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<b>Meta-Analysis</b>
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## Coxib Safety in Patients with Inflammatory Bowel Diseases: A Meta-analysis

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**Background:** Patients with inflammatory bowel diseases (IBD) frequently have extraintestinal manifestations including arthritis, sacroiliitis, and ankylosing spondylitis. While the treatment of these rheumatological conditions with traditional non-steroidal anti-inflammatory drugs (NSAIDs) has been reported to lead to frequent IBD exacerbation, the safety of cyclooxygenase-2 (COX-2) inhibitors (Coxibs) remains unclear.

**Objectives:** Our aim is to carry out a meta-analysis to verify if Coxibs, employed to treat rheumatological manifestations, are associated with an increased risk of exacerbation of IBD compared to placebo.

**Study Design and Setting:** A MEDLINE, SCOPUS, ISI-Web of Knowledge, and EMBASE search of all studies published in English from 1965 to April 15, 2015, was conducted. Articles on the safety of Coxibs in patients with IBD were identified using the terms "Coxibs or cyclooxygenase-2 inhibitors or COX-2 inhibitors AND inflammatory bowel disease."

**Methods:** The criteria of exclusion of the studies were NSAIDs administration within 2 weeks before starting Coxibs. For the "proportion" meta-analysis, the studies had to report the proportion of patients that had to discontinue the Coxibs therapy due to an exacerbation of IBD; for the "relative risk" meta-analysis, the studies had to be prospective with a comparison between patients taking Coxibs and patients taking placebo. Two authors independently reviewed titles and abstracts of references retrieved from the literature search and selected potentially relevant studies. Differences in opinion were resolved by discussion until consensus was reached. If an agreement failed to be reached, a third author was consulted. The quality of each study was assessed on a 5-point scale adapted from studies by the Quebec Task Force on Whiplash-Associated disorders and Jadad.

**Results:** The search identified 72 publications of which 7 studies reported the proportion of patients with IBD that had to stop the Coxibs therapy because of a worsening of the activity of IBD. The pooled proportion of flare up of IBD in patients that received Coxibs was 14.4% (95% CI: 6.7 – 24.4%). There was no statistically significant difference between patients that assumed Coxibs and those that assumed placebo (total fixed effect relative risk = 0.86, 95% CI: 0.39 – 1.88,  $P = 0.7$ ).

**Limitations:** A proportion of patients received maintenance therapy with azathioprine or 6-mercaptopurine and these co-interventions could have protected against a Coxib-induced flare; furthermore, the duration of Coxib assumption in the prospective studies is shorter compared to that of the medical practice. Three of the studies included in our meta-analysis had an insufficient quality but due to the higher number of recruited patients, the studies with a better quality had a higher weight in the final result. Moreover, to assess the relative risk of flare up of IBD only randomized controlled trials have been used in the second meta-analysis.

**Conclusions:** This meta-analysis showed that Coxibs are safe in most patients with IBD. Controlled trials of Coxibs compared with NSAIDs would be useful, at least in patients suffering from rheumatic pain refractory to standard treatment.

**Key words:** Acute pain, ankylosing spondylitis, arthritis, coxibs, chronic pain, inflammatory bowel disease, rheumatic manifestations, sacroiliitis

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Inflammatory bowel diseases (IBD) are chronic heterogeneous disorders of the bowel resulting from multi-factorial environmental precipitants in genetically susceptible individuals (1). Patients with IBD frequently have rheumatological manifestations including IBD-associated arthritis, sacroiliitis, and ankylosing spondylitis (2).

Safe therapy for acute and chronic pain of these rheumatological manifestations constitutes unmet medical needs. The treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been reported to lead to frequent IBD exacerbations (3,4) and thus, these drugs are usually not indicated in these patients and are listed among the factors causing the flare of IBD, although there are still conflicting data (5).

