Gastrointestinal safety of amtolmetin guacyl in comparison with celecoxib in patients with rheumatoid arthritis

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Multicentre Study from the Department of Rheumatology, Physical Medicine and Rehabilitation, Medical Faculty University, Zagreb (Croatia); Department of Rheumatology, University of Liege, Liege (Belgium); Department of Clinical Medicine III, Carl Gustav University, Dresden (Germany); Department of Rheumatology, Clinical Medicine IV, Carl-Thiem Clinic, Cotbus (Germany); Department of Rheumatology, Hospital of Horovice, Horovice (Czech Republic); Department of Rheumatology, University Hospital, Klimentskà Polyclinic, Prague (Czech Republic); Department of Allergology and Immunology and Department of Rheumatology II, Polyclinic of the Hospitaller Brothers of St. John of God in Budapest, Budapest (Hungary); Department of Internal Medicine 1, County Hospital of Zala, Zalaegerszeg (Hungary); Department of Rehabilitation, "Markusovsky" Hospital and outpatient Clinic of Vas County, Szombathely (Hungary); University of Debrecen, Medical and Health Science Centre, Institute for Internal Medicine, III Department, Division of Immunology, Debrecen (Hungary)

Abstract

Objective

Selective inhibitors of cyclo-oxygenase-2 (COX-2) appear to be safer than conventional NSAIDs on the gastrointestinal (GI) tract. Amtolmetin guacyl (AMG), a NSAID that inhibits both COX-1 and COX-2, has an anti-inflammatory effect comparable to that of traditional NSAIDs, with a better GI safety profile. The primary end-point of this study was to evaluate the gastrointestinal safety of amtolmetin guacyl in comparison with celecoxib in patients affected with rheumatoid arthritis. The assessment of efficacy was the secondary end-point.

Methods

This study was a 24-week, randomized, parallel group, double-blind, double dummy, multicentre trial; 235 patients were enrolled and 180 patients (85 in the AMG group and 95 in the celecoxib group) completed the study. Each patient received twice daily amtolmetin guacyl 600 mg or celecoxib 200 mg. Assessment of safety was performed by upper GI endoscopy, gastrointestinal symptoms evaluation, electrocardiography, blood and urine laboratory tests, adverse events recording. Assessment of efficacy was performed by using the American College of Rheumatology (ACR-20) responder index.

Results

Neither amtolmetin guacyl nor celecoxib determined a worsening of baseline gastro-duodenal endoscopy findings. The percentage of patients with normal findings did not significantly change after treatment with both drugs, being virtually identical with AMG (i.e. 75.29%) and increasing from 75.79% to 77.66% with celecoxib. Moreover an evaluation of the other safety parameters did not reveal any difference between the two treatment groups. Therapeutic efficacy was equivalent in both groups, with no statistical difference between the two drugs at all time intervals.

Conclusions

In patients affected with rheumatoid arthritis, AMG and celecoxib proved to be equivalent, showing comparable gastrointestinal safety and therapeutic efficacy of treatment.

Key words

Amtolmetin guacyl (AMG), celecoxib, NSAIDs, gastrointestinal safety, rheumatoid arthritis.

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Introduction

Rheumatoid arthritis is an autoimmune disease characterized by chronic joint inflammation with a fluctuating course that can lead to progressive and destructive arthropathy, followed by deformities and disability (1, 2). Its management involves the use of new and traditional disease-modifying anti-rheumatic drugs (DMARDs) (3), which can affect the course of the disease, and non-steroidal anti-inflammatory drugs (NSAIDs), which provide symptomatic relief by controlling pain and inflammation. Although these latter compounds represent a very effective class of drugs, their use is associated with a broad spectrum of untoward reactions in the liver, kidney, skin and gut (4, 5); gastrointestinal (GI) side effects are, however, the most common adverse event encountered with this class of drugs (6-10). GI problems encompass a wide range of different clinical pictures, spanning from mild symptoms such as dyspepsia, heartburn and abdominal discomfort to more serious events, like peptic ulcer and its life-threatening complications, bleeding and perforation. Indeed, gastroduodenal mucosa possesses an array of defensive mechanisms and NSAIDs have a deleterious effect on most of them (11).

