Abatacept Shown Effective to Be for RA in Review

BY SALLY KOCH KUBETIN

Abatacept has been shown to be an effective biologic agent for use in the treatment of rheumatoid arthritis, according to findings of a Cochrane review of seven studies involving almost 3,000 patients.

Of the 2,908 patients in this review, 1,863 were randomized to abatacept and 1,045 to placebo. Most were white women, and their average age was 48-56 years, depending on the trial. Most trials used a dose of 10 mg/kg of abatacept, and patients continued to use a disease-modifying antirheumatic drug in addition to abatacept for the duration of the study, according to the review's authors, Lara Maxwell of the University of Ottawa and Dr. Jasvinder A. Singh of the Minneapolis VA Medical Center.

Patients treated with abatacept were 2.2 times more likely than those on placebo to have an ACR 50 response (the primary end point) at the end of year 1 (relative risk, 2.21). There was a 21% absolute risk difference between the two groups. The number needed to achieve an ACR 50 was five patients.

Physical function significantly improved and both disease activity and pain lessened in patients who were treated with abatacept, compared with placebo.

Findings from one of the seven randomized, controlled trials in the review showed that abatacept significantly slowed radiographic progression of joint damage at 12 months, compared with placebo. However, it is unclear whether that finding had any clinical relevance. The other six studies did not assess radiographic progression.

The rate of adverse events was greater in abatacept-treated patients than in those on placebo (RR, 1.05). The number of infections after 12 months was significantly greater in the abatacept group vs. the placebo group (Peto odds ratio, 1.91). Serious adverse events were increased when abatacept was used in combination with other biologics (RR, 2.3), an observation that led the authors to recommend that abatacept should not be used in combination with other biologics to treat RA.

Of the seven studies included in the review, only two were free of any risk of bias arising from flawed methodology. Four of the seven did not address incomplete efficacy outcome data; two of those four also did not address incomplete safety outcome data; and a fifth study provided unclear information on both adequate sequence generation and allocation concealment. In addition, because all the included trials were funded by abatacept's manufacturer, it is possible that the findings overestimated the treatment benefit, according to Ms. Maxwell and Dr. Singh (Cochrane Database Syst. Rev. 2009 Oct. 7 [doi:10.1002/14651858. D007277.pub2]).

The studies that were included in this Cochrane review were identified through an extensive literature search. The selected trials were all randomized, controlled studies evaluating the effectiveness and safety of abatacept either alone or in combination with a DMARD or another biologic, vs. placebo alone or a DMARD or biologic, in patients with moderate to severe RA.

The cost of 1 year of abatacept therapy is estimated to be approximately $22,000. The prevalence of RA among white adults aged older than 18 years in the United States is 0.6%.

Abatacept is the first biologic agent to work by disrupting T-cell activation. The drug is a selective costimulation modulator, inhibiting T-lymphocyte activation by binding to CD80 and CD86, thereby blocking interaction with CD28.

All the trials included in this review were funded by Bristol-Myers Squibb Co., the manufacturer of abatacept.

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Cochrane: Rituximab Is the Most Effective Biologic for RA

BY SALLY KOCH KUBETIN

Rituximab seems to be the most effective biologic disease-modifying antirheumatic drug used in the treatment of rheumatoid arthritis, according to a Cochrane systematic review of the literature. Anakinra appeared to be the least effective of the agents evaluated.

All six biologics studied provided clinically important improvement in pain and disability. However, the degree of relief differed among the agents, which also included abatacept, adalimumab, etanercept, and infliximab.

Absolute improvement (defined as ACR 50) was reported in 51% more people on rituximab than on placebo. Compared with those taking placebo, 42% more people taking adalimumab achieved that level of improvement, as did 40% more people taking etanercept, 26% more people taking abatacept, 24% more people taking infliximab, and 6% more people on anakinra, according to the report's authors, who are all members of the Cochrane Musculoskeletal Group and were led by Dr. Jasvinder A. Singh of the Minneapolis VA Medical Center.

People on abatacept, etanercept, or rituximab were no more likely than those on placebo to drop out of the trial because of side effects. For infliximab, the absolute difference of people who dropped out of the trial, compared with placebo, was 6%; for anakinra, that difference was 4%; and for adalimumab, that difference was 3%.

