Increasing RA Activity Means More Infections

BY DENISE NAPOLI

FROM ANNALS OF THE RHEUMATIC DISEASES

VITALS

Major Finding: For every 0.6-point increase on the DAS28, there was a corresponding 4% increase in outpatient infections; for every 5 points on the CDAI, there was a 14% increase, for all CDAI scores less than 10.

Data Source: More than 2,000 infections that were registered through the CORRONA database between March 2002 and December 2007.

Disclosures: Several of the authors reported contracts and professional affiliations with the CORRONA database. Several also reported financial relationships with multiple pharmaceutical companies, including Amgen, Centocor, Pfizer, Roche/Genentech, and UCB.

Increasing disease activity in rheumatoid arthritis is associated with a higher risk for both outpatient infections and more serious infections requiring hospitalization in patients receiving stable therapy.

Moreover, this finding was true even among patients with mild disease activity, according to Dr. Karen Au of the division of rheumatology at the University of California, Los Angeles.

Dr. Au and her colleagues looked at 6,246 patients with RA who were listed on the CORRONA (Consortium of Rheumatology Researchers of North America) registry, which includes data contributed by 80 academic and private practices across the United States.

A history of infection increased the likelihood of having an outpatient infection, as did use of methotrexate, use of TNF inhibitors, and poorer functional class.

The patients' mean age was 60 years; 75% were women. CDAI (Clinical Disease Activity Index) scores were available for 6,020 patients. DAS28 (disease activity score based on a 28-joint count) was calculated throughout the study period for 3,666 patients (Ann. Rheum. Dis. 2011;70:785-91).

"To minimize confounding related to recent changes in disease-modifying medications on the rate of infections, we limited the study to RA patients on stable therapy" (defined as no change in the dose of either methotrexate, TNF (tumor necrosis factor) inhibitor, corticosteroid, or any other disease-modifying anti rheumatic drug over three consecutive visits spanning at least 6 months), they said.

Overall, 2,282 infections were reported during the study period, from March 2002 to December 2007; 1,382 patients had one or more outpatient infections and 50 patients had serious infections that required hospitalization.

Most of the infections tallied (2,223 of the total 2,282) were outpatient.

When outpatient infections alone were considered, researchers found that for all patients with CDAI scores less than 10 of a possible 76 (corresponding to the mildest class of disease), there was a 14% increase in outpatient infections for each 5-point increase in score, after the researchers controlled for covariates including body mass index, smoking, disease duration, therapy, and coexisting cardiovascular disease (incidence rate ratio, 1.14; $P = .003$).

And although no further linear relationship was noted, patients with moderate (CDAI scores of 10-22) and high (CDAI scores greater than 22) disease activity had increased infections, compared with patients with mild disease activity, although only the moderate category was statistically significant (IRR for moderate activity compared with low activity, 1.19; 95% confidence interval, 1.06-1.34; IRR for high activity, 1.07; 95% CI 0.90-1.27).

Among patients for whom DAS28 data were available, there was a 4% increase in outpatient infections for each 0.6-point increase in the score, which persisted throughout the entire DAS28 spectrum (IRR, 1.04; $P = .03$).

A history of infections increased the likelihood of having an outpatient infection (IRR, 2.84-3.15; P less than .001), as did use of methotrexate, use of TNF inhibitors, and poorer functional class.

Although infections requiring hospitalization were much less frequent among the study participants, the authors were able to identify that for every 0.6-point increase in the DAS28, there was a corresponding significant 25% increase in the rate of infections that required hospitalization.

On the CDAI scale, there was no significant trend between an increasing score and inpatient infections on multivariate analysis, likely because of the small number of inpatient infections observed, according to the authors.

Prednisone use of 7.5 mg daily or more was also independently associated with infections that required hospitalization, as was a history of infection. Previous studies have shown that RA patients have a twofold increased risk of developing infections, compared with patients who do not have RA, and they are also at higher risk of serious infections requiring hospitalization, they said.

Indeed, they added, the "continued increased mortality observed in RA patients compared with the general population can be explained partly by a higher susceptibility to infections."