The pharmacological scenario has changed over the last decade thanks to the development of molecules like selective cyclo-oxygenase (COX) enzymes inhibitors, with the aim of limiting undesirable effects, which for the most part should derive from the inhibition of COX-1. Two COX enzymes, isoform COX-1 and COX-2, are responsible for the conversion of arachidonic acid to prostaglandins (6). COX-1 is expressed constitutively in most tissues (7), and prostaglandins produced by COX-1 are thought to play a major role in the maintenance of gastrointestinal homeostasis, including gastric cytoprotection (8). In the bowel, COX-1 is expressed in crypt epithelial cells (9). As the epithelial cell migrates towards the villus, it differentiates, stops expressing COX-1, and loses its ability to proliferate. In contrast to the normal bowel, COX-2 are expressed in inflamed bowel tissue by epithelial cells, lamina propria mononuclear cells, and neural cells of the myenteric plexus, upon stimulation by pro-inflammatory cytokines (9-11). Clinically, inhibition of COX-1 causes upper and lower gastrointestinal (GI) tract toxicity including gastric ulcers, bowel ulcers, bowel strictures, and enteritis. On the contrary, inhibition of COX-2 results in clinically beneficial anti-inflammatory and analgesic effects and significantly decreases the incidence of upper GI adverse events such as ulceration and bleeding over NSAIDs (12).

Because of their specific inhibition, the selective COX-2 inhibitors or Coxibs (i.e. celecoxib, etoricoxib, rofecoxib, valdecoxib, lumiracoxib) may be associated with a lower risk of exacerbation in patients with IBD, but whether these drugs can be used safely in these patients is still controversial. Some Coxibs have been associated with an increased risk of adverse events which led to their withdrawal from the market: rofecoxib was associated with an increased risk of myocardial infar-

tion (13); valdecoxib was associated with an increased risk of cardiovascular adverse events (14) and reports of serious skin infections (15); and lumiracoxib was associated with severe liver injury (16). Presently, celecoxib and etoricoxib are the only Coxibs available for medical use.

A recent Cochrane review (17) (including only 2 studies) concluded that the results for disease exacerbation and adverse events induced by the short-term use of celecoxib and etoricoxib versus placebo were uncertain in IBD patients, and thus, no definitive conclusions regarding the tolerability and safety of these drugs in such context could be drawn.

We report herein, the first meta-analysis about 7 studies aiming to clarify the safety of Coxibs in patients with IBD.

## **METHODS**

### **Search Strategy**

The MOOSE reporting guidelines for meta-analyses have been followed.

Articles published in English on the safety of Coxibs in patients with IBD (defined by a combination of clinical, radiographic, endoscopic, and histologic criteria) were identified through MEDLINE, SCOPUS, ISI-Web of Knowledge, and EMBASE searches using the terms "Coxibs or cyclooxygenase-2 inhibitors or COX-2 inhibitors AND inflammatory bowel disease." The final date of the search was April 15, 2015.

Reference lists from published articles were also employed. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles.

The criteria of inclusion of the studies were:

- a) original studies;
- b) the drugs considered as Coxibs were celecoxib, etoricoxib, rofecoxib, parecoxib, valdecoxib, lumiracoxib, and meloxicam;
- c) exclusion of NSAIDs administration within 2 weeks before starting Coxibs;
- d) for the "proportion" meta-analysis, the studies had to report the proportion of patients that had to discontinue the Coxibs therapy due to an exacerbation of IBD (using the modified disease activity index (18) for patients with Crohn's disease [CD] and using the Mayo score (19) for patients with ulcerative colitis [UC]);
- e) for the "relative risk" meta-analysis, the studies had to be prospective with a comparison between

patients taking Coxibs and patients taking placebo.

There was no restriction for the study design type or the sample size.

Two authors (EP and AG) independently reviewed titles and abstracts of references retrieved from the literature search and selected potentially relevant studies. The full-text versions of selected studies were then assessed by the 2 authors to determine whether the inclusion criteria were satisfied. Differences in opinion were resolved by discussion until consensus was reached. If an agreement failed to be reached, a third author (DGR) was consulted.

The quality of each study was assessed on a 5-point scale adapted from studies by the Quebec Task Force on Whiplash-Associated disorders (20) and Jadad (21) for each of the following items: (1) type of study; (2) number of patients; (3) clarity of the inclusion and exclusion criteria; (4) type of statistical analysis performed; and (5) eventual adjustment for confounding factors. A score of 0 (weak study, with definite shortcomings), 1 (acceptable quality but some weaknesses), or 2 (high quality, without important weaknesses) was applied for each item. The maximal total score for a good study was 10 points. Data abstraction and an estimate of the quality score were performed independently by 4 of the authors (DGR, EP, AG, and RP) who compared the results and then reached a consensus. Assessment was not blind to names and origins of the authors of the publications.

