ORIGINAL PAPER

Hellenic Journal of Atherosclerosis 4(1):56–58

The effect of simvastatin or its combination with ezetimibe on mean platelet volume in patients with primary dyslipidemia

E. Moutzouri, A. Kei, M. Elisaf

Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece

INTRODUCTION: A growing body of evidence points towards mean platelet volume as an independent risk factor for cardiovascular disease. Statins are the cornerstone of lipid lowering treatment and are associated with improved outcomes either in primary or secondary prevention of cardiovascular disease. This benefit has been attributed not only to their lipid-lowering effects, but also to various pleiotropic properties. Ezetimibe is a newer hypolipidemic treatment, which effectively reduces low density lipoprotein cholesterol (LDL-C). Treatment with ezetimibe plus a low statin-dose is common in everyday clinical practice and induces similar or even greater reductions in LDL-C compared with a higher statin dose.

MATERIAL-METHODS: To compare the effects of simvastatin 40 mg or simvastatin/ezetimibe 10/10 mg, daily on mean platelet volume levels in dyslipidemic patients. This was a prospective, randomized, open-label, blinded endpoint (PROBE) study. After a 3-month period of lifestyle changes patients (n=100) with LDL-C levels above those recommended by the NCEP ATP III based on each patient risk factors, were randomly al-

Moses Elisaf

2nd Department of Internal Medicine, School of Medicine, University of Ioannina, GR-451 10 Ioannina, Greece

Tel.: (+30) 2651-007 509, Fax: (+30) 2651-007 516

e-mail: egepi@cc.uoi.gr

ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Ελληνική Επιθεώρηση Αθηροσκλήρωσης 4(1):56–58

Η επίδραση της σιμβαστατίνης ή του συνδυασμού σιμβαστατίνης με εζετιμίμπη στον μέσο όγκο αιμοπεταλίων σε ασθενείς με πρωτοπαθή δυσλιπιδαιμία

Ε. Μουτζούρη, Α. Κεή, Μ. Ελισάφ

Β΄ Παθολογική Κλινική, Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα, Ελλάδα

ΕΙΣΑΓΩΓΗ: Σύγχρονα δεδομένα δείχνουν ότι ο μέσος όγκος αιμοπεταλίων πιθανόν αποτελεί ανεξάρτητο παράγοντα καρδιαγγειακού κινδύνου. Η θεραπεία με στατίνες αποτελεί τον ακρογωνιαίο λίθο της υπολιπιδαιμικής αγωγής ενώ σχετίζεται με ευνοϊκά αποτελέσματα τόσο στην πρωτογενή όσο και στη δευτερογενή πρόληψη της καρδιαγγειακής νόσου. Οι ωφέλιμες δράσεις των στατινών δεν οφείλονται μόνο στις υπολιπιδαικές τους δράσεις αλλά και στις αποκαλούμενες «πλειοτροπικές δράσεις». Η θεραπεία με τον συνδυασμό εζετιμίμπης και χαμηλής δόσης μίας στατίνης είναι συνήθης στην κλινική πράξη και επιτυγχάνει ίση ή και μεγαλύτερη μείωση της LDL-χοληστερόλης σε σύγκριση με μονοθεραπεία με στατίνη σε υψηλότερη δοσολογία.

ΥΛΙΚΟ-ΜΕΘΟΔΟΣ: Η σύγκριση της επίδρασης της σιμβαστατίνης 40 mg ή του συνδυασμού σιμβαστατίνης με εζετιμίμπη 10/10 mg ημερησίως, στον μέσο όγκο αιμοπεταλίων σε ασθενείς με υπερχοληστερολαιμία. Η μελέτη σχεδιάστηκε ως δοκιμή PROBE (προοπτική, τυχαιοποιημένη, ανοιχτή με τυφλή αξιολόγηση τελικού στόχου). Υπερχοληστερολαιμικοί ασθενείς (N=100), που δεν

Μωυσής Ελισάφ

Β΄ Παθολογική Κλινική, Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων, 451 10 Ιωάννινα