The strength of this study, they pointed out, lies in the size and quality of the prospectively collected clinical data in the CORRONA database. ■

AS Treatments Give Clinical but Not Radiographic Benefit

BY SHARON WORCESTER

FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO – Despite dramatic clinical benefit, the standard treatments for ankylosing spondylitis do not appear to alter the natural history of the disease.

"We'd like to believe we're actually doing something substantial for our patients in addition to actually relieving symptoms," said Dr. Michael H. Weisman, adding that this is an area of "hot, current controversy."

Nonsteroidal anti-inflammatory drugs, for example, are clinically very useful for treating patients with ankylosing spondylitis (AS). In a study of NSAID treatment for AS and mechanical back pain, good clinical response occurred in 75% of the AS patients, compared with only about 15% of the patients with mechanical back pain (Rev. Rheum. Engl. Ed. 1995;62:10-5), Dr. Weisman said.

The response of AS patients to NSAIDs is so good, in fact, that it can be helpful for confirming the diagnosis. A greater complete response may indicate that AS is the cause of symptoms, he said.

Another study demonstrated that 70% of AS patients who received etoricoxib had a good clinical response, compared with about 20% who received placebo (Arthritis Rheum. 2005;52:1205-15).

However, the effects of NSAIDs on radiographic progression of disease are questionable, at best, said Dr. Weisman, director of the division of rheumatology and professor of medicine at Cedars-Sinai Medical Center, Los Angeles.

Although findings from one study showed that there was less radiographic progression of disease after 2 years in patients on continuous versus on-demand NSAIDs, with a mean change on the modified Stoke Ankylosing Spondylitis Spinal Score of 0.4 vs. 1.5, respectively (Arthritis Rheum. 2005;52[6];1756-65) , most experts "take this particular study with a grain of salt," Dr. Weisman said.

That's in part because the mean difference in dose between the continuous and on-demand patients was only 50 mg/day. It's very difficult to believe that a difference of 50 mg in celecoxib could make a difference in actually reducing the amount of bone formation in AS, he said.

New understanding into the biology of AS may help researchers discover why syndesmophytes form and from there help them develop new therapeutic targets.

Tumor necrosis factor (TNF) blockers also provide excellent clinical benefit and are approved for use in AS. Patients experience tremendous response, perhaps to even a greater degree than do rheumatoid arthritis patients and, unlike RA patients, there appears to be no increased risk of serious infection with treatment, he noted.

In a recent meta-analysis of randomized, placebo-controlled studies of anti-TNF drugs in AS, no difference was seen in the rate of serious infections in those who received active treatment versus those who received placebo (Ann. Rheum. Dis. 2010;69:1756-61).

However, while anti-TNF agents have the potential to alter the natural history and prognosis of AS, there is also no evidence in any studies of etanercept, infliximab, or adalimumab that treatment over 2 years inhibits radiographic progression of disease.

This is a source of frustration, Dr. Weisman said.

Disease progression in AS is generally very slow. Only about 25% of patients experience disease progression. Inflammation appears to play a role, with syndesmophytes developing significantly more frequently in vertebral corners in patients with inflammation versus those without inflammation (20% vs. 5% of patients in one study). Paradoxically, though, syndesmophytes develop more frequently in vertebral corners where inflammation has resolved than in those where it persisted after anti-TNF therapy, Dr. Weisman said.

This raises concerns about whether the control of inflammation using anti-TNF agents actually liberates bone formation in these patients, he noted.

In addition to the inflammation/syndesmophyte associations, syndesmophytes sometimes form in patients with normal x-rays or MRIs, he said.

"We really don't know why syndesmophytes form in this disease," he added, noting that, while there has been some understanding of the fact that AS biology differs from RA biology (AS is a bone-forming disease, for example), new understanding of the biology is beginning to emerge. Perhaps this new understanding, along with the discovery of bone-related genes, will help define subsets of individual pathways that can be targeted, he suggested.

Dr. Weisman had no disclosures to report. ■