Sustained Benefits Seen With Biologics in PsA

BY NANCY WALSH
New York Bureau

NEW YORK — Increasing experience with the biologic agents in psoriatic arthritis is showing that these drugs are effective across all domains of this complex disease.

Tumor necrosis factor (TNF) inhibitors in particular have proven beneficial in the treatment of the peripheral arthritis, skin and nail disease, axial disease, dactylitis, and enthesitis associated with psoriatic arthritis (PsA).

Traditional disease-modifying antirheumatic drugs such as methotrexate, in contrast, may be useful for the arthritis and skin and nail disease, but are less effective for the other disease manifestations, according to Dr. Philip Mease, of the University of Washington, chief of rheumatology research, Swedish Medical Center, and head, Seattle Rheumatology Associates.

The impact of anti-TNF drugs on PsA comorbidities is unknown, but good CV outcomes are seen in RA registries.

DR. MEASE

This difference in therapeutic efficacy may relate to important differences in pathophysiology between PsA and rheumatoid arthritis (RA).

For example, the synovitis in PsA is associated with less sublining infiltrate and with greater vascularity than in RA. There is also an increased expression of toll-like receptors 2 and 4 and an increased number of polymorphonuclear leukocytes, suggesting a greater role for the innate immune system and possibly microbial antigen stimulation, Dr. Mease said at a rheumatology meeting sponsored by New York University.

In PsA there also is a role for unique lineages of monocytes effector cells that differentiate into macrophages, osteoclasts, Langerhans cells, and dendritic cells via specific microenvironmental signals, he said.

Trials of anti-TNF drugs in PsA have permitted, but not required, both background methotrexate, nonsteroidal anti-inflammatories, and low-dose prednisone, and patients with oligoarticular disease have been included.

For infliximab, newly published 98-week data from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) demonstrate a similar degree of sustained effectiveness.

In the open-label extension phase of the current trial, 62% of the 78 patients continuing on the drug at week 98 had achieved an American College of Rheumatology 20 (ACR20) response, while 45% and 35% had ACR50 and ACR70 responses, respectively.

Among those whose baseline PASI score was 2.5 or greater, 64% achieved a 75% improvement (J. Rheumatol., First Release March 15, 2008).

Similar results also have been seen with adalimumab, with 70% of patients reaching a PASI 75 response and improvements in disability being sustained out to week 48 (Arthritis Rheum. 2007;56:476-88).

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For etanercept, 2-year data demonstrated sustained effectiveness in ACR scores over time and inhibition of progression of radiologic damage. Approximately 40% of patients achieved Psoriasis Area Severity Index (PASI) 75 responses (J. Rheumatol. 2006;33:712-21).

But unanswered questions remain regarding the use of anti-TNF drugs for PsA, such as whether additional benefits result from adding methotrexate, Dr. Mease said.

Because the trials thus far have been inconsistent as to whether background methotrexate was used, what is needed to answer this question is a trial that enrolls methotrexate-naive patients and randomizes them to methotrexate monotherapy, anti-TNF monotherapy, or the combination, he said.

"We also don't know what the impact of these drugs will be on PsA comorbidities," he said.

RA registries are showing benefits in terms of cardiovascular outcomes, and this may also be the case in PsA. The answers will only come from sources such as the Consortium of Rheumatology Researchers of North America (CORRONA) database, which is collecting long-term data not only on outcomes in RA but also on PsA, osteoarthritis, and osteoporosis.

It also remains to be seen if other comorbidities associated with PsA will benefit from anti-TNF therapy, including infection, lymphoma, and depression.

"A further question is what we should do about patients who are inadequately responding to these anti-TNFs," he said. A variety of other therapies are being assessed, including other anti-TNFs such as golimumab, intra-articular anti-TNF agents, other cytokine targets such as interleukin-12/interleukin-23, B-cell ablation with rituximab, and small molecules such as the JAK3 inhibitor.

Another new area of exploration in the spondylarthropathies is the use of anti-TNF drugs in preradiographic ankylosing spondylitis (AS), Dr. Mease noted.