The researchers searched the Cochrane Database of Systematic Reviews for literature reviews with the term "rheumatoid" in the title that had concluded by May 20, 2009; included at least one randomized, controlled trial; had clinically relevant outcomes; and included clear inclusion and exclusion criteria for studies. Only trials of adults were considered. The review was limited to studies of standard rheumatoid arthritis dosing regimens of the six agents, used either alone or in combination with another biologic or conventional DMARD, compared with either placebo alone or placebo plus a biologic or conventional DMARD.

Primary outcomes were ACR 50 and withdrawal because of any adverse event. Six reviews were included in this overview. The biologic DMARDs included in this review were abatacept (seven studies), adalimumab (eight studies), anakinra (five studies), etanercept (four studies), infliximab (three studies), and rituximab (three studies) (Cochrane Database Syst. Rev. 2009 Oct. 7 [doi:10.1002/14651858.CD007848.pub2])

The six biologic DMARDs in this overview had similar efficacy for primary outcomes with three exceptions: Anakinra was less effective than etanercept (relative risk, 0.44) and less effective than rituximab (RR, 0.45), and adalimumab was more efficacious than anakinra (RR, 2.34).

In terms of safety, adalimumab was more likely to lead to withdrawal, compared with etanercept (odds ratio, 1.89); anakinra was more likely than etanercept (OR, 2.05), and etanercept was less likely to lead to withdrawal for side effects than was infliximab (OR, 0.37).

Dr. Singh reported receiving speaker honoraria from Abbott Laboratories; research grants from Amgen Inc., Allergan Inc., Takeda Pharmaceutical Co., and Savient Pharmaceuticals Inc.; and a consultant fee from Savient. ■

Septic Arthritis Rates Rose With Anti-TNF Therapy

BY DENISE NAPOLI

PHILADELPHIA — Septic arthritis was twice as common in patients taking anti–tumor necrosis factor drugs for rheumatoid arthritis as in patients with the disease who did not take anti-TNFs.

However, the results may not be fully translatable to a U.S. population of RA patients, according to Dr. Deborah P. Symmons, who presented the findings during a press briefing at the annual meeting of the American College of Rheumatology.

In the United Kingdom, she explained, patients must have failed two disease-modifying antirheumatic drugs and have a high disease activity score in order to be eligible for treatment with TNF blockers. "Those people may have more serious disease" than do those in the United States, said Dr. Symmons, professor of rheumatology and musculoskeletal epidemiology at the University of Manchester (England).

Dr. Symmons and her associates studied the records of 11,757 RA patients from the British Society for Rheumatology Biologics Register who received anti-TNF drugs from October 2001 through May 2008. Patients were followed for 6 months or until death. Septic arthritis was counted in all patients who received that diagnosis either while taking anti-TNFs or within 90 days of their last dose. The control group was 3,515 patients with active RA who were taking only DMARDs.

According to Dr. Symmons, 179 cases of septic arthritis that met study criteria occurred during the study period, for an incident rate of 1 per 200 patients (5 cases per 1,000 patient-years). In contrast, among the DMARD-only control group, there were 17 cases of septic arthritis, for an incidence of 1.9 cases per 1,000 patient-years.

That amounted to a hazard ratio for contracting septic arthritis of 2.0 for the anti-TNF patients, compared with controls (95% confidence interval, 1.1-3.5) after adjustment for age, sex, disease severity, prior joint replacement, comorbidity, and steroid use.

Additionally, the investigators reported that 51% of septic arthritis cases occurred in patients' "native" joints (that is, not prosthetic joints), which are generally considered to have a higher risk of septic arthritis. However, "in both groups, having a replaced joint increased the patient's risk for an infection, but that risk was not further increased by use of an anti-TNF drug," said Dr. Symmons.

Use of an anti-TNF agent did not increase the risk of septic arthritis more than did having a prosthetic knee.

DR. SYMMONS

The risk was highest with the use of etanercept, compared with infliximab and adalimumab. Staphylococcus bacteria made up 50% of infection in the DMARD group, and fully 75% of infections in the anti-TNF group.

Dr. Symmons reported affiliation with the British Society for Rheumatology. The researchers wrote that they had no other conflicts to disclose. ■