# Cholesterol-Lowering Drugs Also Cut Inflammation

BY ROBERT FINN
*San Francisco Bureau*

Two different cholesterol-lowering drugs reduce inflammation, 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 disease, untreated hypertension, diabetes, elevated cholesterol, 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 simvastatin 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 patients with RA than in 20 age-matched, healthy controls (9.42 m/s vs. 7.69 m/s, respectively). Likewise, flow-mediated dilatation (FMD) of the brachial artery, a marker of endothelial function, was reduced at baseline in RA patients, compared with controls. Both drugs reduced PWV while increasing FMD, but in neither case did the improvements 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 simvastatin. 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. The erythrocyte sedimentation rate (ESR) 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 15.3 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 appears that it was the reduction in cholesterol itself that was responsible for reducing aortic stiffness and endothelial function, wrote Kaisa M. Mäki-Petäjä and her colleagues at the University of Cambridge (England).

And because the agents also reduced ESR and CRP—both markers of inflammation—as well as the rheumatoid arthritis composite DAS28, the investigators suggested that cholesterol-reducing therapies may benefit RA patients. These agents are well tolerated, improve clinical outcome in patients at risk for heart disease, and reduce surrogates of cardiovascular risk.

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

The effects of simvastatin and ezetimibe differed significantly 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 more 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. ■

# *Fear of Loss of Control Drives Patients to Resist New Therapies*

BY DENISE NAPOLI
*Assistant Editor*

Professed patient satisfaction with their current rheumatoid arthritis therapy had less to do with actual therapeutic success than the fact that their disease did not worsen while on a given treatment, according to the findings of a large survey.

In their survey of 6,135 rheumatoid arthritis (RA) patients in the United States, Dr. Frederick Wolfe and Kaleb Michaud, Ph.D., both of the National Data Bank for Rheumatic Disease, in Wichita, Kan., found that overall, 66% of patients did not think there was a better treatment than what they were currently receiving; of those patients not receiving biologic agents (part of the recommended aggressive multidrug therapy for optimal RA treatment), the number was 58%.

The survey, conducted in January 2006, involved a 28-page questionnaire that assessed sociodemographic data as well as disease severity, disease duration, and past and present RA treatment. Median participant age was 62.7 years; median RA duration was 15 years. Nearly 80% were female.

Overall, roughly 64% said they would not want to change therapy unless their condition worsened. Of those, 87% cited a fear of side effects as a reason why they wouldn't switch therapies; fear of losing control if the new treatments didn't work was cited by 81% ; and the belief that there were no better drugs for their disease was given by 76% of patients. The roughly two-thirds of patients who reported side effects to an arthritis drug at some point in their lifetime were least likely to be willing to change therapy (OR 1.8) and most likely to be concerned about the risk of side effects with a therapy switch (OR 1.2).

Despite patients' professed unwillingness to switch, 71% of patients who said they were satisfied with their treatment had moderate or greater arthritis activity on the Patient Activity Score, and 47% had Health Assessment Questionnaire scores greater than 1.0, which correlates with a severe disease rating, they reported (Arthritis Rheum. 2007;56:2135-42).

"Given relatively stable RA and prior experience with RA treatments, maintenance of current status [not getting worse] appears to be given high priority by patients," wrote the investigators. They added that although cost of new drugs, inconvenience, and potential administrative hassles with their insurance carrier also contributed to patients' unwillingness to try potentially better, new therapies, "they played a small role in thinking about therapies," compared with fear of side effects and fear of losing control, which led patients with even severe disease to resist switching therapies. "Patients' reluctance [to change therapy] may contain wisdom about homeostasis that goes beyond the experimentation of clinical trials and that is based on experience and preferences for the future. The idea of 'not getting worse' may be an important outcome that has not been considered sufficiently in therapeutic decision making."

Dr. Wolfe acknowledged that the National Data Bank, a nonprofit research data bank, has received pharmaceutical support in the past, but the current study was independent. ■

## Image of the Month

An urgent brain CT was ordered but appeared normal.

A cervical spine radiograph showed an increased atlantoaxial (C1-C2) distance of 5 mm.

However, MRI showed a septic arthritis from C1-C2 with enhancement of the dura.

There was no evidence of bony destruction or spinal cord compression.

Although any infectious agent may cause arthritis, bacterial pathogens are the most significant because of their rapidly destructive nature.

For this reason, the current discussion concentrates on bacterial septic arthritides.

Failure to recognize and to appropriately treat septic arthritis significantly increases morbidity and may even lead to death.

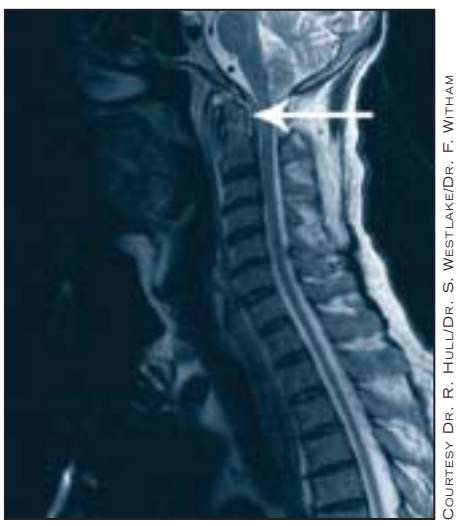
According to Dr. Sarah Westlake, who is a rheumatology specialist registrar at Queen Alexandra Hospital in Portsmouth, (England), only two patients previously have been described with C1-C2 septic arthritis.

"As in our patient, early radiograph features of prevertebral soft tissue swelling can be very subtle and bony destruction of septic arthritis or endplate destruction of diskitis can take 2-8 weeks to evolve," she said.

Cervical septic arthritis or diskitis can be life threatening. That is because there is a heightened risk of cervical spine subluxation as well as medullary compression.

"It should therefore be considered in any patient with sepsis and severe neck pain, even with normal cervical spine radiographs," she explained.

MRI and blood cultures are the diagnostic tests of choice.



Courtesy Dr. R. Hull/Dr. S. Westlake/Dr. F. Witham

**Septic arthritis from C1-C2 is seen (arrow), with enhancement of the dura.**

However, if the blood cultures turn out to be negative, diskovertebral biopsy for diskitis or joint aspiration for septic arthritis could be considered by a suitably-trained radiologist, said Dr. Westlake.

Blood cultures were performed on this patient on three separate occasions. The subsequent cultures grew methicillin-resistant *S. aureus*.

"*S. aureus* is the most common organism causing nongonococcal arthritis. The virulence of *S. aureus* is associated with its ability to attach to host tissue within the joint, evade host defenses, and cause damage to the joint," according to Kelley's Textbook of Rheumatology, 7th edition.

The patient was treated with a 6-week course of vancomycin and an additional 6 weeks of rifampicin and doxycycline.

There were no neurologic complications that occurred at any time.

**—Kerri Wachter**