Site Reactions Reported With Topical NSAID

VITALS

Major Finding: Among older patients treated topically for knee osteoarthritis for 12 weeks, adverse events occurred in 56% of those using diclofenac sodium 1% gel and in 44% of those using placebo, with one serious adverse event possibly related to treatment.

Data Source: A post hoc analysis of data on 538 patients aged 65 years or older from three double-blind, randomized, controlled trials.

Disclosures: Dr. Barthel conducted the study under a research contract for Novartis, which makes the gel. His associates in the study were employees of Novartis or of Endo Pharmaceuticals, which markets the gel.

BY SHERRY BOSCHERT

LONG BEACH, CALIF. — A higher rate of adverse events in older patients with knee osteoarthritis treated topically for 12 weeks with a nonsteroidal anti-inflammatory drug, compared with placebo, was caused mainly by application-site reactions but included one serious cardiovascular event that might have been related to the drug treatment, a post hoc analysis of data on 538 patients found.

The investigators analyzed data on people aged 65 years and older with symptomatic knee osteoarthritis (433 of them with comorbid hypertension, diabetes, or cardiovascular disease). Their source was three larger randomized, double-blind trials—two of them unpublished—that had looked at broader populations. Patients applied 4 g/day of either diclofenac sodium 1% gel (Voltaren) or the drug's vehicle to one painful knee.

One 80-year-old woman with hypertension and diabetes, among 274 patients on diclofenac sodium 1% gel, developed deep vein thrombosis and pulmonary embolism that possibly was related to treatment, Dr. H. Richard Barthel and associates reported in a poster presentation at the annual meeting of the American Medical Directors Association.

Overall, 56% of patients on diclofenac gel developed adverse events, compared with 44% of 264 patients treated with placebo, added Dr. Barthel, a rheumatologist in Santa Barbara, Calif., who conducts research under contract for Voltaren maker, Novartis.

The study was not powered to assess statistical significance. Voltaren is approved to treat osteoarthritis pain in joints amenable to topical treatment, such as knees and hands.

NSAIDs are known to increase risk for cardiovascular or renal problems in a dose-related fashion, especially in older patients and people with hypertension, diabetes, or cardiovascular disease. Topical formulations may reduce this risk by reducing systemic exposure to NSAIDs compared with oral formulations. The ad hoc analysis compared the gel only to placebo, not to oral therapy, and found higher rates of adverse events for the drug vs. placebo.

Application-site reactions occurred in 8.8% on diclofenac gel and 1.1% on placebo. Serious adverse events occurred in 2.6% on diclofenac and 1.1% on placebo. Adverse cardiovascular events were seen in 2.6% on diclofenac and 1.1% on placebo. Adverse renal events were seen in 1.1% on diclofenac and 0.4% on placebo.

Among more common adverse events, 11% of subjects on diclofenac and 10% on placebo reported headache, 8% on diclofenac and 7% on placebo reported arthralgia, and 8% on diclofenac and 6% on placebo reported back pain.

The analysis included 307 patients with hypertension, 84 with diabetes, and 42 with cardiovascular disease. The investigators looked at rates of adverse events in patients with one of these comorbidities, compared with events in patients without the comorbidity. For example, in the hypertension subgroup, adverse events were seen in 54% of 159 people randomized to diclofenac gel, compared with 45% of 148 people using placebo. In patients without hypertension, adverse events occurred in 58% of 115 on diclofenac gel and 42% of 116 on placebo.

In the diabetes subgroup, adverse events occurred in 19 (51%) of 37 patients treated with diclofenac and in 21 (48%) of 47 treated with placebo. In patients without diabetes, adverse events occurred in 56% of 237 on diclofenac and in 44% of 217 on placebo.

In the subgroup with cardiovascular disease, adverse events occurred in 15 (56%) of 27 people on diclofenac and in 2 (13%) of 15 on placebo, although none developed an adverse cardiovascular event. ■

MY TAKE

Topical Diclofenac Can Fill a Tx Gap

The therapy of osteoarthritis remains insufficient in many patients. It is particularly problematic in the elderly who often have concomitant diseases that limit our options for several of the oral medications, particularly NSAIDs and potent analgesics. The recent Food and Drug Administration approval of diclofenac has changed the therapeutic paradigm. Diclofenac gel 1% has been approved for osteoarthritis of the knee, hand, and other superficial joints, and Pennsaid has been approved for osteoarthritis of the knee.