Τηλ.: 2651-007 509, Fax: 2651-007 516

e-mail: egepi@cc.uoi.gr

located to open-label simvastatin 40 mg (N=50) or simvastatin/ezetimibe 10/10 mg (N=50) daily. Both groups were similar with regard to demographics, risk factors, medications and baseline lipid values. Mean platelet volume was blindly assessed at baseline and 3 months post-treatment in both groups.
RESULTS: Both simvastatin 40 mg and simvastatin 10 mg with ezetimibe 10 mg daily for 12 weeks did not affect mean platelet volume (from 10.9±0.6 fl to 10.9±0.6 fl and from 11.1±0.9 fl to 11.2±0.9 fl, respectively, P=NS versus baseline, P=NS between groups).
CONCLUSIONS: Neither simvastatin nor its combination with ezetimibe changes mean platelet volume in patients with primary hypercholesterolemia

πέτυχαν τον στόχο της LDL-χοληστερόλης μετά από 3 μήνες υγιεινοδιαιτητικής αγωγής, τυχαιοποιήθηκαν σε θεραπεία με σιμβαστατίνη 40 mg (N=50) ή συνδυασμό σιμβαστατίνης 10 mg με εζετιμίμπη 10 mg (N=50). Οι δύο ομάδες δεν διέφεραν ως προς τα δημογραφικά στοιχεία, τους παράγοντες κινδύνου, τη φαρμακευτική αγωγή και τα επίπεδα λιπιδίων, πριν την έναρξη της θεραπείας. Ο μέσος όγκος αιμοπεταλίων μετρήθηκε και στις 2 ομάδες πριν και μετά από 3 μήνες θεραπείας.
ΑΠΟΤΕΛΕΣΜΑΤΑ: Τόσο η σιμβαστατίνη 40 mg όσο και ο συνδυασμός σιμβαστατίνης 10 mg με εζετιμίμπη.
ΣΥΜΠΕΡΑΣΜΑΤΑ: Ούτε η σιμβαστατίνη ούτε ο συνδυασμός της σιμβαστατίνης με εζετιμίμπη επηρεάζουν το μέσο όγκο αιμοπεταλίων σε ασθενείς με υπερχοληστερολαιμία.

Key words: Simvastatin, ezetimibe, mean platelet volume, platelets.

Λέξεις ευρετηρίου: Σιμβαστατίνη, εζετιμίμπη, μέσος όγκος αιμοπεταλίων, αιμοπετάλια.

1. Introduction

A growing body of evidence is pointing towards platelet indices as independent risk factors for cardiovascular disease. Increased mean platelet volume (MPV) has been associated with higher rate of myocardial infarction, stroke and vascular mortality.[1–3]

Statins are the cornerstone of both primary and secondary cardiovascular disease (CVD) prevention. Experimental and clinical studies have demonstrated that statins are associated with antiplatelet and antithrombotic effects via several mechanisms not yet completely elucidated.[4–7] Whether ezetimibe exhibit non-lipid lowering related actions remains a controversy.[8]

We have previously described the effects of simvastatin 40 mg and simvastatin/ezetimibe 10/10 mg, on small dense low-density lipoprotein cholesterol (sdLDL-C) concentration in subjects with primary hypercholesterolemia.[9] We now report on a pre-specified analysis regarding the effect of these treatment modalities on platelet indexes.

2. Patients and methods

Study population and protocol have been previously described.[9] In brief, consecutive patients with primary hypercholesterolemia (N=100) participated in the present study. After 12 weeks of dietary intervention, patients who continued to meet the inclusion criteria were randomly allocated to receive open-label simvastatin 40 mg or simvastatin/ezetimibe 10/10 mg for 12 weeks.

3. Results/Discussion

Neither simvastatin 40 mg nor the combination of simvastatin 10 mg with ezetimibe 10 mg significantly affected MPV (from 10.9±0.6 fl to 10.9±0.6 fl and from 11.1±0.9 fl to 11.2±0.9 fl, respectively, P=NS versus baseline, P=NS between groups).

In general, platelet size, expressed as MPV, reflects platelet activity as larger platelets represent immature, hyperactive platelets which release more prothrombotic mediators, thereby promoting atherothrombotic processes.[10,11] MPV is an emerging risk factor for overall vascular mortality and ischemic heart disease.[12,13] Experimental and clinical studies have demonstrated that statins are associated with antiplatelet and antithrombotic effects via several mechanisms not yet completely elucidated.[4–7] It is not known whether this combination therapy has the same pleiotropic effects as a statin monotherapy.