### Statistical Analysis

When heterogeneity was present the random effects model was preferred to the fixed effects model. Cochran's Q was used to test the heterogeneity and a *P*

value < 0.1 was used as a cut-off for significance (22).

The results of the different studies, with 95% confidence interval (CI) and the overall effect with 95% CI, were illustrated in a forest plot graph; the pooled effects have been represented using a diamond.

A Freeman-Tukey transformation was used to calculate the weighted summary "proportion."

The Mantel-Haenszel method was used for calculating the weighted pooled "relative risk."

Statistical analyses were conducted using Med Calc version 14.8.1 software.

### RESULTS

The MEDLINE search identified 72 publications on this subject. In 7 studies, the proportion of patients with IBD which had to stop the Coxibs therapy because of a worsening of the activity of IBD was reported (Table 1).

#### Included Studies

1. El Miedany et al (23) A multicenter, double-blind, placebo randomized controlled trial. Patients with IBD. Rheumatic manifestations included arthritis, arthralgia, soft tissue rheumatism. Age range: 18 – 65 years. Exclusion criteria: pregnancy, current smoking or former smoker for less than one year duration, patients on antibiotic therapy. Sample size: 146 participants (76 cases). Therapy with etoricoxib for 3 months. Follow up: 3 months. Types of bowel-related adverse events: not reported.
2. Sandborn et al (24) A multicenter, double-blind, placebo randomized controlled pilot trial. Patients with UC in remission. Rheumatic manifestations included nonspecific arthritis, arthralgia, or other condition amenable to NSAID therapy. Age range:

Table 1. Studies about proportion of IBD activity worsening in patients treated with Coxibs.

Study	Type of study	Disease	Rheumatic manifestations	Coxib	Quality
El Miedany et al (23)	Double-blind, placebo randomized controlled trial	IBD	Arthritis, arthralgia, soft tissue rheumatism	Etoricoxib 60 to 120 mg	6
Sandborn et al (24)	Double-blind, placebo randomized controlled trial	UC	Nonspecific arthritis, arthralgia, or other condition amenable to NSAID therapy	Celecoxib 200 mg	8
Biancone et al (25)	Prospective, open-label	IBD	Arthralgia	Rofecoxib 12.5 mg	5
Matuk et al (26)	Retrospective	IBD	Arthritis, myalgia, arthralgia	Celecoxib or Rofecoxib	2
Biancone et al (27)	Prospective	IBD	Arthralgia	Rofecoxib 12.5 mg	2
Reinisch et al (28)	Prospective, open-label	IBD	Peripheral arthropathies, arthralgia	Rofecoxib 12.5 to 25 mg	5
Mahadevan et al (29)	Retrospective	IBD	Arthritis, arthralgia, myalgia, abdominal pain	Rofecoxib 12.5 to 50 mg or celecoxib 200 to 400 mg	2