These drugs appear to cause gastroduodenal damage by two main mechanisms: a physiochemical disruption of the gastric mucosal barrier and a systemic inhibition of gastric mucosal protection, through inhibition of cyclo-oxygenase (prostaglandin endoperoxide G/H synthase, COX) activity of the GI mucosa. A reduced synthesis of mucus and bicarbonate, an impairment of mucosal blood flow and an increase in acid secretion represent the main consequences of NSAID-induced prostaglandin (PG) deficiency (12). Additional mechanisms which may add to the damage have been demonstrated. These include the uncoupling of oxidative phosphorylation, reduced mucosal cell proliferation and DNA synthesis as well as neutrophil activation (12). The outstanding candidate mechanism for initiating NSAID damage is their action to inhibit cyclo-oxygenase-1 (COX-1) as all conventional NSAIDs have this action (and not other agents) and all are essentially associated with similar damage. The strength of this idea is that it is simple; there are reasonable associations between NSAID-induced reductions in mucosal prostaglandin levels and the damage ,and one report (13) suggests that antibodies directed against COX cause in rabbits damage to the gastrointestinal tract that is identical to that induced by NSAIDs.

After the discovery of the two COX isoforms (that is COX-1 and COX-2) compounds specifically designed to inhibit COX-2, sparing COX-1 at therapeutic doses, have been developed. Although increasing evidence indicates that also COX-2 is normally expressed in the mucosa of the digestive tract where it plays a physiological role, assisting the housekeeping action of COX-1 in gastroprotection (14, 15), the so-called "selective COX-2 inhibitors" display a significantly improved risk-benefit ratio compared with non-selective NSAIDs. Indeed, COX-1 expression represents the dominant isoform in healthy mucosa (14) and PGs generated by COX-2 become important only during ulcer healing (14, 15) and in the presence of *Helicobacter pylori* infection (14, 16). In addition, it is worth mentioning that selective COX-2 inhibitors, like celecoxib and rofecoxib, besides sparing PG synthesis in the GI mucosa, do not display any topical irritancy as they are non-acidic, nor do they increase gastric or intestinal permeability or cause mucosal inflammation (17). Their failure to significantly affect the two basic biochemical mechanisms of NSAID-induced damage may account for their remarkable GI tolerability. Large clinical trials have indeed demonstrated that they are as therapeutically effective as conventional NSAIDs (18, 19), while being safer at gastroduodenal level (20, 21). Not only have endoscopic studies shown a significant reduction in the incidence of gastric and duodenal ulcers (22, 23), but clinical trials have pointed out a significant reduction in peptic ulcer complications .

Amtolmetin guacyl (2-methoxyphenyl-1-methyl-5-p-methylbenzoyl-pyrrole-2-acetamido acetate, AMG) is an NSAID (24) recently introduced into the Italian market and approved for the treatment of rheumatoid arthritis, os-

teoarthritis, extra-articular rheumatism and post-surgical pain. It affects both COX-1 and COX-2, the COX-2/COX-1 selectivity ratio, evaluated in studies using bovine aortic endothelial cells and LPS-stimulated macrophages, being 4.4 (Vane *et al*., *unpublished results*). Like COX-2 selective compounds, the drug displays an effective anti-inflammatory action with improved GI tolerability, but, conversely from them, maintains an antiplatelet activity (25, 26).

Clinical trials have shown that its anti-inflammatory, analgesic and antipyretic effects are comparable to those of reference NSAIDs (27-29). Two meta-analyses (30, 31) provided evidence that AMG displays a substantially lower incidence (7.2% and 28.3% respectively) of gastric adverse events in comparison with traditional NSAIDs. The frequency and severity of gastric mucosal lesions at endoscopic evaluation was lower for AMG in comparison with other NSAIDs, the odds ratio being 0.3 (95% CI 0.1 to 0.7) for severe lesions and 0.1 (95% CI 0.1 to 0.4) for mild and severe lesions, respectively (30).

