PRECISION: Differences Emerge Between RA and OA Patients

Kate Johnson | November 16, 2016

WASHINGTON, DC — Rates of all-cause mortality are significantly higher when patients with rheumatoid arthritis are treated with naproxen than when they are treated with ibuprofen or the selective cyclooxygenase (COX)-2 inhibitor celecoxib (*Celebrex*, Pfizer), according to a subanalysis of data from the PRECISION trial.

However, this increase does not apply to patients with osteoarthritis.

The PRECISION trial — Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen (NCT00346216) — showed similar cardiovascular safety for all three agents in a pool of patients with rheumatoid arthritis or osteoarthritis, as reported by *Medscape Medical News* (*N Engl J Med.* Published online November 13, 2016).

But in a subanalysis of the data, which looked at rheumatoid arthritis and osteoarthritis patients separately, "the most striking and surprising finding was the mortality difference" between naproxen and celecoxib users with rheumatoid arthritis, said PRECISION investigator Daniel Solomon, MD, from Brigham and Women's Hospital in Boston.

"Why we saw that is not clear. It may be a play of chance, or it could be something real," he said here at the American College of Rheumatology 2016 Annual Meeting. "I think our job is to look at those deaths."

Rethinking Prescribing Practices

On the basis of the PRECISION results, "I think there's going to be a reconsideration of prescribing around NSAIDs and coxibs," he told *Medscape Medical News*. However, he cautioned not to read too much into the increased mortality in patients with rheumatoid arthritis (there were 15 deaths in the naproxen group and 30 in the celecoxib group).

"Subgroup analyses always have to be taken as hypothesis-generating," he emphasized. "The main finding from the PRECISION trial is noninferiority for cardiovascular end points. Period."

In the wake of the worldwide recall of rofecoxib (*Vioxx*, Merck), the US Food and Drug Administration asked that Pfizer launch the postmarketing PRECISION trial to explore the potential for increased cardiovascular risk and serious life-threatening gastrointestinal (GI) bleeding, ulceration, and perforation. The black-box warnings implemented at that time for all NSAIDs still stand today.

Although the overall PRECISION findings are reassuring for clinicians, they require deeper examination for the practicing rheumatologist, said PRECISION investigator Elaine Husni, MD, chair of rheumatology and director of the Arthritis and Musculoskeletal Center at the Cleveland Clinic.

"We thought it would be interesting for rheumatologists to see if there are nuances between the populations because we treat them separately," she told *Medscape Medical News*.

With results from the PRECISION trial, "I can make more individual choices because I have more data," she explained. "But whether I can definitely say that all osteoarthritis patients should be on this and all rheumatoid arthritis patients should be on this, no, I don't think that would be a fair assessment of the trial."

Rheumatoid arthritis patients made up only 10% of the PRECISION population, yet "it is interesting to note that the percentage of subjects with an event was larger in the rheumatoid arthritis than in the osteoarthritis arm across many of the outcomes," Dr Solomon pointed out.

The subgroup analysis looked at four secondary outcomes: major adverse cardiovascular events; composite serious GI

events; serious renal events; and all-cause mortality.

Table. Mean Daily Doses of the Study Drugs

Patient Group	Celecoxib, mg	Ibuprofen, mg	Naproxen, mg
Rheumatoid arthritis	282	2044	850
Osteoarthritis	200	2044	852

For patients with osteoarthritis, major adverse cardiovascular events were 16% higher in the ibuprofen group than in the celecoxib group ($P = .03$), and renal events were 42% higher ($P = .003$). In addition, GI risk was 32% higher in the ibuprofen group than in the celecoxib group ($P = .01$) and was 27% higher in the naproxen group than in the celecoxib group ($P = .04$).

For patients with rheumatoid arthritis, risk for all-cause mortality was higher in the naproxen group than in the celecoxib group ($P = .02$).

"In the osteoarthritis group, the three drugs were almost superimposable in their reduction in pain; however, in the rheumatoid arthritis group, ibuprofen users had a more profound reduction than either celecoxib ($P = .02$) or naproxen users," Dr Solomon reported.

Rheumatologists use NSAIDs every day and we all face difficult patients with contraindications because of previous GI bleeds or gastritis," said Isabelle Amigues, MD, a rheumatology fellow at the Columbia University Department of Medicine in New York City.

"With this reassurance that patients on COX-2 inhibitors do not have increased risk of CV complications, compared with patients taking nonselective NSAIDs, we once again have the option of using COX-2 inhibitors," she told *Medscape Medical News*.

Many everyday rheumatology patients will likely be positively affected. "For example," she explained, "patients with spondyloarthropathy who do not meet the criteria for biologic agents but who have a history of GI bleeds will now be able to take COX-2 inhibitors without fear that it will increase their risk of CV events."

But Alfonso Bello, MD, from the Illinois Bone & Joint Institute in Glenview, said he is underwhelmed.

"It's funny, but at this point, everybody has kind of moved on," he told *Medscape Medical News*.

"This is really important for all of us who prescribe NSAIDs all the time, but the initial information that celecoxib doesn't look different from the other NSAIDs is not surprising. It answers the primary question of whether a coxib is different from an NSAID from a cardiovascular perspective, and it looks like it is not."

But he urged caution when interpreting the GI advantages of celecoxib, given that dosing adjustments were permitted for all three study drugs and patients were prescribed the proton pump inhibitor esomeprazole without any tracking of compliance.

The trial was funded by Pfizer. Dr Solomon reports receiving research grants from Pfizer on non-NSAID-related topics, and receiving royalties for chapters related to NSAIDs and selective COX-2 inhibitors. Dr Bello is a former employee of Searle/Pfizer and has received consulting and speaking fees in the past from Horizon Pharma, AbbVie, Questcor, and UCB. Dr Amigues has disclosed no relevant financial relationships. PRECISION site investigator Elaine Husni, MD, from the Cleveland Clinic, reports receiving grants from Genzyme/Sanofi and Pfizer, and personal fees from AbbVie, Bristol-Myers Squibb, Amgen, UCB Pharma, Regeneron, and Janssen. Senior PRECISION investigator Steve Nissen,

MD, from the Cleveland Clinic, reports receiving grants from Pfizer.

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Send comments and news tips to news@medscape.net.

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