- 18 – 75 years. Exclusion criteria: endoscopic evidence of active colitis; history of gastroduodenal ulcer within one month; received any NSAIDs (including aspirin), anti-ulcer medication, or antacids within 2 weeks; received corticosteroids within one month; needed treatment with antibiotics, analgesics (except acetaminophen 4 g/day), or corticosteroids during the study; or had a known sulfonamides allergy and/or hypersensitivity to cyclooxygenase inhibitors. Sample size: 217 participants (110 cases). Therapy with 2 weeks of celecoxib. Follow up: 14 days. Types of bowel-related adverse events: abdominal pain (1%), colitis ulcerative (2%), aggravated colitis ulcerative (5%), diarrhea (1%), flatulence (2%), frequent bowel movements (1%); 11% of patients in both groups experienced GI adverse events.
3. Biancone et al (25) A prospective study. Patients with clinically inactive IBD. Rheumatic manifestations included arthralgia. Age range: 18 – 80 years. Exclusion criteria: concomitant use of NSAIDs, active peptic ulcer, previous use of COX-2 inhibitors. Sample size: 75 participants (45 cases). Therapy for at least 3 days with rofecoxib. Follow up: 3 months. Types of bowel-related adverse events: abdominal pain (11%), diarrhea (7%), bloody stools (2%); the percentage of IBD patients and controls showing GI symptoms was comparable (22% vs. 20%). However, although 9 of the 10 patients showing side-effects required drug discontinuation (9/45, 20%), only one of the 6 controls required rofecoxib withdrawal (1/30 = 3%) ( $P < 0.001$ ).
  4. Matuk et al (26) A retrospective study. Patients with IBD. Rheumatic manifestations included arthritis, arthralgia, soft tissue rheumatism. Age range: not reported. Exclusion criteria: none. Sample size: 33 participants (33 cases). Therapy for at least 3 days with celecoxib or rofecoxib therapy. Follow up: more than 3 years. Types of bowel-related adverse events: abdominal pain (33%), aggravated IBD (39%), diarrhea (30%), flatulence (3%), bloody stools (27%); no comparison with controls.
  5. Biancone et al (27) A prospective study. Patients with clinically inactive IBD. Rheumatic manifestations included arthralgia. Age range: 18 – 70 years. Exclusion criteria: history of peptic ulcer, concomitant use of NSAIDs, previous use of COX-2 inhibitors. Sample size: 28 participants (21 cases). Therapy for at least 3 days with rofecoxib therapy. Follow up: 2 weeks. Types of bowel-related adverse events: abdominal pain (5%), diarrhea (10%), bloody stools (5%); no controls referred adverse events.
  6. Reinisch et al (28) A prospective study. Patients with clinically inactive IBD. Rheumatic manifestations included arthropathy, arthralgia. Age range: 18 – 70 years. Exclusion criteria: CD restricted to the rectum; ileostomy or colostomy; intestinal resection within the past 12 months; complications requiring surgery; systemic infection; significant hepatic, renal, or cardiovascular disease; a hemoglobin level of less than 105 g/L; pregnant or breast-feeding women; patients who, in the investigator's opinion, were unlikely to comply with the protocol. Sample size: 32 participants (32 cases). Therapy for at least 20 days with rofecoxib. Follow up: 20 days. Types of bowel-related adverse events: diarrhea (3%), bloody stools (3%), nausea (3%), mild epigastric pain (3%); no comparison with controls.
  7. Mahadevan et al (29) A retrospective study. Patients with IBD. Rheumatic manifestations included arthritis, arthralgia, soft tissue rheumatism. Age range: 23 – 66 years. Exclusion criteria: none. Sample size: 27 participants (27 cases). Therapy for at least one week with celecoxib or rofecoxib. Follow up: 9 months. Types of bowel-related adverse events: aggravated IBD (7%), asymptomatic colonic ulcers found on surveillance colonoscopy (4%); no comparison with controls.

### Meta-analysis Results

The pooled proportion of flare up of IBD in patients that received Coxibs was 14.4% (95% CI: 6.7 – 24.4%) (random effects model was applied because the results of the studies had heterogeneity with a  $P < 0.0001$  of Cochran's Q) (Table 2, Fig. 1).

Since the studies are focused on different drugs, we analyzed individually the drugs for which more than one study is present in literature (Celecoxib [24,26], Rofecoxib [25-28]) (Table 3, Fig. 2, Table 4, Fig. 3).

The pooled proportion of flare up of IBD in patients that received Celecoxib was 23.7% (95% CI: 2.6 – 85.4%) (random effects model was applied because the results of the studies had heterogeneity with a  $P < 0.0001$  of Cochran's Q); the pooled proportion of flare up of IBD in patients that received Rofecoxib was 18.8% (95% CI: 12.4 – 26.8%) (fixed effects model was applied because the results of the studies had no heterogeneity with a  $P = 0.41$  of Cochran's Q).

In the majority of patients, GI symptoms appeared

Table 2. *Meta-analysis: proportion of flare up of IBD.*

Study	Sample size	Proportion (%)	95% CI
El Miedany et al (23) 2006	76	10 .53	4 .66 to 19 .69
Sandborn et al (24) 2006	110	2 .73	0 .57 to 7 .76
Biancone et al (25) 2004	45	20 .00	9 .58 to 34 .60
Matuk et al (26) 2004	33	39 .39	22 .91 to 57 .86
Biancone et al (27) 2003	21	19 .05	5 .45 to 41 .91
Reinisch et al (28) 2003	32	9 .38	1 .98 to 25 .02
Mahadevan et al (29) 2002	27	7 .41	0 .91 to 24 .29
Total (random effects)	344	14 .38	6 .69 to 24 .37

