TNF Inhibitors May Slow Plaque Progression

BY MICHELE G. SULLIVAN

FROM ARTHRITIS & RHEUMATISM

Tumor necrosis factor–inhibiting drugs may moderate atherosclerosis progression in patients with rheumatoid arthritis, a prospective study has suggested.

Compared with patients who did not get the drugs, those treated with TNF inhibitors had a 37% lower rate of plaque progression in the common carotid artery, Dr. Jon T. Giles and his colleagues reported in Arthritis & Rheumatism (2011 [doi:10.1002/art.30542]).

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Major Finding: Among 154 patients with rheumatoid arthritis, those taking TNF inhibitors had significantly less arterial plaque load progression than did those not taking the drug.

Data Source: A subanalysis of the ESCAPE RA study.

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"Our observation that TNF-inhibitor treated patients [had a 37% reduction in arterial plaque] provides some human confirmation of a link between cytokines and atherosclerosis," wrote Dr. Giles of New York Presbyterian–Columbia University Medical Center, New York, and his coauthors. "However, it is unclear whether this effect is due to TNF inhibition per se, and is thus a unique effect of the TNF inhibitors, or is a general anti-inflammatory effect."

The study also found a significantly increased rate of progression with glucocorticoid exposure – a relationship that seemed to be attenuated by the concurrent use of statins.

The 3-year study was a subanalysis of the ESCAPE RA (Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis) cohort study, which looked at subclinical cardiovascular disease. This analysis examined intima-medial thickness in the common and internal carotid arteries and the internal carotid artery bulb among 154 patients with rheumatoid arthritis, none of whom had prior cardiovascular disease. All underwent carotid ultrasound at 1 and 3 years.

The patients' mean age was 59 years at baseline, and they had had rheumatoid arthritis for a mean of 8.5 years.

In all, 42% were taking TNF inhibitors, and 86% were taking a nonbiologic disease-modifying antirheumatic drug. The mean cumulative prednisone dose was 3.1 grams.

Overall, plaque deposits grew at a median rate of 16 mcm/year in the common carotid artery; 82% showed some level of increase. The median plaque increase in the internal carotid artery was 25 mcm/year; 82% of patients also showed some level of plaque increase in this artery.

At baseline, 38% of patients showed no stenosis in the internal carotid artery due to plaque, 55% showed plaque stenosis of up to 24%, and 7% had plaque stenosis of 35%-50%. There were no patients with arterial plaque stenosis of more than 50%.

Among the 58 patients without plaque at baseline, 8 (14%) showed some new plaque at 3 years – a progression rate of 4 patients per 100 person-years. Among the 96 patients with plaque at baseline, 5% (5) had increased plaque at 3 years – a progression rate of 1.6 patients per 100 person-years. In the remaining 91 patients with plaque at baseline, 89% had the same degree of plaque at 3 years and 6 patients (7%) showed less plaque stenosis, the authors noted.

In a multivariate analysis, two disease characteristics were significantly associated with plaque progression in the common carotid artery: disease duration and TNF-inhibitor use.

The rate of change in common carotid plaque was doubled in the first tertile of disease duration (up to 6 years), compared with the second or third tertiles (7-14 years and more than 14 years). The rate of change was not significantly different from the second to third tertiles of disease duration.

Baseline TNF inhibitor use reduced the annual progression rate by 37% compared with those not using the drugs.

DR. GILES

Framingham risk score did significantly affect plaque change in the group with shortest disease duration, however. The rate of change was significantly higher among those with higher risk scores or diabetes than in those with lower risk scores (33 vs. 20 mcm/year). "In contrast … progression rates were identical for RA patients with longer-standing disease, regardless of Framingham score," the authors wrote.

Statin therapy exerted a significant, positive effect on plaque progression in those with longer-standing disease. Compared with patients who were not taking a statin at baseline, those who were had significantly less annual progression of plaque (1 vs. 15 mcm/year). Statins exerted no significant effect on patients with the shortest disease duration.