Pharmacological studies performed in various animal models have shown that AMG is not only devoid of any damaging effect on gastric mucosa, but actually displays a gastroprotective effect (26), which extends down to the bowel (32). This peculiar pharmacological activity has been confirmed in humans where AMG protects the gastric mucosa from ethanol damage with an efficacy comparable to that of misoprostol (33). Gastric mucosal protection is likely to be due to the presence of a vanillic moiety in the molecule of AMG which, through stimulation of capsaicin receptors, causes Calcitonin Gene Related Peptide (CGRP) release and a consequent increase in nitric oxide (NO) production, which both counterbalance the deleterious effects of prostaglandin depletion due to COX inhibition (34). Activation of capsaicin receptors takes place through direct contact of the drug with the gastric mucosa and therefore it is maximal when the product is given on an empty stomach. This suggested the fasting administration of AMG in clinical practice to better exploit its gastroprotective activity.

Taking all the above considerations into account, this study was designed to compare the GI safety and the clinical efficacy of AMG and celecoxib, a widely used and GI safe COX-2 selective inhibitor, in patients affected by rheumatoid arthritis.

Patients and methods

Patients

Out-patients of either sex aged over 18 years who fulfilled the American College of Rheumatology (ACR) criteria for clinical diagnosis of rheumatoid arthritis in acute phase with Functional Capacity Classification of I-III, requiring continuous, prolonged NSAID therapy were eligible for the study. Patients were excluded from the trial if they had other rheumatic diseases, psoriasis, uncontrolled diabetes, untreated hyperthyroidism, significant renal impairment (serum creatinine > 1.5 mg/dl), significant hepatic impairment (AST or ALT values over twice the upper limit of the normal range), neurological, haematological or autoimmune (other than rheumatoid arthritis) diseases, cancer or any chronic disease. Patients were also excluded if they had a history of ulcer or gastric bleeding or any clinically significant upper gastrointestinal mucosal damage (i.e. > 10 erosions in the stomach and/or duodenum; oesophageal, gastric or duodenal ulcers). Other exclusion criteria were: treatment with steroids at doses greater than the equivalent of 7.5 mg of prednisone per day; treatment initiation or dosage alteration of any DMARD and/or Disease–Controlling Anti-Rheumatic Drug (DCARD) during the 90 days preceding the study and throughout the study; intake of anti-ulcer drugs; allergy, sensitivity or intolerance to study drugs and/or study drugs formulation ingredients; use of antineoplastics (other than methotrexate as antiarthritic therapy) during the 30 days preceding the study; history of alcohol or drug abuse; pregnancy or lactation.

Number of subjects

A total of 304 patients (152 per each treatment group) had to be randomized in the study in order to reach the 90% power of the test on the basis of the percentage of gastrointestinal events induced by both treatments and foreseen dropouts. Since the number of patients lost during the study was less than that expected, the sample size was recalculated and the trial was stopped after the randomization of 235 patients (118 to the AMG group and 117 to the celecoxib group).

Study design

This was a multicentre, double-blind, double dummy, active controlled, randomized, parallel group trial. It consisted of 2 phases: a single-blind placebo run-in period (one week) and a double-blind active treatment period (24 weeks). Using a computer-generated 1:1 randomization list by the coordinating centre, the patients were assigned to receive one of the following treatments: AMG 600 mg tablets or celecoxib 200 mg capsules, both given twice a day. AMG tablets (kindly provided by Medosan Ricerca, Rome, Italy) were administered 2-3 hours from meals, while celecoxib capsules were administered regardless of meal consumption (Fig. 1).

Prior to enrolment, the patients received a full explanation of the nature and purpose of the study, provided written informed consent and underwent a physical examination and laboratory testing. Follow-up clinic visits took place at weeks 4, 12 and 24 after the start of both treatments.

