001/jama.2022.5218. Published online ahead of print.
2. Vergallo R, Crea F. Atherosclerotic plaque healing. *N Engl J Med* 2020;**383**:846–857.
3. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, *et al.* A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364**:226–235.
4. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y, *et al.* Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;**41**:383–391.
5. Hou J, Xing L, Jia H, Vergallo R, Soeda T, Minami Y, *et al.* Comparison of intensive versus moderate lipid-lowering therapy on fibrous cap and atheroma volume of coronary lipid-rich plaque using serial optical coherence tomography and intravascular ultrasound imaging. *Am J Cardiol* 2016;**117**:800–806.
6. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, *et al.* Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016;**316**:2373–2384.
7. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, *et al.* Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010;**55**:2399–2407.
8. Karlson BW, Wiklund O, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother* 2016;**2**:212–217.
9. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
10. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, *et al.* Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**: 2097–2107.