Baseline use of TNF inhibitors reduced the annual progression rate by 37% compared with those not using the drugs at baseline (14 vs. 22 mcm/year). This difference remained significant even after adjusting for demographics, lifestyle characteristics, Framingham score, and other disease characteristics.

In the internal carotid artery, prior glucocorticoid exposure was significantly related to higher annual plaque change. "This association was modified by statin use, as the association of cumulative prednisone exposure with the adjusted average yearly change … was attenuated, yet remained significant, in participants receiving statins at baseline," the authors noted.

For the internal carotid artery bulb, the authors found four significant predictors of plaque change: hormone replacement therapy, cumulative average swollen joint count, cumulative C-reactive protein level, and age. Neither exposure to TNF inhibitors nor exposure to glucocorticoids was related to plaque progression in the bulb.

C-reactive protein did not exert a linear effect on plaque progression or on the appearance of incident plaque until it reached 12 mg/L or more. This threshold of change was significantly lower in patients with higher Framingham scores or diabetes at baseline (5 mg/L).

The role of statins in modifying progression is complicated, the authors stated. "Notably, statin use was associated with almost no progression of [common carotid plaque] in RA patients with longer disease duration, an observation supporting the use of statins in RA," they said.

"Interestingly, however, statin use was not associated with lower [common carotid progression] among participants with earlier disease. This may suggest differing mechanisms for [common carotid plaque] progression in early vs. late disease."

The additional finding that statins attenuated the risk exerted by glucocorticoid exposure "deserves additional study and, short of a confirmatory trial, suggests that statins could be considered in RA patients receiving glucocorticoids." ■

Oral Contraceptives Use at RA Onset Preserved Function

BY BRUCE JANCIN

FROM ARTHRITIS & RHEUMATISM

The use of oral contraceptives before or at the time of symptom onset in women with inflammatory polyarthritis appears to confer long-term benefits in functional outcome.

In the largest-ever prospective study of the relationship between oral contraceptives and disease outcome, data from the Norfolk (U.K.) Arthritis Register showed that OC use prior to symptom onset was associated with a 35% reduction in median Health Assessment Questionnaire (HAQ) scores at 5 years of follow-up, compared with women who hadn't taken OCs beforehand.

Moreover, the benefit of taking OCs around the time of symptom onset was even greater. Women on OCs at symptom onset had a 21% lower median HAQ score at 5 years, after adjustment for age, parity, and other potential confounders, than women who weren't taking OCs at symptom onset but had previously done so.

OC use during follow-up was also associated with lower HAQ scores, but this finding reached significance only for the subset of women with moderate or severe functional disability at their previous assessment.

The study involved 523 users and 140 nonusers of OCs prior to onset of inflammatory polyarthritis, along with 73 OC users and 192 nonusers at symptom onset, and 95 users and 170 nonusers during follow-up, which lasted a median of 4.9 years. The median score on the HAQ, a validated measure of functional ability, was 1.0 on a 0-3 scale at symptom onset, indicative of moderate disability, Dr. Deborah P.M. Symmons and her coworkers reported in Arthritis & Rheumatism (2011;63:2183-91).

Although the Norfolk Arthritis Register is open to patients with inflammatory polyarthritis, it has previously been established that 75% of enrollees meet American College of Rheumatology diagnostic criteria for rheumatoid arthritis within 5 years of symptom onset.

The investigators offered two potential mechanisms to explain the observed relationship between OC use and disease outcome. One possibility is that the hormonal environment fostered by OCs results in an increase in heat-shock proteins, resulting in an immunotolerant state that reduces rheumatoid arthritis symptoms. Another potential mechanism is that the artificial luteal phase induced by combined estrogen/progesterone OCs tempers rheumatoid arthritis symptoms; this is consistent with an earlier report by other investigators that rheumatoid arthritis symptoms in 14 women were significantly reduced just after ovulation, wrote Dr. Symmons, a professor of rheumatology and musculoskeletal epidemiology at the University of Manchester (England), and her colleagues.

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