This study, conducted in accordance with the current ICH-GCP Guidelines and the Declaration of Helsinki as amended, was approved by the National Authorities of each Country involved and the Local Ethical and Drug Committees of each participating Centre.

Concomitant treatments

Concomitant medications (except for the drugs reported in the exclusion criteria), considered necessary for patient health and wellbeing, were allowed at the discretion of the Investigator.

Assessment of safety

Primary safety criteria were: gastric and/or duodenal damage (erosions, ulcers or both), assessed by an upper gastrointestinal endoscopy performed at the beginning and at the end of the

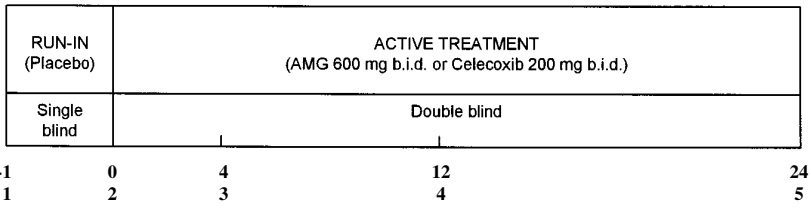

Fig. 1.

study; the assessment included the examination of the oesophagus, stomach, pyloric channel and duodenum. The endoscopic findings were scored from 0 to 7 as follows: 0 = normal mucosa; 1 = 1 – 10 petechiae; 2 = > 10 petechiae; 3 = 1 – 3 erosions; 4 = 4 – 10 erosions; 5 = > 10 erosions; 6 = oozing or intraluminal blood; 7 = ulcer or visible vessels. A break in the mucosa without a fibrous base was considered as an erosion whereas, when a fibrous base was present, the mucosal lesion was defined as an ulcer. Score 0-2 was considered normal findings, while score 3-7 was considered abnormal.

Each patient was given a gastric score (based on gastric mucosal findings) and a duodenal score (based on the pyloric channel and duodenal mucosal findings). Moreover, each patient was given a "maximal" gastro-duodenal score defined as the higher of the gastric or duodenal ones.

Secondary safety criteria were: gastrointestinal symptoms, ECG abnormalities, blood and urine laboratory tests and adverse events. Gastrointestinal symptoms (including heartburn, epigastric and/or abdominal pain, nausea, vomiting, dyspepsia, flatulence, diarrhoea) were evaluated by using a specific questionnaire at the beginning and after 4, 12 and 24 weeks of treatment.

A 12-lead ECG and laboratory tests, including haematological and biochemical analysis, performed on blood and urine samples collected under fasting conditions, were assessed at study entry and at study end or withdrawal.

All adverse events observed by the investigator or reported by the patients were recorded during the entire study period.

Assessment of efficacy

The assessment of efficacy was performed at the beginning of the study and after 4, 12 and 24 weeks of treatment. The primary outcome measure was ACR-20 Responder Index (35, 36), representing the number of patients achieving 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 following core set measures: Patient's global assessment, Physician's global assessment, pain, functional disability, acute phase reactants.

The Physician's global assessment and the Patient's global assessment were scored from 1 (very good) to 5 (very poor) with higher scores indicating greater disease activity. Pain was scored on a 4-point scale (mild, moderate, severe, incapacitating). Functional Capacity was evaluated in accordance with the ACR classification (36).

Statistical analysis

Statistical analysis was performed on the Per Protocol (PP) cohort, defined as all treated patients that had completed the study. When the GI safety data were considered, also the Intent-to-Treat (ITT) analysis was done, i.e. all randomized patients who received at least one dose of study medication were taken into account. Indeed, both GI symptoms and mucosal lesions can occur even after one single administration of an NSAID (8, 10). For this kind of analysis, the LOCF (Last Observation Carried Forward) method was applied in the presence of missing or not available observations.