**Test for heterogeneity**

Q	32,32
DF	6
Significance level	$P < 0.0001$

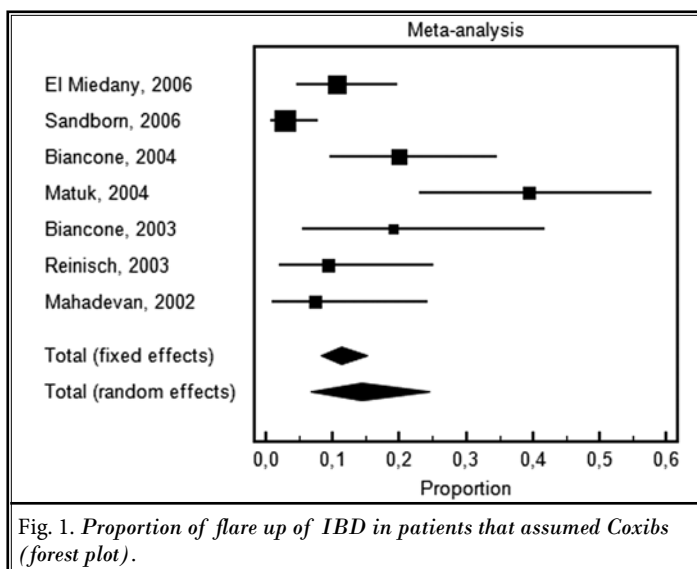


Table 3. *Meta-analysis: proportion of flare up of IBD for Celecoxib.*

Study	Sample size	Proportion (%)	95% CI
Sandborn et al (24) 2006	110	2 .73	0 .57 to 7 .77
Matuk et al (26) 2004	12	58 .33	27 .67 to 84 .84
Total (random effects)	122	23 .67	2 .62 to 85 .40

**Test for heterogeneity**

Q	21,83
DF	1
Significance level	$P < 0.0001$

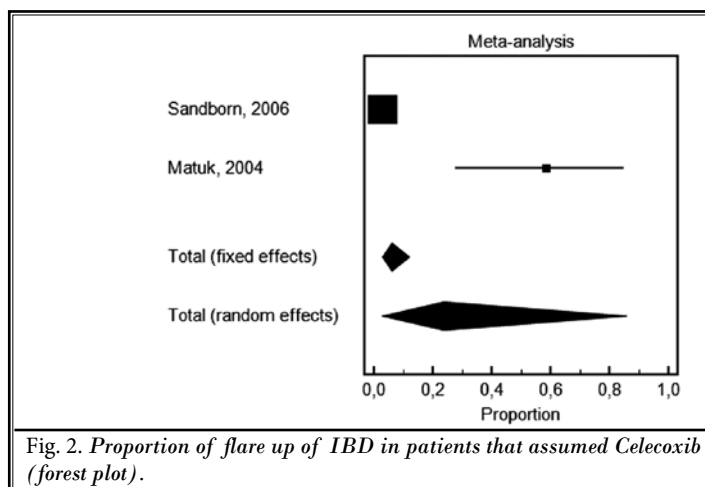


Table 4. Meta-analysis: proportion of flare up of IBD for Rofecoxib.

**Meta-analysis: proportion**

Study	Sample size	Proportion (%)	95% CI
Biancone et al (25) 2004	45	20 .00	9 .58 to 34 .60
Matuk et al (26) 2004	23	26 .09	10 .23 to 48 .41
Biancone et al (27) 2003	21	19 .05	5 .45 to 41 .91
Reinisch et al (28) 2003	32	9 .38	1 .98 to 25 .02
Total (fixed effects)	121	18 .80	12 .37 to 26 .76

**Test for heterogeneity**

Q	2,89
DF	3
Significance level	$P = 0.41$

after a few days of treatment (duration of treatment prior to disease exacerbation ranged from less than one week to 6 weeks, for those patients taking rofecoxib, and 3 days to 4 weeks for those taking celecoxib) (25) and subsided promptly on drug discontinuation; in several cases, however, disease activity continued to persist despite discontinuation of Coxibs and required medical therapy to induce disease remission.

