Cholesterol-Lowering Drugs Also Cut Inflammation

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Two different cholesterol lowering drugs reduce in-flammation, disease activity, and aortic stiffness, and also improve endothelial function in patients with rheumatoid arthritis.

Participants in this randomized, double-blind crossover study included 20 patients with active rheumatoid arthritis (RA), defined as a disease activity score 28 (DAS28) greater than 3.5 and a C-reactive protein (CRP) level above 6 mg/L. None of the participants had cardiovascular dis-ease, untreated hypertension, diabetes, elevated choles-terol, or renal disease, and none was a smoker.

Following a 2-week period during which all participants received placebo, they were given either 20 mg simvas-tatin or 10 mg ezetimibe for 6 weeks each, separated by a 6-week washout period before receiving the other drug for 6 weeks.

At baseline, the aortic pulse-wave velocity (PWV), a marker of aortic stiffness, was significantly higher in pa-tients with RA compared to age-matched, healthy controls (9.42 m/s vs. 7.69 m/s, respectively). Likewise, flow-me-diated dilation (FMD) of the brachial artery, a marker of endothelial function, was reduced at baseline in RA pa-tients, compared to healthy controls. Both drugs reduced PWV while increasing FMD, but in neither case did the im-provements achieve statistical significance.

Both drugs reduced total cholesterol significantly, from 5.3 mmol/L at baseline to 4.7 mmol/L for ezetimibe, and from a baseline of 5.4 mmol/L to 4.1 mmol/L for sim-vastatin. Likewise, both drugs reduced LDL cholesterol, from a baseline value of 3.08 mmol/L to 2.53 mmol/L for ezetimibe, and from a baseline of 3.18 mmol/L to 1.95 mmol/L for simvastatin.

Improvements—albeit less statistically significant ones—were seen in two markers of inflammation on both drugs. CRP dropped from a baseline of 18.2 mm/hour to 12.9 mm/hour for ezetimibe, and from a baseline of 18.6 mm/hour to 13.8 mm/hour for simvastatin. C-Reactive protein (CRP) dropped from a baseline of 14.2 mg/L to 8.8 mg/L for ezetimibe, and from a baseline of 19.3 mg/L to 10.3 mg/L for simvastatin.

The patients’ disease activity score also decreased somewhat, from a DAS28 of 4.41 at baseline to 3.86 for ezetimibe, and from a baseline DAS28 of 4.65 to 3.98 for simvastatin (J. Am. Coll. Cardiol. 2007;50:852-8).

Because two cholesterol-lowering agents operating by two different mechanisms each had these effects, it ap-pears that both agents worked independently. Of note, one was responsible for reducing aortic stiffness and en-thoeldelial function, wrote Kaisa M. Mäki-Petäjä and her colleagues at the University of Cambridge (England). The other reduced CRP—both markers of inflammation—as well as the rheuma-toid arthritis composite DAS28, the investigators sug-gested that cholesterol-reducing therapies may benefit RA patients. These agents are well tolerated, improve clini-cal outcome in patients at risk for heart disease, and re-duce surrogates of cardiovascular risk.

The investigators acknowledged, however, that future studies will be needed to establish whether reducing ar-terial stiffness and improving endothelial function with drugs intended to reduce hyperlipidemia will translate into an overall improvement in cardiovascular outcome measures.

The effects of simvastatin and ezetimibe differed sig-nificantly in a number of parameters. Simvastatin was better at reducing total cholesterol, LDL cholesterol, and oxidized LDL cholesterol. But they were equally effective in all other measures, including reducing inflammatory markers and aortic PWV, and increasing FMD. They were also equally effective in improving the tender-joints count and the swollen-joints count, the authors wrote.

Throughout the study, patients remained on their RA therapy, which consisted of methotrexate in 13 patients, NSAIDs in 14, prednisolone in nine, and other disease-modifying drugs in seven. In all, 18 patients took two or three drugs concomitantly and none was off RA drugs completely.

Ms. Mäki-Petäjä disclosed that her doctoral studies are funded by GlaxoSmithKline Inc., and one of the other investigators on the study disclosed receiving funding from Pfizer. Neither company is involved in marketing simvastatin or ezetimibe, both of which are manufactured by Merck & Co.