Descriptive analysis was performed for all demographic variables. Analysis to assess the normal distribution was performed by Fisher's exact test or, where appropriate, by Wilcoxon two-sample test, applied in order to verify the homogeneity of means at baseline. The analysis of safety parameters was based on the comparison of the proportions of patients with or without gastrointestinal diseases. The hypothesis of frequencies equivalence was tested by means of Fisher's exact test for contingency tables; comparisons of safety parameters within and between groups was tested by Fisher's exact test and, where appropriate, by McNemar's test and t-test for paired samples. Efficacy parameters were evaluated by Fisher's exact test.

The statistical tests were two-sided at the 5% level of significance. Statistical analysis was performed by using SAS 8.2 statistical modules running under Windows OS.

Results

Patients

Data analysis was performed on the 180 patients that completed the study (85 in the amtolmetin guacyl group and 95 in the celecoxib group). Patients not included in the analysis were considered withdrawals. Demographic and clinical characteristics of the two groups of patients (Table I) show that they were quite homogeneous.

Safety

Endoscopy. Gastric and duodenal scores are considered separately and are reported in Tables IIa and IIb, while in Table III the number of patients with normal or abnormal gastroduodenal findings is reported. No differences between the two treatments were observed: in fact both groups, homogeneous at baseline, remained comparable at the end of treatment; both AMG and celecoxib failed to worsen gastro-duodenal endoscopic findings. In actual fact, with both drugs, the number of patients with normal gastric score increased, albeit not significantly. At baseline, all patients with abnormal scores presented only gastric erosions (i.e. score 3 or 4); at the end of treatment, 1 patient in the group treated with AMG and 4 patients treated with celecoxib had a score 7, corresponding to the presence of ulcers or visible vessels.

As far as the duodenal score is concerned, the number of subjects with normal score increased after treatment with AMG, while it decreased after treatment with celecoxib. At the end of treatment, the patients with abnormal scores were 3 and 6 in the AMG group and celecoxib group, respectively.

Table I. Baseline characteristics of the patients included in the trial.

Characteristic	AMG (n = 85)	Celecoxib (n = 95)
Age (yrs)	57.2 ± 11.4	55.3 ± 11.9
Males/females (n)	18 / 67	21 / 74
Weight (Kg)	73.3 ± 16.0	71.9 ± 13.6
Height (cm)	164.1 ± 8.7	164.6 ± 7.5
Concomitant treatment for rheumatoid arthritis (n)		
Glucocorticoids	39 (44.7%)	48 (50.5%)
Metotrexate	42 (49.4%)	44 (46.3%)
Other disease-modifying drugs	34 (40.0%)	42 (44.2%)
Prior use of NSAIDs (n)	42 (49.4%)	48 (50.5%)
User of low-dose aspirin (n)	4 (4.7%)	4 (4.2%)
Clinical evaluation of RA:		
Tender joints (n)	21.9 ± 15.7	22.2 ± 15.9
Swollen joints (n)	11.0 ± 7.4	11.8 ± 7.4
Physician's global assessment (score)	3.3 ± 0.8	3.0 ± 0.8
Patient's global assessment (score)	3.3 ± 0.7	3.2 ± 0.9
Pain (score)	2.5 ± 0.6	2.4 ± 0.7
CRP (μg/ml)	16.5 ± 17.8	16.8 ± 23.0
American College of Rheumatology functional class (n)		
I	6 (7.1%)	12 (12.6%)
II	43 (50.6%)	53 (55.8%)
III	36 (42.3%)	30 (31.6%)

Values are expresses as means ± SD.
Baseline characteristics did not differ significantly between groups.

When maximal gastroduodenal scores are considered, among 64 patients of the AMG group with normal endoscopy at baseline, 54 remained normal also at the final visit and out of 21 who had abnormal endoscopy at baseline, 10 improved at the final examination, showing normal findings. In the celecoxib group, among 71 patients with normal endoscopy at baseline, 61 remained normal also at the final visit (1 patient was excluded due to lack of final endoscopy) and out of 23 who had abnormal endoscopy at baseline, 12 improved at the final visit, showing normal findings. Between groups, the comparison did not highlight statistically significant differences in gastroduodenal endoscopy findings at baseline, nor at the final examination, as well as the within-groups comparison (McNemar's test, p = 0.6698 for celecoxib and p = 1.0000 for AMG). When the number of patients with normal and abnormal gastro-duodenal findings are considered (Table III), both PP and ITT analyses did not reveal any significant change from baseline values after treatment with either AMG or celecoxib.