A meta-analysis about the comparison between the Coxibs and placebo groups concerning the occurrence of gastrointestinal adverse events that led to premature withdrawal has been performed in 2 multicenter, randomized, double-blind, placebo-controlled trials in patients with IBD and suffering from rheumatological manifestations (Table 5, Fig. 4).

There was no statistically significant difference of flare up of IBD in patients that assumed Coxibs from patients that assumed placebo (total fixed effect relative risk: 0.86, 95% CI: 0.39 – 1.88,  $P = 0.7$ ); there was no heterogeneity (Cochran's Q  $P = 0.79$ ). All the adverse events were reversible.

**Discussion**

The results of this meta-analysis show that Coxibs are safe in most patients with IBD, especially when compared with the high frequency of intestinal adverse events reported by the same patients to previously applied NSAIDs (27). The absolute rate of flare up of IBD in patients that assumed a whole class of Coxibs was quite low (14.4%).

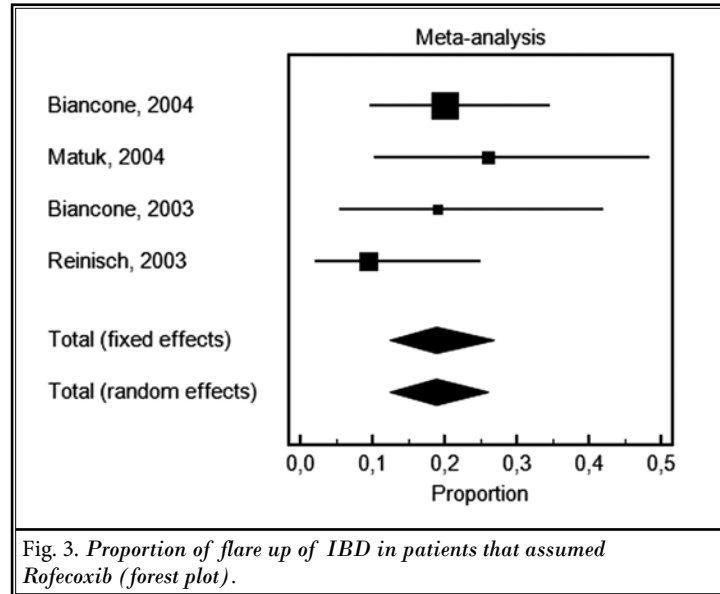


Fig. 3. Proportion of flare up of IBD in patients that assumed Rofecoxib (forest plot).

This is confirmed by the fact that GI adverse events led to premature withdrawal with similar frequencies in the Coxibs and placebo groups (relative risk of flare up of IBD: 0.86, 95% CI: 0.39 – 1.88,  $P = 0.7$ ).

Importantly, no patient experienced cardiovascular adverse events.

In the majority of patients, GI symptoms appeared after a few days of treatment and subsided promptly on drug discontinuation (25).

The IBD patient often does not present with merely the IBD. Comorbidities are coupled with the overall presentation (extraintestinal manifestations like renal complications, asthma, cardiomyopathy, etc.). Risks for prescribing a Coxib that could be associated with IBD are listed in Table 6.

The different characteristics of the IBD populations between the studies may account for the heterogeneity, including the number of tested patients (from 21 [27] to 110 [24]), type and extent of IBD, and the disease activity. A possible explanation for the higher incidence of disease flare, in some retrospective studies, could be due to the underestimation of the IBD patients



Table 5. *Meta-analysis: relative risk of flare up of IBD.*

Study	Intervention	Controls	Relative risk	95% CI	z	P
El Miedany et al (23) 2006	8/76	8/70	0.92	0.37 to 2.32		
Sandborn et al (24) 2006	3/110	4/107	0.73	0.17 to 3.18		
Total (fixed effects)	11/186	12/177	0.86	0.39 to 1.88	-0.38	0.70

exposed to Coxibs: This could have resulted in an artificially high incidence of disease exacerbation as those patients who experienced disease flare are more likely to report it.

While the pooled meta-analysis result addresses the safety of Coxibs in IBD patients in term of disease exacerbation, cardiovascular safety aspects should not be neglected. In the studies considered, the number of patients was too small to characterize the more life-threatening cardiovascular toxicities.