Ali et al showed that statins *in vitro* may inhibit platelet function, by activating peroxisome proliferator-activated receptors (PPARs) in platelets.[6] In a study in patients with stable coronary artery disease and type 2 diabetes or impaired glucose tolerance, high dose simvastatin or low dose simvastatin plus ezetimibe did not affect basal or adenosine diphos-

phate (ADP), or thrombin-induced platelet P-selectin expression, or fibrinogen binding, platelet-leukocyte aggregation or ADP-induced platelet aggregation.[14] In another study in 56 patients with coronary artery disease, atorvastatin 40 mg significantly reduced platelet activation markers (P-selectin) after ADP-induced stimulation, while its combination with ezetimibe did not significantly affected platelet activation.[15]

Data regarding the effects of drugs on MPV are few. Treatment with rosuvastatin (10 mg/day for 12 weeks) was associated with MPV reduction (from 8.4±1.2 fl to 8.1±1.3 fl, P<0.001) in dyslipidemic patients, in a lipid independent manner.[7,16]

In our study, we found that neither simvastatin nor its combination with ezetimibe affects MPV in hypercholesterolemic subjects. This difference as compared to rosuvastatin may be partly abscribed to the lipophilic nature of simvastatin compared with the hydrophilic nature of rosuvastatin.

References

1. Slavka G, Perkmann T, Haslacher H et al. Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. *Arterioscler Thromb Vasc Biol* 2011, 31:1215–1218
2. Jindal S, Gupta S, Gupta R et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. *Hematology* 2011, 16:86–89
3. Pikija S, Cvetko D, Hajduk M et al. Higher mean platelet volume determined shortly after the symptom onset in acute ischemic stroke patients is associated with a larger infarct volume on CT brain scans and with worse clinical outcome. *Clin Neurol Neurosurg* 2009, 111:568–573
4. Mitsios JV, Papathanasiou AI, Goudevenos JA et al. The antiplatelet and antithrombotic actions of statins. *Curr Pharm Des* 2010, 16:3808–3814
5. Matetzky S, Fefer P, Shenkman B et al. Statins have an early antiplatelet effect in patients with acute myocardial infarction. *Platelets* 2011, 22:103–110
6. Ali FY, Armstrong PC, Dhanji AR et al. Antiplatelet actions of statins and fibrates are mediated by PPARs. *Arterioscler Thromb Vasc Biol* 2009, 29:706–711
7. Coban E, Afacan B. The effect of rosuvastatin treatment on the mean platelet volume in patients with uncontrolled primary dyslipidemia with hypolipidemic diet treatment. *Platelets* 2008, 19:111–114
8. Kalogirou M, Tsimihodimos V, Elisaf M. Pleiotropic effects of ezetimibe: do they really exist? *Eur J Pharmacol* 2010, 633:62–70
9. Florentin M, Liberopoulos EN, Moutzouri E et al. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. *Curr Med Res Opin* 2011, 27:685–692
10. Thompson CB, Jakubowski JA, Quinn PG et al. Platelet size and age determine platelet function independently. *Blood* 1984, 63:1372–1375
11. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007, 357:2482–2494
12. Wang RT, Li Y, Zhu XY et al. Increased mean platelet volume is associated with arterial stiffness. *Platelets* 2011
13. Lippi G, Filippozzi L, Salvagno GL et al. Increased mean platelet volume in patients with acute coronary syndromes. *Arch Pathol Lab Med* 2009, 133:1441–1443
14. Malmstrom RE, Settergren M, Bohm F et al. No effect of lipid lowering on platelet activity in patients with coronary artery disease and type 2 diabetes or impaired glucose tolerance. *Thromb Haemost* 2009, 101:157–164
15. Piorkowski M, Fischer S, Stellbaum C et al. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? *J Am Coll Cardiol* 2007, 49:1035–1042
16. Jagroop IA, Tsiara S, Mikhailidis DP. Mean platelet volume as an indicator of platelet activation: methodological issues. *Platelets* 2003, 14:335–336

Ημερομηνία Υποβολής 01/12/2011
Ημερομηνία Έγκρισης 28/03/2012