Gastrointestinal symptoms. Table IV lists gastrointestinal symptoms reported by patients at the beginning and at the end of the study. Statistical analysis showed no significant difference in any of them between the two treatments. However, the symptom evaluation performed after 4 weeks of therapy revealed for AMG a significant lower inci-

Table II. Gastric and duodenal scores at baseline and 24 weeks after drug treatment in patients given AMG or celecoxib.

a

Treatment	Visit	Gastric score							
		Normal			Abnormal				
		0	1	2	3	4	5	6	7
AMG (n = 85)	Baseline	48 (56.47%)	16 (18.82%)	0 (0%)	13 (15.29%)	8 (9.41%)			
Celecoxib (n = 95)	Baseline	56 (59.95%)	16 (16.84%)	1 (1.05%)	12 (12.63%)	10 (10.53%)			
									p = 0.9597
AMG (n = 85)	24 weeks	50 (58.82%)	12 (14.12%)	3 (3.53%)	11 (12.94%)	5 (5.88%)	3 (3.53%)	0 (0%)	1 (1.18%)
Celecoxib (n = 94)	24 weeks	62 (65.96%)	8 (8.51%)	5 (5.32%)	8 (8.51%)	5 (5.32%)	1 (1.06%)	1 (1.06%)	4 (4.26%)
									p = 0.5532

b

Treatment	Visit	Duodenal score							
		Normal			Abnormal				
		0	1	2	3	4	5	6	7
AMG (n = 85)	Baseline	77 (90.59%)	4 (4.71%)	0 (0%)	2 (2.35%)	2 (2.35%)			
Celecoxib (n = 95)	Baseline	86 (90.53%)	6 (6.32%)	0 (0%)	2 (2.11%)	1 (1.05%)			
									p = 0.8950
AMG (n = 85)	24 weeks	78 (91.76%)	4 (4.71%)	0 (0%)	0 (0.%)	0 (0%)	0 (0%)	0 (0%)	3 (3.53%)
Celecoxib (n = 95)	24 weeks	81 (85.26%)	6 (6.32%)	2 (2.11%)	2 (2.11%)	3 (3.16%)	0 (0%)	0 (0%)	1 (1.05%)
									p = 0.1818

Statistical analysis: Fisher's exact test.

Table III. Number of patients given AMG or celecoxib with normal and abnormal findings at endoscopy at baseline and 24 weeks after drug treatment.

PP analysis						ITT analysis					
Treatment	Patients	Time	Patients with normal findings (score 0-2)	Patients with abnormal findings (score 3-7)	p	Treatment	Patients	Time	Patients with normal findings (score 0-2)	Patients with abnormal findings (score 3-7)	p
AMG	85	Baseline	64 (75.3%)	21 (24.7%)	n.s.	AMG	118	Baseline	94 (79.7%)	24 (20.3%)	n.s.
Celecoxib	95	Baseline	72 (75.8%)	23 (24.2%)		Celecoxib	116	Baseline	90 (77.6%)	26 (22.4%)	
AMG	85	24 weeks	64 (75.3%)	21 (24.7%)	n.s.	AMG	118	24 weeks	92 (78.0%)	26 (22.0%)	n.s.
Celecoxib	94	24 weeks	73 (77.7%)	21 (22.3%)		Celecoxib	116	24 weeks	91 (78.4%)	25 (21.6%)	

dence of dyspepsia (Fisher's exact test, p = 0.0301).

Electrocardiographic evaluation. At screening, in the AMG group 92.9% of patients had normal tracings, while in the celecoxib group 90.5% of patients had normal tracings; at the final visit the normal tracings for AMG and celecoxib groups were 94.1% and 93.6%, respectively. No statistically significant differences in ECG findings were observed, neither in the between-groups comparison (at baseline Fisher's exact test, p = 0.6004 and at final examination Fisher's exact test, p = 1.0000) nor in the within-groups comparison (McNemar's test: p=0.5637 for the AMG group and p=0.1797 for the celecoxib group).

