Nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of pain control in rheumatoid arthritis (RA), but they can pack a nasty punch, causing insidious damage that may erupt suddenly and critically without warning. Two newly published large-scale studies from Europe document the occult risks of kidney disease and gastrointestinal damage with NSAID use.

Because patients with RA generally require more NSAIDs and have an increased baseline risk of kidney and cardiovascular damage, these hazards are all the more relevant for this subgroup of patients.

Both studies observe that following guidelines for the use of NSAIDs can reduce these risks considerably, but predictably they find that adherence to these guidelines is poor.

**Renal Risks**

A longitudinal study of kidney function involving more than 4,100 RA patients from Switzerland found a greater risk of rapid renal decline in NSAID users whose kidneys were impaired to begin with. However, regardless of an individual history of renal disease, the authors noted, NSAIDs may lead to reversible acute kidney injury or end stage renal disease (ESRD) due to vasoconstriction, tubular necrosis, and acute interstitial nephritis.

In fact, they write, GFRs may decrease “within days after the initiation of NSAID therapy” but “clinically apparent events are poorly predictable and may occur years later.” Because RA patients often need higher doses of NSAIDs and “given the broad definition of NSAID contraindication in today’s practice guidelines, it is obvious that NSAIDs are frequently used in a way that breaches current safety recommendations,” the researchers asserted in a recent issue of the *Annals of the Rheumatic Diseases.*

This is startling in that the participants of their study are part of the ongoing Swiss clinical quality management (SCQM) database, established to track the effectiveness and safety of antirheumatic therapies among patients treated by board-certified rheumatologists.

The majority of the RA patients, followed between 1997 and 2006, were women in their mid-50s with median disease duration of 4 years. All participants underwent at least two assessments of kidney function. Many had some degree of renal disease at baseline.

In the study group, 2,739 had at least one pharmacy record for prescription or over-the-counter NSAID during a mean follow-up period of 3.2 years and were considered “NSAID users.” Those with no record of use were considered “NSAID naïve.” Around half the NSAID users (n=1,290) had been treated with a cyclooxygenase type 2 (COX-2) selective inhibitor, such as celecoxib (Celebrex).

During follow-up, both “NSAID naïve” and “NSAID users” had similar declines in kidney function, as seen in reduced glomerular filtration rates (GFRs) calculated with the widely-accepted Cockroft-Gault formula (eGFRCG).

Only for those with advanced kidney impairment (a eGFRCG below 30 mL/min) were NSAIDs found to be an independent predictor of accelerated renal decline, with the steepest declines seen in higher-stage chronic kidney disease (CKD stages 4 and 5).

Significant negative predictors of renal decline included age, arterial hypertension (around 22% of the RA patients had high blood pressure), as well as previously diagnosed kidney and heart disease. The team proposes an eGFRCG of less than 30 mL/min as a cut-off to indicate contraindication of
NSAIDs in RA and a definitive renal risk situation. Beyond that point, they say, vigilance is justified for any RA patient.
There are many degrees of renal failure and measures for kidney impairment, including creatinine clearance, comments Massachusetts rheumatologist Lee S. Simon MD, a former director of the division of Analgesic, Anti-Inflammatory and Ophthalmologic Drugs for the FDA’s Center for Drug Evaluation and Research and editor of a recent supplement on the topic in *Arthritis Research & Therapy*.3

“No NSAID should be used in patients whose creatinine clearance is less than 30 cc per minute,” Simon told *Rheumatology Network*, pointing out that NSAIDs are associated with interstitial nephritis.
However, renal failure is “rare among people with normal kidney function who are not dehydrated,” added Simon, who’s now a pharmaceutical industry drug-development consultant.

**The Burning Issue of Ulcers**
As with kidney impairment, ulcers and other GI problems related to NSAID use may not always announce their presence. Many patients who develop serious NSAID-related GI complications have no warning signs or symptoms before they’re hospitalized for an acute event, according to a multi-national study of more than 4,000 patients reported in the same issue of the *Annals*.2

The EVIDENCE study, conducted at 363 centers across Europe, was designed to reflect what happens in real-life clinical practice when patients with rheumatic diseases and GI risk factors start or re-start NSAIDs.

Among the 4,144 participants, 11% had RA, while a majority had osteoarthritis. They had been taking various doses and kinds of NSAIDs (including aspirin, diclofenac, and ibuprofen) for about a month before enrollment in the trial, and around half remained on continuous prescription NSAIDs for most of the six-month follow-up.
All had at least one GI risk factor, and 27% had a history of uncomplicated but systematic GI events, including gastritis, ulcers, and dyspepsia. One in ten was judged high-risk due to past GI bleeding or anticoagulant use.

Noting that people with even a single risk factor need gastroprotection, the researchers found adherence to guidelines “unacceptably” low. Only 28% of these patients had been prescribed proton pump inhibitors (PPIs) such as omeprazole.
The incidence of GI events -- 18.5 per 100 person-years for uncomplicated GI events and 0.7 for complicated GI events -- was higher than in similar studies. A July 2013 supplement to *Arthritis Research & Treatment* devoted to NSAIDs cited the American College of Gastroenterology (ACG) and the European League Against Rheumatism (EULAR) among others, as recommending NSAIDs be used at the lowest possible dose for the shortest amount of time -- and PPIs (or misoprostol) used for gastroprotection, even with COX-2 selective inhibitors.3

**Matters of the Heart**
Cardiovascular risks are another factor to consider in this situation: Patients with RA have an increased risk of cardiovascular events, and NSAID users have an estimated 35% increased risk of heart attacks. Simon has a protocol designed to minimize this risk.

“We have no data regarding non-acetylated salicylates [e.g., choline magnesium trisalicylate (Trilisate) and salsalate (Disalcid)], which act as NSAIDs and have not been associated with risk of CV events. Furthermore, naproxen has a lower risk followed by celecoxib than the other NSAIDs,” Simon remarked. “Thus I might try non-acetylated salicylates first, then naproxen and, if the patient has a strong GI risk history, also a gastroprotective agent and/or celecoxib.”

**References:**


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