The limitations of these studies are that a proportion of patients received maintenance therapy with azathioprine or 6-mercaptopurine and these co-interventions could have protected against a Coxib-induced flare; furthermore, the duration of Coxib assumption in the prospective studies is shorter compared to that of the medical practice. Three of the studies included in our meta-analysis had an insufficient quality (26,27,29), but due to the higher number of recruited patients, the studies with a better quality (23,24) had a higher weight in the final result. Moreover, to assess the relative risk of flare up of IBD, only randomized controlled trials have been used in the second meta-analysis (23,24).

The studies are focused on different Coxibs, so we performed a subanalysis of each drug individually and the proportion of flare up of IBD resulted: 23.7% for Celecoxib, 18.8% for Rofecoxib (14.4% for the whole class). While the result for Rofecoxib seems to be consistent (no heterogeneity,  $P = 0.41$ ), the result for Celecoxib has a too big confident interval (2.6 to 85.4% of IBD flare); so, with the published data in literature, it is impossible to conclude whether there is a correlation with one medication having more side effects.

Of the drugs considered as Coxibs (celecoxib, etoricoxib, rofecoxib, parecoxib, valdecoxib, lumiracoxib, and meloxicam), no studies were found that met the inclusion criteria for parecoxib, valdecoxib, lumiracoxib, and meloxi-

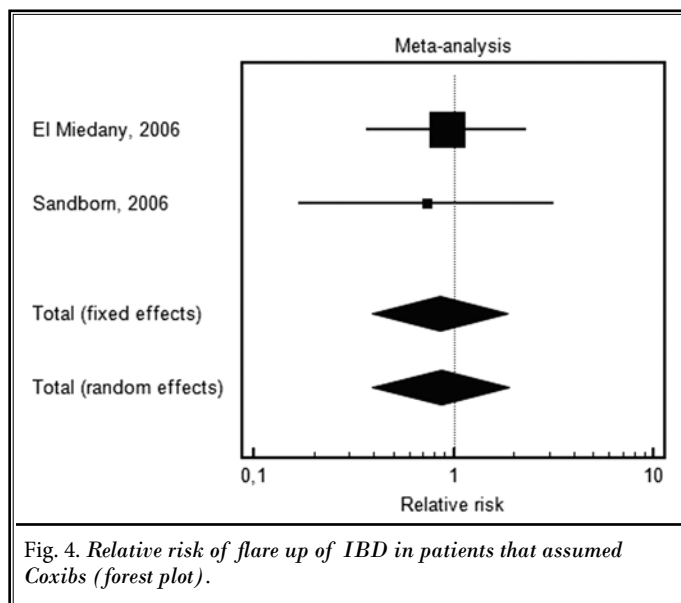


Fig. 4. *Relative risk of flare up of IBD in patients that assumed Coxibs (forest plot).*

Table 6. *Risks for prescribing a Coxib that could be found in IBD.*

Contraindications
Sulfonamides allergy
Active bleeding peptic ulcer
Asthma
Hypersensitivity to cyclooxygenase inhibitors
Pregnancy or breastfeeding
Cirrhosis Child C
Creatinine clearance less than 30 ml/min
Congestive heart failure NYHA II-IV
Ischemic heart disease

cam, so no assertions can be made about these drugs with these patients.

The risk of aggravating intestinal symptoms by the administration of Coxibs may occur mainly in patients with active IBD, as COX-2 is important in mucosal repair mechanisms. In the analyzed studies, the percentage of GI adverse events was lower in the studies in which treatment with Coxibs was started in patients with IBD in remission (range 11% [24] to 22% [25]) than in those in which the treatment was started without taking into account the activity of the IBD (up to 58% [26]).



## CONCLUSIONS

The limited data available suggest that Coxibs are safe in most patients with IBD (no difference in GI adverse events in the Coxibs and placebo groups).

There is a need for careful follow-up of patients with inactive IBD during the first few days of treatment with Coxibs, due to possible relapse requiring drug discontinuation. Furthermore, these drugs should not

be used in case of active IBD, until their safety in this context has been assessed by controlled trials.

While the results of this meta-analysis provide a first step in showing the safety of Coxibs in IBD patients, double-blind placebo-controlled trials of Coxibs compared to NSAIDs would be useful, at least in patients suffering from rheumatic pain refractory to paracetamol, a drug well tolerated in this cohort (30).

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