Methotrexate Linked to Serious Infections in RA

BY DAMIAN McNAMARA

MIAMI — The rate of serious infectious events is significantly higher for rheumatoid arthritis patients who are treated with methotrexate, compared with those taking placebo, according to a meta-analysis of 17 randomized, controlled trials.

The overall rate of infectious events that required hospitalization and/or parenteral antibiotic treatment was 2.3 per 100 patient-years of exposure.

This finding offers clinicians a specific number to consider when they compare serious infectious risks between methotrexate and other treatments, including biologic agents, Dr. Jennifer Powers said during a poster discussion session at the annual meeting of the American Academy of Dermatology.

VITALS

Major Finding: The rate of infectious events among rheumatoid arthritis patients that required hospitalization and/or parenteral antibiotic treatment associated with methotrexate was 2.3 per 100 patient-years of exposure.

Data Source: Meta-analysis of 17 randomized, placebo-controlled clinical trials.

Disclosures: The study authors had no relevant disclosures.

Dr. Daniel E. Furst noted in an interview that the issue of infection in patients on methotrexate is one physicians often forget about, but it is significant because methotrexate's infection risk should be a factor when physicians consider whether to initiate biologic therapy.

Unfortunately, the research does not address whether the infection risk is even higher in patients who receive both methotrexate and a biologic agent than in patients on one or the other as monotherapy. But the findings still are of interest, said Dr. Furst, who is Carl M. Pearson professor of rheumatology at the University of California, Los Angeles.

In contrast, there was no statistically significant higher risk for a serious infectious event associated with methotrexate in a meta-analysis of five psoriasis trials (2.2 serious infectious events per 100 patient-years) or a meta-analysis of five psoriatic arthritis studies (0.9 events per 100 patient-years).

The small number of eligible studies in psoriasis and psoriatic arthritis might explain the lack of statistical significance, Dr. Powers said.

It could also be that patients with rheumatoid arthritis generally are sicker, said Dr. Powers, a first-year resident at Grand Rapids (Michigan) Medical Education and Research Center.

The Food and Drug Administration first approved methotrexate in 1953 and granted a new indication to treat rheumatoid arthritis in 1988. These approvals predate the era when the agency required more stringent reporting of infectious adverse events, Dr. Powers said.

She and her colleague, Dr. Richard W. Martin, conducted a literature search for randomized, placebo-controlled studies published from January 2005 through May 2009 in Embase Biomedical Answers, the National Library of Medicine's Medline database, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library. Patients in each study received oral methotrexate (7.5-30 mg/week) for at least 12 weeks.

Previous observational studies reported conflicting results. "It was interesting to me when going over the literature [to find] how controversial infection with methotrexate is and how little consensus there is," Dr. Powers said. "These are rare cases, but they are out there.

"There are not great data about serious infectious events in methotrexate," Dr. Powers continued. "So there was a hole in the literature we wanted to fill."

Randomized, controlled studies were included in the meta-analyses only if they met objective quality criteria. For example, the participants had to be adults with clearly defined disease, and they could not be taking more than 10 mg of prednisone. Also, studies were excluded if 20% or more of the patients were lost to follow-up.

Biologic agents have transformed psoriasis treatment, but they are associated with increased serious infectious events and significant expense. Because of this, there is revived interest in the comparative efficacy of standard versus the newer therapies, the authors wrote.

"This is really an important counterpoint when we are discussing [serious infectious event] risks for methotrexate. …It is generally accepted that methotrexate has lower risk of [serious infectious events] than biologics," Dr. Powers said.

For example, the product labeling for ustekinumab (Stelara) notes that serious infections have occurred with the use of that agent. In addition, the risk of serious infections that can lead to hospitalization and death are included on black box warnings for etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira).

A meeting attendee said the findings would be more robust if the methotrexate trials in the meta-analyses went beyond 12 weeks.

Dr. Powers agreed with that observation, adding that these results "are definitely limited by the fact that there are trials out there that do not follow patients for a longer time." ■

Clinically Quiescent Lupus Probably Best Left Untreated

BY KATE JOHNSON

MONTREAL — Patients with systemic lupus erythematosus that is serologically active but clinically quiescent do not require treatment with steroids or immunosuppressive agents until the disease flares, according to a study presented at the annual meeting of the Canadian Rheumatology Association.

Until now, patients with such discordant findings have presented a clinical dilemma, said Dr. Amanda Steiman, who presented the study's findings.

"Many physicians have wondered whether or not treatment is warranted in light of just the serological activity in the absence of any clinical disease," she said in an interview. "Does lupus progress subclinically during a quiescent period?"

Her study followed 55 patients with serologically active, clinically quiescent (SACQ) systemic lupus erythematosus over 10 years, and compared their outcomes to those of 110 controls with classic SLE who were matched for age, sex, disease duration, and time of clinic entry.

Patients and controls were also matched for baseline damage according to the SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index), incidence of renal damage, and incidence of coronary artery disease.

'The SACQ period can be a very prolonged period without a flare, and at our center we have not been treating these patients. Our study supports the practice of active surveillance.'

SACQ was defined as a minimum of 2 years without clinical activity and persistent serologic activity as defined by elevated anti–double stranded DNA and/or hypocomplementemia. Antimalarials were permissible during an SACQ period, but steroids or immunosuppressives were not.

The study found that, compared with controls, SACQ patients showed very little subclinical progression. At 3 years, SDI damage in the SACQ patients was 0.7 vs. 1.13 in controls; this pattern persisted at 5 years (0.89 vs. 1.36), 7 years (0.94 vs. 1.71), and 10 years (1.26 vs. 2.26).

Similarly, whereas 3.6% of the SACQ patients vs. 6.4% of controls had coronary artery disease at baseline, new cases of CAD (myocardial infarction, angina, or sudden cardiac death) occurred in 1.8% of SACQ patients vs. 7.3% of controls over the 10-year study.

One (1.8%) SACQ patient vs. 15.5% of controls had renal damage at 5 years, and at 10 years these numbers rose to 3.6% of SACQ patients and 23.6% of controls.

The SDI differentiates disease-related vs. treatment-related damage, said Dr. Steiman, who is a rheumatology fellow at the University of Toronto.

"Especially later in the course of lupus—these patients were 11 years plus into their lupus course—a lot of the damage is related to treatment morbidity," she said in an interview. "If we can avoid that for a good number of years, then we are going to spare the people the morbidity associated with the treatment."

Findings from a previous study by Dr. Steiman's associates showed that patients with SACQ represent about 6% of the SLE population. About 60% flare and require treatment after a median of 3 years. Findings from the present study show that SACQ patients used antimalarials, corticosteroids, and immunosuppressives at rates of 60%, 18%, and 5%, respectively, during the study period, compared with 77%, 76%, and 44% in controls.

"The SACQ period can be a very prolonged period without a flare, and at our center we have not been treating these patients. Our study supports the practice of active surveillance without treatment, so that's reassuring." ■

Disclosures: *Dr. Steiman stated that she had no conflicts to disclose.*