In this post hoc pooled analysis of 538 patients, we see an increase in irritation at the site of application, but a minimal increase in adverse events involving blood pressure, renal function, hepatic dysfunction, and gastrointestinal ulcer disease. Pharmacokinetic studies have demonstrated that systemic absorption of the topical diclofenac is 40 times less than oral diclofenac. This improved safety allows us to provide therapy to patients otherwise unable to receive anti-inflammatory drugs. It will be no surprise if the guidelines for therapy of osteoarthritis from the United States will soon approximate those from Europe, where topical NSAIDs are part of the therapeutic algorithm for osteoarthritis. Are they completely safe? No. Is there no long-term cardiovascular risk? It has not been studied. Hence, the "black box" warning is applied to these agents that primarily list topical changes under adverse events.

ROY D. ALTMAN, M.D., *is professor of medicine in the division of rheumatology and immunology at the University of California, Los Angeles. He has been a consultant to Novartis, Eli Lilly, Ferring Pharmaceuticals, and Rottapharm/Madaus.*

Anti-TNF Therapy Offers Top Risk:Benefit Ratio in AS

BY BRUCE JANCIN

SNOWMASS, COLO. — Long-term adherence to anti–tumor necrosis factor agents appears to be better—and rates of malignancy and serious infection lower—in patients who are treated for ankylosing spondylitis than in those with rheumatoid arthritis or some of the other rheumatic conditions for which the drugs are indicated.

Another major distinction between ankylosing spondylitis (AS) patients and those with other rheumatic diseases in terms of anti-TNF response is that rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients are significantly more likely to remain on treatment long term if they're on concomitant methotrexate, whereas AS patients' unequalled adherence to anti-TNF therapy is not affected by whether or not they're also on methotrexate, Dr. Robert D. Inman said at a symposium sponsored by the American College of Rheumatology.

These observations come from the Norwegian Disease-Modifying Antirheumatic Drug (NOR-DMARD) registry. The Norse study also demonstrated that AS patients were an adjusted 34% less likely than those with RA to terminate therapy with infliximab (Remicade), etanercept (Enbrel), or adalimumab (Humira) during the first year after starting their biologic. The PsA group was 24% less likely than RA patients to discontinue anti-TNF therapy within a year (Arthritis Rheum. 2008;59:234-40).

The reasons cited for discontinuing anti-TNF therapy varied according to disease category. Lack of efficacy was cited as the primary reason by only 18% of PsA patients who quit, compared with 36% of those with AS and 39% of RA patients. Adverse events were cited as the reason for stopping treatment by 69% of PsA patients who discontinued therapy, compared with 44% of those with AS and 49% of RA patients.

The particularly favorable risk:benefit ratio for anti-TNF therapy in AS patients was highlighted in a recent analysis of data on more than 19,000 adalimumab-treated patients in 36 clinical trials that were conducted over a 10-year period. Adalimumab-treated AS patients had rates of malignancy and serious infections as low as or lower than those in patients with the five other immune-mediated inflammatory diseases for which the biologic agent is indicated, said Dr. Inman, professor of medicine and immunology at the University of Toronto.

For example, the rate of tuberculosis and other serious infections was 1.11 per 100 patient-years in AS patients, compared with 4.65 per 100 patient-years in RA patients, 5.18 in those with Crohn's disease, 2.81 in PsA patients, 2.76 in those with juvenile idiopathic arthritis, and 1.32 per 100 patient-years for psoriasis patients.

The incidence of malignancies other than lymphoma and nonmelanoma skin cancer was greatest in the RA population on adalimumab (0.76 cases per 100 patient-years vs. 0.08 per 100 patient-years in the AS group). Patients with RA also had the highest rate of nonmelanoma skin cancer and the second-highest lymphoma rate of the six autoimmune inflammatory diseases for which adalimumab is approved.

As for the relative efficacy of the various anti-TNF drugs in the setting of AS, there is a dearth of head-to-head comparative studies. However, scrutiny of the various placebo-controlled, randomized trials suggests that the efficacy of various agents in AS "looks very comparable," with 51%-61% of patients on etanercept, infliximab, adalimumab, or golimumab showing a 20% improvement in ASAS 20 (Assessment in Ankylosing Spondylitis 20) at 24 weeks, according to Dr. Inman. ■

Disclosures: *Dr. Inman disclosed serving as a consultant to Sanofi-Aventis, Amgen Inc., Wyeth, Abbott Laboratories, Schering-Plough Corp., and Centocor Inc.*