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Review

Osteoarthritis year 2010 in review: pharmacological therapies

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ABSTRACT

This review highlights a selection of original studies related to the treatment of osteoarthritis in 2010.
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Non-steroidal anti-inflammatory drugs (NSAIDs)-induced lower GI tract: an underestimate of adverse events of conventional NSAIDs?

Based on previous trials comparing a co-prescription of traditional NSAIDs plus proton-pump inhibitor (PPI) and cyclo-oxygenase-2 (COX-2) selective drugs, the risk of having an upper gastrointestinal (GI) event (ulcer, perforation, bleeding and obstruction) is similar in between both groups. However, the risk of lower GI events has never been assessed in a randomized controlled trial. In this study [named CONDOR for "Celecoxib vs omeprazole and diclofenac in patients with osteoarthritis (OA) and rheumatoid arthritis (RA)"], the authors performed a 6-month, double-blind, multicenter randomized controlled trial in patients at increased GI risk (defined by an age over 60 or over 18 with a history of a previous gastro-duodenal ulceration) with OA or RA in order to compare the risk of GI events, upper and lower, associated with celecoxib 200 mg bis in die meaning two times a day (BID) vs diclofenac slow release 75 mg BID plus omeprazole 20 mg once a day[1]. Patients needing low-dose aspirin were excluded. The primary endpoint was a composite of upper and lower events including hamorrhage from defined or undefined origin, small bowel or large bowel perforation, gastric obstruction, clinically significant anemia defined by a decrease of 20 g/L or more, or a decrease in hematocrit of at least 10 percentage points (Table I)[2]. Among 4,484 patients randomly allocated to treatment (assigned in a 1:1 ratio), 0.9% patients receiving celecoxib and 3.8% receiving diclofenac plus omeprazole met criteria for the primary endpoint [Hazard ratio (HR) = 4.3, 95% credible interval (CI) 2.6–7.0, $P < 0.0001$] (Fig. 1). Interestingly, the main reason for this difference was due to a major increase in significant anemia from unknown origin in the diclofenac plus omeprazole group (53/2246) vs the celecoxib group (10/2238). Based on the results of this study, the authors consider that COX-2 selective NSAIDs would be less deleterious for the lower GI tract than conventional NSAIDs + PPI maybe due to an absence of protection of PPI on NSAIDs-induced small bowel and colon mucosa lesions. The main question raised by this study is the clinical significance of a loss of 20 g/L hemoglobin, the main impressive difference between both groups. One can argue that another arbitrary threshold would perhaps lead to different conclusions. Moreover, the results of this study cannot be extrapolated to the large population of patients treated with anti-aggregants like aspirin, meaning that the potential benefit of COX-2 selective agents over conventional NSAIDs on lower GI tract in patients at increased risk for GI events could be challenged by an increased risk, even controversial, of cardiovascular (CV) events in these patients. Even with these limitations, the NSAIDs-induced lower GI tract toxicity should now be taken into account for the assessment of the benefit-risk balance of NSAIDs. Finally, another critical interest of this study is to highlight an underestimate of adverse events of conventional NSAIDs, that is the NSAIDs-induced lower GI tract outcome.

Glucosamine and chondroitin: to be or not to be effective?

For decades, the pros and cons debate on the efficacy of glucosamine and chondroitin for the treatment of OA symptoms and joint degradation. Pros consider that there are now enough data in the literature to prove that these natural cartilage components do have a significant effect at least on pain and function and maybe on delaying OA cartilage degradation based on X-ray databases. Since

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Table I
The composite primary endpoint used in the CONDOR trial (simplified from[2])

With lesion	Without lesion
GD hemorrhage: endoscopic evidence of GD ulceration or erosion or other likely causative lesion, and clinical evidence of recent hemorrhage.	Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage: rank hematemesis, melena, or PR blood loss, with no evidence of likely causative lesion on EGD or colonoscopy (or small bowel investigation).
Gastric outlet obstruction.	
GD, small bowel, or large bowel perforation.	
Large bowel hemorrhage: frank melena or PR blood loss with no evidence of source on EGD and likely causative lesion on colonoscopy.	Clinically significant anemia of presumed occult GI origin, including possible small bowel blood loss: no overt clinical evidence of acute GI hemorrhage but with fall in Hct $\geq$ 110% points and/or Hgb $\geq$ 2 g/dl from baseline, with no evidence of likely causative lesion on EGD or colonoscopy (or small bowel investigation) with no non-GI source of anemia identified, and, in RA patients, disease activity should be stable.
Small bowel hemorrhage: frank melena or PR blood loss with likely causative lesion on small bowel investigation.	
Small bowel obstruction.	
Clinically significant anemia of defined GI origin: no clinical evidence of acute GI hemorrhage but with fall in Hct $\geq$ 10% points and/or Hgb $\geq$ 2 g/dl from baseline, with likely causative lesion on colonoscopy or EGD (or small bowel investigation) with no non-GI source of anemia, and, in RA patients, disease activity should be stable.	
Symptomatic ulcers: cases that do not meet the definition of an ulcer complication but do have endoscopic evidence of a gastric and/or duodenal ulcer, as adjudicated by the GI events committee.	