In an open-label extension study of 22 patients with early axial spondylarthritis but without radiographic sacroiliitis, 46% of patients receiving adalimumab had a sustained 40% improvement in the Assessments in Ankylosing Spondylitis 40 (ASAS40) criteria (Ann. Rheum. Dis. 2007;66[suppl II]:64-5). ■

Celecoxib's CV Risk Is Based Partly on Dose and Schedule

BY BRUCE JANCIN
Denver Bureau

CHICAGO — The cardiovascular risk of celecoxib is a function of both dose and dosing schedule, as well as a patient's baseline cardiovascular risk, according to a new National Cancer Institute–sponsored pooled analysis of six randomized trials.

Individuals at higher baseline cardiovascular risk, according to the Framingham risk score, had substantially higher relative as well as absolute risk of celecoxib-related cardiovascular events than did those patients at low baseline risk, Dr. Scott D. Solomon explained at the annual meeting of the American College of Cardiology.

"These data should help guide rational clinical decisions regarding celecoxib use," said Dr. Solomon of the Brigham and Women's Hospital, Boston.

"The data may provide a measure of confidence in prescribing celecoxib in patients with very low baseline cardiovascular risk, but would argue for caution in prescribing celecoxib in patients with high baseline cardiovascular risk," Dr. Solomon commented.

Of the dosing regimens evaluated in the pooled analysis, 400 mg once daily was associated with a significantly lower event rate than was 200 mg b.i.d., which in turn was safer than 400 mg b.i.d., the cardiologist added.

Dr. Solomon presented the results of the Cross Trial Safety Analysis, involving 7,950 patients with 16,070 patient-years of follow-up in six placebo-controlled trials.

All of the trials investigated celecoxib for conditions other than arthritis.

The data 'should help guide rational clinical decisions regarding celecoxib use.'

DR. SOLOMON

Three studies evaluated the cyclooxygenase-2 (COX-2)–selective NSAID for secondary prevention of colonic polyps; the others involved degenerative eye disease, secondary prevention of breast cancer, and prevention of Alzheimer's disease.

All but one study was sponsored by the NIH.

The rate of the primary study end point—the combination of cardiovascular death, MI, stroke, heart failure, or a thromboembolic event—was 1.1-fold greater in patients on 400 mg of celecoxib once daily than in those on placebo, 1.8-fold greater in patients on 200 mg b.i.d., and 3.1-fold greater in those on 400 mg b.i.d.

The cardiovascular risk associated with the COX-2 inhibitor was unaffected by concomitant use of low-dose aspirin.

The event rate associated with 400 mg of celecoxib once daily wasn't significantly different than with placebo.

However, there were relatively few cardiovascular events in patients on this regimen, making for wide confidence intervals.

Thus, it was theoretically possible that 400 mg once daily was associated with anything from a 40% reduction in cardiovascular events to a twofold increase, Dr. Solomon noted.

Why did celecoxib at 200 mg b.i.d. carry a significantly higher event rate than did 400 mg once daily? The leading hypothesis involves the fact that the drug suppresses prostacyclin for about 12 hours.

Once-daily dosing thus provides the arteries with a respite from the drug's effects, he said.

All doses studied in the analysis are substantially higher than the 200-mg, once daily dosage for which 80%-90% of all celecoxib prescriptions are written. That's the standard dosage in osteoarthritis. But the higher doses are routinely used for patients with rheumatoid arthritis, familial adenomatous polyposis, and acute pain and dysmenorrhea.

The study findings raise the question of whether celecoxib should ever be given to patients with coronary heart disease, or diabetes (considered a CHD risk factor), or rheumatoid arthritis (which is drawing increasing attention as a possible new CHD risk factor).

The trouble with issuing a blanket prohibition in these circumstances, Dr. Solomon said, is that patients who require pain relief have to take something—and it's unclear whether conventional NSAIDs are safer.

Indeed, celecoxib's black box warning states, "All NSAIDs may have a similar risk."

The answer to that key question is expected to come from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen) trial. PRECISION is an ongoing Pfizer Inc.–sponsored randomized trial involving 21,000 patients with osteoarthritis or rheumatoid arthritis with, or at increased risk for, cardiovascular disease.

The end points are symptom relief and cardiovascular, renal, and GI safety. The celecoxib dosage is 200 mg once daily, with some patients being titrated to b.i.d. therapy.

"I am a little bit reassured by the data [in the pooled analysis] with the 400-mg once-a-day dose," commented PRECISION principal investigator Dr. Stephen Nissen, chairman of cardiovascular medicine at the Cleveland Clinic Foundation. ■