

# Adjunct PPI Confers Effective Gastroprotection

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Adding a proton pump inhibitor to a nonsteroidal anti-inflammatory drug provides as much protection against NSAID-induced gastropathy as a cyclooxygenase-2 inhibitor (coxib), according to a new study September 2007 issue of the journal *Gastroenterology*.

Adding a proton pump inhibitor (PPI) to a coxib may provide some additional pro-

tection, but in recent years some coxibs have been shown to cause serious cardiovascular disease, wrote Wayne A. Ray, Ph.D., and his colleagues at Vanderbilt University, Nashville, Tenn.

The observational study used data from TennCare, the state of Tennessee's Medicaid program. Patients aged 40 years and older with a new episode of prescribed NSAID or coxib use between 1996 and 2004 were included. After excluding patients with serious illnesses such as cancer,

HIV infection, cirrhosis, and chronic alcoholism, and those with less than 2 years of baseline data, the study included 234,010 new episodes of NSAID use and 48,710 new episodes of coxib use, with a total of 363,037 person-years of follow-up.

The investigators adjusted for a large number of demographic variables; prior history of peptic ulcer disease; use of low-dose aspirin, other antiplatelet drugs, anticoagulants, or systemic corticosteroids; new residence in a nursing home; and new

nongastrointestinal hospital admission.

They found that the use of NSAIDs without gastroprotective cotherapy was associated with 5.65 peptic ulcer hospitalizations per 1,000 person-years, which is 2.8 times the incidence for comparable patients who were former users of either NSAIDs or coxibs.

Use of a PPI, a double-dose histamine-2 receptor antagonist, or misoprostol along with an NSAID reduced the risk of peptic ulcer hospitalization by 39%. Of the various gastroprotective therapies, PPIs were associated with the greatest risk reduction—54%—among NSAID users.

Unprotected use of a coxib resulted in a 40% reduction in the risk of peptic ulcer hospitalization, compared with unprotected use of an NSAID. Using a gastroprotective therapy in addition to a coxib re-

**Of all of the various gastroprotective therapies, proton pump inhibitors were associated with the greatest risk reduction—54%—among NSAID users.**

sulted in a further 10% reduction in risk (for a total of 50%), with no statistically significant advantage for PPIs over other gastroprotective therapies.

In a subanalysis adjusted for dose, naproxen proved to be associated with

the highest risk of peptic ulcer hospitalization, with an adjusted rate of 7.8 per 1,000 patient-years. Ibuprofen, rofecoxib, and celecoxib all were associated with significantly lower risks of hospitalization.

Another subgroup analysis showed that an NSAID with gastroprotection was significantly better for several patient groups than an NSAID alone. These groups included patients over the age of 65 years and those with a history of previous ulcers.

In other subgroups with medical comorbidities, those taking low-dose aspirin, and those on antiplatelet or anticoagulant therapy, gastroprotection had no statistically significant improvement over unprotected NSAIDs. The researchers said this was partly because of relatively small numbers of patients in some of the subgroups.

The study was supported by the Agency for Healthcare Research and Quality, and the investigators stated that they received no support from any pharmaceutical company. "[It] is increasingly unlikely that large clinical trials of gastroprotective cotherapy in NSAID users will be conducted," they wrote. "Proton pump inhibitors are available generically, which limits the incentives for pharmaceutical manufacturers to fund such studies. Furthermore, because NSAID-induced gastropathy is frequent and potentially life threatening, the ethics of randomizing patients to NSAID use without gastroprotective cotherapy are questionable."

The researchers recommended future trials directly comparing coxibs to NSAIDs with a PPI, and said additional investigation is "urgently needed" to study the benefits of adding a PPI to celecoxib and other coxibs. ■

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## Are certain patients at greater risk for rapidly progressing RA?

Joint damage is responsible for much of the disability associated with rheumatoid arthritis (RA).<sup>1</sup> Early diagnosis and effective treatment may play a critical role in preventing functional decline and loss of quality of life—especially in patients with poor prognosis.<sup>2</sup>

The course of radiologic damage in RA is not completely understood. The amount of damage seen on radiographs of RA patients can vary widely. It remains unclear whether erosions and joint space narrowing are equally important in determining degree of radiologic damage. In addition, there is little detailed information on the rate of progression of radiologic abnormalities from disease onset. Some studies suggest a nonlinear, first-order kinetics model with most of the damage progression occurring in the initial years; other studies suggest a linear, stable rate of progression throughout the course of the disease.<sup>3</sup>

Despite these questions, there is little doubt about the correlation between radiologic damage and disability in RA.<sup>1</sup> Data from 10 prospective, longitudinal studies indicate significant correlations that become more obvious as disease duration increases.<sup>1</sup> It has been suggested that physical disability in early RA is largely determined by disease activity, while in late RA, joint damage plays a more important role.<sup>4</sup> In addition, patients at risk for long-term disability are those with seropositive erosive disease and high initial average Health Assessment Questionnaire scores.<sup>1</sup>

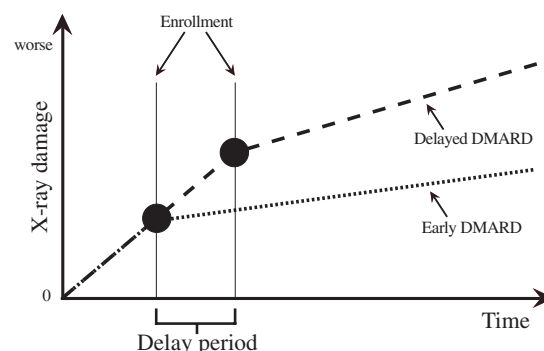
There is a clear case for identifying and treating RA patients early. Finckh, et al, conducted a meta-analysis of 12 studies to examine the correlation between late therapeutic initiation and joint damage. An average delay in treatment start of 9 months altered disease progression over the long term. However, early initiation of therapy reduced radiologic damage, resulting in a dramatically altered disease progression curve. (See Figure 1.)<sup>5</sup>

Despite the evidence that rapidly progressing RA benefits from early and aggressive treatment, early diagnosis has proven difficult in many patients. In many cases, American College of Rheumatology criteria may not be met in patients who nevertheless will deteriorate rapidly.<sup>6</sup>

There are measurable variables at initial visit that can identify patients at high risk for rapid radiologic progression. (See Table 1.) Of particular interest is arthritis of the large joints, especially the knee.<sup>7</sup> In a Linn-Rasker, et al, regression analysis of 1009 patients, arthritis of the knee at initial presentation was revealed to be a strong predictor of a more destructive course of disease.<sup>7</sup> Also compelling is a study by Taylor, et al, that demonstrated a clear relationship between sonographic measurements of synovial thickening and vascularity at baseline to magnitude of radiologic joint damage at Week 54.<sup>8</sup>

These markers may present a means to identify rapidly progressing RA patients early in the course of the disease, rather than risking unsuccessful treatment with less aggressive therapies. Early and more aggressive treatment for appropriately identified patients has the potential to reduce further radiologic joint damage and functional decline.<sup>2</sup>

**Figure 1. Early therapeutic initiation alters RA progression over time<sup>5</sup>**



**Table 1. Measurable variables at initial visit to identify high-risk patients<sup>4,6-9</sup>**

- Swollen joint count
- Erythrocyte sedimentation rate
- Serum IgM rheumatoid factor
- Arthritis of the large joints, particularly the knee
- Anti-cyclic citrullinated peptide antibodies
- Synovial thickening and vascularity at baseline

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