Abbreviations: GD = gastroduodenal, Hgb = hemoglobin, Hct = hematocrit, EGD = esophagogastroduodenoscopy.

these products have no major side effects, the benefit-risk ratio would be in favor of prescribing them in order to decrease the number of prescriptions of analgesics/anti-inflammatory drugs, much more toxic. On the other hands, Cons consider that the quality of the published studies is questionable, and raise concerns about potential conflicts of interest in some of them. Moreover, they challenge the clinical significance of these small effect-sizes seen in these studies, and could be even lower due to a number of unpublished negative trials. This year, one study brought more fuel to the cons' fire[3]. It is a network meta-analysis looking at the effects of glucosamine, chondroitin, or *placebo* in hip and knee OA patients. A network meta-analysis is a direct comparison within trials combined with indirect evidence from other trials by using a Bayesian model that allowed the synthesis of multiple time points. This sophisticated analysis allows a comparison either of these preparations with *placebo* or head to head. The main outcome measure was pain intensity whereas the secondary outcome was the change in minimal width of joint space. The minimal clinically important difference between preparations and *placebo* was prespecified at −0.9 cm on a 10 cm visual analog scale (VAS). The sources of the data were electronic databases and conference proceedings from inception to June 2009, expert contact, and relevant websites. Only large scale randomized controlled trials in more than 200 patients with hip or knee OA that compared glucosamine, chondroitin, or their combination with *placebo* or head to head were selected. Ten trials in 3,803 patients were included. On a 10 cm VAS the overall difference in pain intensity compared with *placebo* was −0.4 cm (95% CI −0.7 to −0.1 cm) for glucosamine, −0.3 cm (−0.7 to 0.0 cm) for chondroitin, and −0.5 cm (−0.9 to 0.0 cm) for the combination (Fig. 2). For none of the estimates did the 95% CIs cross the boundary of the minimal clinically important difference. Industry independent trials showed smaller effects than commercially funded trials ($P = 0.02$ for interaction). The differences in changes in minimal width of joint space were all minute, with 95% CIs overlapping zero. The authors conclude that compared with *placebo*, glucosamine, chondroitin, and their combination do not reduce joint pain or have an impact on narrowing of joint space. Of course, as in any studies, some weaknesses could lead to misinterpretations. For example, the selection of randomized trials having on average at least 100 subjects in each treatment arm could be debated even if this choice relies upon previous analysis showing that small studies, with fewer than 100 patients/treatment arm, are prone to numerous methodological deficiencies and reporting biases[4]. Another point of discussion is the type of methodology which leads to an absence of comparison like to like as in conventional meta-analysis. Finally, for the pros, the fact that these supplements have a very small effect in several trials does not mean that it should not be part of the arsenal for treating OA since this effect-size is very similar or identical to what is seen with acetaminophen with a better safety profile. So, the discussion is not closed and we can expect that it will go on in 2011….

The first biotherapy for knee and hip OA: life…and death of tanezumab?

A few months ago, a phase II trial with an antibody raised against the Nerve Growth Factor (NGF) called tanezumab, published in the New England Journal of Medicine, unchained enthusiasm since it opened the first opportunity for a biotherapy in OA[5]. This proof-of-concept trial was based on preclinical studies showing that NGF regulates the structure and function of responsive sensory neurons, including small-diameter nociceptive afferents. Lane *et al.* randomly assigned 450 patients with OA of the knee to receive tanezumab (administered at a dose of 10, 25, 50, 100, or 200 μg/kg of body weight) or *placebo* on days 1 and 56. The primary efficacy measures were knee pain while walking and the patient's global assessment of response to therapy. They also assessed pain, stiffness, and physical function using the WOMAC, the rate of response using the OMERACT–OARSI criteria and safety. When averaged over weeks 1 through 16, the mean reductions from baseline in knee pain while walking ranged from 45% to 62% with various doses of tanezumab, as compared with 22% with *placebo* ($P < 0.001$) (Fig. 3). Tanezumab, as compared with *placebo*, was also associated with significantly greater improvements in the response to therapy as assessed with the use of the patients' global assessment measure (mean increases in score of 29–47% with various doses of tanezumab, as compared with 19% with *placebo*; $P \leq 0.001$). The rate of response according to the OMERACT–OARSI criteria ranged from 74% to 93% with tanezumab treatment, as compared with 44% with *placebo* ($P < 0.001$). However, these impressive results in term of efficacy (higher than usually seen with an NSAID) have to be challenged with the neurological side effects seen in all the studies performed with tanezumab: one of the most common adverse events among tanezumab-treated patients was paresthesia (7% in the Lane's study). A pivotal phase III trial in knee OA has been presented at the last 2010 European League Against Rheumatism (EULAR) meeting[6] and a phase III trial in hip OA has been extensively presented at the last 2010 American College of Rheumatology (ACR) meeting[7]: both studies confirmed the results of the previous phase II knee OA study (although less impressive in term of efficacy), also in term of the neurological safety issue.

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