

# Gastrointestinal Events in Rheumatoid Arthritis: Time for the Lower Gastrointestinal Tract!



The manifestations of rheumatoid arthritis (RA) extend beyond the symmetrical inflammation of the joints as accumulating evidence indicates an increased risk for comorbid conditions like gastrointestinal (GI) events. In recent decades there has been considerable interest in (upper) GI events, particularly in light of widespread use of non-steroidal antirheumatic drugs (NSAID) and associated “NSAID gastropathy”<sup>1</sup>.

The wide spectrum of NSAID gastropathy includes GI complaints such as dyspepsia, gastroduodenal ulcers, potentially life-threatening complications such as bleedings and perforations, and obstruction. NSAID gastropathy prompted development of cyclooxygenase 2 inhibitors (COX-2), and presently, there is abundant evidence that COX-2 give about 100% reduction in serious GI events such as (perforated) ulcers, and (major) bleedings or obstructions<sup>2</sup>. Alternative strategies for prevention of NSAID gastropathy might be the combination of NSAID with a proton-pump inhibitor (PPI) or misoprostol<sup>3</sup>. However, in comparison to placebo, the use of COX-2 is at the cost of a doubling of cardiovascular events, particularly myocardial infarctions. But this also holds for the NSAID, with (most probably) the exception of naproxen<sup>4</sup>.

Until recently, the focus of the NSAID-related GI adverse events has been on the upper GI tract, but there are some reports that NSAID are also associated with lower GI adverse events. The landmark pathology study of Allison and coworkers, who investigated 713 patients post mortem, of whom 249 had used NSAID and 464 had not, revealed small-intestine ulceration in 21 of the NSAID users (8.4%) versus 3 of the non-NSAID users (0.6%)<sup>5</sup>. As a comparison, upper GI tract ulcerations were observed in 21.7% and 12.3%, respectively.

Several observational studies have documented that NSAID are associated with lower GI adverse events and a question that emerges is whether this risk is lower with COX-2. A post-hoc analysis of a large randomized dou-

ble-blind trial where more than 8000 patients were randomized to either rofecoxib 50 mg/day or naproxen 500 mg twice daily revealed that serious lower GI events occurred 50% less frequently in the rofecoxib group in comparison to the naproxen group (9 vs 18 events, respectively)<sup>6</sup>. Subgroup analysis of a trial in more than 8000 patients where celecoxib 400 mg twice daily was compared with either ibuprofen 3 times daily 800 mg or diclofenac twice daily 75 mg showed significantly less hematochezia in the celecoxib group (n = 17, 0.4%) in comparison to the ibuprofen/ diclofenac group (n = 40, 1.0%). In contrast, a trial comparing etoricoxib 60 or 90 mg per day (n = 17,412) or diclofenac 75 mg twice daily (n = 17,289) and where approximately 40% of the patients received PPI comedication revealed no significant lower GI advantage for the COX-2 in comparison to the NSAID<sup>7</sup>. Obviously, it is preliminary to conclude that celecoxib has a safer lower GI tract profile than etoricoxib since the comparator NSAID differ in their COX-1-inhibiting capacity, which might translate into clinically relevant differences in lower GI adverse events between the various NSAID. Moreover, in the trial with etoricoxib, the results might have been confounded by use of aspirin and/or PPI.

When comparing COX-2 with NSAID in combination with PPI, there are no major differences with respect to upper GI safety. However, the efficacy of PPI in the lower GI tract is not known, and current literature is contradictory; from a theoretical point of view PPI might not work in the lower GI tract<sup>8</sup>, whereas animal models contradict each other: one suggests exacerbation of small intestinal lesions by inducing dysbiosis<sup>9</sup>, whereas another suggests prevention of NSAID-induced small-intestine lesions<sup>10</sup>. A first clinical answer comes from the CONDOR study<sup>11</sup>. In this 6-month randomized double-blind trial almost 4500 patients with RA or osteoarthritis were treated with either celecoxib twice daily 200 mg or diclofenac twice daily 75 mg in combination with omeprazole. The primary endpoint

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was a composite of clinically significant upper and lower GI events encompassing GI bleeding and clinically significant anemia (hemoglobin decrease  $\geq 1.25$  mmol/l) of defined GI origin or of presumed GI origin, including possible small-bowel blood loss. The primary endpoint occurred in 20 celecoxib-treated patients (0.9%) and 81 diclofenac/ omeprazole-treated patients (3.8%). Clinically significant anemia of presumed occult GI origin was observed in 10 and 53 patients, respectively. Most of these patients underwent either gastroscopy (n = 56) or colonoscopy (n = 27) that revealed no overt lesions, indicating potential bleeding from the lower GI tract. Translation of the results of this trial into clinical practice is difficult. One could advocate regular hemoglobin testing but this appears premature in view of the low frequency and the unknown clinical significance of these asymptomatic bleedings. On the other hand, the impact of lower GI blood loss on healthcare costs may be substantial<sup>12</sup>.

Nevertheless, the results suggest that PPI are less protective in the lower GI tract than COX-2. Moreover, there is a lack of contemporary data of lower GI events and determinants thereof (e.g., are the risk factors the same as for upper GI lesions?) in patients with RA.

This unmet need is partly solved by the controlled study in incident RA patients of Myasoedova and colleagues in this issue of *The Journal*<sup>13</sup>. Using the Rochester epidemiology project medical linkage system these investigators were able to ascertain virtually all new RA cases within Olmsted County, Minnesota, USA, between 1980 and 2008, who were followed until December 31, 2009. The reference cohort consisted of randomly selected age and sex-matched controls from the same underlying population. A total of 813 patients with RA and 813 controls were recruited for this study. Objectified upper and lower GI events occurred at rates of 2.8 and 2.1 per 100 person-years in the RA population, versus 1.7 and 1.4 per 100 person-years, respectively, in the control population.

Ulcers and bleeding occurred 70%–80% more in the RA population in comparison to the controls. Infectious colitis and drug-induced colitis were among the lower GI events that were roughly doubled in the RA population. Within the drug-induced colitis group, NSAID and DMARD resulted, in the RA group, in a 16- and 18-fold risk increase, respectively, versus the control population. Within the RA population, glucocorticoid use and history of upper GI disease were independent predictors of lower GI events. Upper GI bleeds and perforation were the only GI events that were independent predictors of mortality. Time trend analyses showed that upper GI events declined whereas lower GI events were constant over time.

Altogether, this investigation confirms the findings of a cross-sectional survey in 283 RA patients and 233 control persons recently published by the same group<sup>14</sup>, and extends the evidence that lower GI (adverse) events in RA occur much more frequently than anticipated. The decline of upper

GI events during the last 20–30 years was also noted by other investigators and might be related to the implementation of preventive measures for NSAID gastropathy<sup>15</sup>. As this was not accompanied by a decrease of lower GI events, this suggests that measures for prevention of NSAID gastropathy are not effective for lower GI tract complications of NSAID use, although the present article also suggests that COX-2 users have fewer lower GI tract events than non-COX-2 users. Additionally, smoking and other dietary habits could have contributed to the non-decline of lower GI events in RA during the last 20 years.

Altogether, the findings of Myasoedova, *et al* reinforce the need for screening strategies for lower GI disease, particularly when risk factors such as smoking and glucocorticoid or NSAID use are present. A first step will be to increase awareness among our colleagues to the significantly increased risk of lower GI events in our patients with RA. A second step would be development of strategies for prevention of NSAID-associated lower GI tract toxicity followed by implementation studies.

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