Ezetimibe, a cholesterol absorption inhibitor reduces the levels of LDL considerably, when added to statin. Its use in USA is widespread (34 million prescriptions in 2006). Its worldwide sale of over $ 5 billion, with nearly one million prescriptions/wk, is 15.2% of all lipid lowering prescriptions. In India too, almost all major pharmaceutical firms have many preparations combining statin with ezetimibe. However the effect of ezetimibe on cardio-vascular events or progression of atherosclerosis remains undocumented.

In ‘Ezetimibe and Simvastatin in Familial Hypercholesterolemia, ENHANCES Atherosclerosis Regression (ENHANCE)’ trial, a multicentric, multinational trial, 720 patients were treated with 80 mg of simvastatin and 10 mg of ezetimibe or a placebo, for a period of 24 months to assess the effect on carotid artery intima-media thickness. At end of 2 yrs the carotid artery intima-media thickness was 0.0058 ± 0.0037 mm in simvastatin alone group and 0.0111 ± 0.0038 in simvastatin – ezetimibe group (P=0.29). The LDL level was 192.7 ± 60.3 mg per deciliter in the former and 141.3 ± 52.6 in the combined group (dif. of 16.5% P <.01) C-Reactive protein difference was 25.7% (P < .01). Side-effects were similar. Thus in a two year clinical trial, the addition of ezetimibe to Simvastatin had no incremental beneficial effect on progression of atherosclerosis, as measured by carotid artery intima-media thickness, despite additional lowering of levels of LDL and C-RP.

This has raised some important questions.
(1) Is the concept ‘Lower the Better’ for LDL no longer true?

It has been our belief since almost 2 decades. During last few years, numerous controlled trials of statin, resins or partial ileal bypass have conclusively shown that both clinical and imaging benefits have correlated with the level of LDL.

(2) Is the rate of change in carotid intima-media thickness, an effective surrogate point for the rate of clinical cardiovascular events?

30 out of 34 studies on correlation between intima-media thickness and coronary atherosclerosis have shown modest positive correlation. In one study, annual increase of 0.03 mm in thickness tripled the rate of coronary events over 8.8 yrs. In seven statin trials, progression of intima-media thickness has slowed and shown even regression. Thus it appears that carotid intima-media thickness is a good surrogate end point for clinical CVS events. But it appears that 1-2 yrs are required for this effect.

(3) How important is statin pretreatment?

Brown and Taylor have advanced an hypothesis that ‘ENHANCE’ results might be explained by previous statin treatment, leading to plaque lipid depletion and hence no further changes. However 19% of patients who had no statin pretreatment, also showed similar results. Ezetimibe lowers LDL, by diminishing intestinal cholesterol absorption by inhibiting the Niemann-Pick C1-like 1 (NPC1L) enterocyte receptor. It is theoretically possible that it may trigger other proatherogenic gene regulatory mechanisms including the inhibition of scavenger receptor B1 (SRB1) and ATP binding cassette transporter A1 (ABCA1). Ezetimibe also lacks pleiotropic effects of statins viz. reduced vascular and platelet reactivity, antiinflammatory action and improvement in endothelial function. It is possible that lipid-independent effects of statins that are not shared by ezetimibe are involved in production of vascular benefit and prevention of coronary events.

In the mean time, what should a practising physician do?

‘ENHANCE’ is only an imaging trial. There can be lots of problems with imaging trial. Also imaging is also only a biomarker, like LDL is. Many may rely more on LDL and continue to prescribe it. This question as to whether ezetimibe reduces cardiovascular events, is addressed in 3 ongoing trials involving over 20,000 patients, including the trial VCTOO202878 (IMPROVE-IT:Vyporin Efficacy International Trial). The last one will have 18000 patient. However the results would be available only in 2011. Till that data is available it would be advisable to use maximum optimal dose of statin to reduce LDL to therapeutic levels. Niacin, fenofibrate and resins must be considered, if necessary Ezetimibe should be reserved for patients, who can not tolerate these agents. Many will continue to use it, as it lowers LDL and CRP and have no side effects.

ACC issued a statement that patient should not panic about ENHANCE results. It recommends that ezetimibe is still a reasonable option for patients who can not tolerate statins, or who tolerate only low doses of statin or who do not achieve LDL goal, inspite of high dose of statin.

REFERENCES

Professor Emeritus, Nanavati Heart Institute, Mumbai - 400 056.


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Announcement

8th International Symposium on Diabetes
Venue: Mumbai Date: 24th & 25th January 2009
Theme: Diabetes Update 2009

Course Directors: Prof. K. Sreekumaran Nair, David Murdock Dole Professor and Professor of Medicine, Division of Endocrinology, Mayo Clinic, 200 First Street S.W. Rochester, MN 55905 USA.
Dr. AK Das, Additional Director of Health Services and Director, Department of Medicine, JIPMER, Pondicherry.

CME credits will be awarded

For further details contact: Dr. Shashank R Joshi, Organising Secretary, Joshi Clinic, 12, Golden Palace, Turner Road, Bandra (W), Mumbai – 400 050.
Tel: 91-22-26402769; Fax: 91-22-26443572 Email: srijoshi@vsnl.com
Advance Registration: Rs. 3,000/- Before 30th September 2008
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