Laboratory tests. Laboratory tests on blood and urine did not evidence any statistically significant alteration in the examined parameters except for uric acid, in the AMG group, which slightly increased, without exceeding in any case the upper reference value and probably being of no clinical relevance. Blood haemoglobin values before and after treatment were not significantly different in patients of both groups, suggesting the absence of any gastrointestinal bleeding during the study period. The mean values of systolic and diastolic blood pressure, as well as heart rate, did not change during the treatment with both drugs.

Efficacy

Clinical improvement, assessed by ACR-20 responder index, (Table V) did not show any differences between the two groups at the different time intervals during treatment. In particular, both drugs showed a similar efficacy at 4, 12 and 24 weeks. The observed response rates were comparable with those reported in literature for conventional NSAIDs in rheumatoid arthritis (37) .

Table IV. Gastrointestinal symptoms in patients given AMG or celecoxib at baseline and 24 weeks after drug treatment.

Symptom	AMG T = 0	Celecoxib T = 0	p	AMG 24 weeks	Celecoxib 24 weeks	p
Heartburn	3 (3.5%)	3 (3.2%)	n.s.	5 (5.9%)	8 (8.4%)	n.s.
Epigastric pain	0	1 (1.0%)	n.s.	4 (4.7%)	5 (5.3%)	n.s.
Abdominal pain	0	0	n.s.	1 (1.2%)	4 (4.2%)	n.s.
Nausea	1 (1.2%)	0	n.s.	2 (2.3%)	2 (2.1%)	n.s.
Vomiting	0	1 (1.0%)	n.s.	0	1 (1.0%)	n.s.
Dyspepsia	0	2 (2.1%)	n.s.	5 (5.9%)	4 (4.2%)	n.s.
Flatulence	0	1 (1.0%)	n.s.	7 (8.2%)	6 (6.3%)	n.s.
Diarrhoea	2 (2.3%)	0	n.s.	1 (1.2%)	2 (2.1%)	n.s.
Other	0	0	n.s.	1 (1.2%)	0	n.s.
Total	6	8	n.s.	26	32	n.s.

Statistical analysis : Fisher's exact test.

Adverse events (AEs)

The incidence of adverse events (AEs), calculated on all randomized patients, during the study period was similar for both drugs (Table VI). The percentage of patients with treatment-related gastrointestinal AEs (reported in Table VII) was 21.2% for the AMG group and 26.5% for the celecoxib group. Figure 2 shows the cumulative incidence of gastrointestinal events during the study.

Non-gastrointestinal adverse events were 12 and 11 for AMG and celecoxib, respectively; the AMG-treated patients complained of headache (n = 3), allergic skin reactions (n = 3), worsening of pathology (n = 3), hypotension (n = 1) and abnormal laboratory parameters (n = 2); the celecoxib treated patients experienced tinnitus (n = 1), ECGraphic abonormalities (n = 1), allergic skin reactions (n=3), abnormal laboratory parameters (n = 4), hypertension (n = 1), haemorrhage (n = 1).

Serious adverse events. During the study, 11 serious adverse events were reported in 7 patients (4 in the AMG group and 3 in the celecoxib group); none of these events was considered drug-related for AMG and only 1 (angioedema) was connected to celecoxib administration.

Withdrawal. 54 patients over a total of 235 prematurely interrupted the study; the most frequent reason for drop out was the lack of cooperation or consent withdrawal from patients (Table VIII). Only 11 withdrawals were due to treatment-related adverse events: 7 for AMG and 4 for celecoxib. These adverse events were gastrointestinal complaints (n = 4), allergic reaction (n = 1), hypotension (n = 1) and headache (n =

Table V. Evaluation of ACR-20 responders amongst patients with rheumatoid arthritis given AMG or celecoxib for 24 weeks.

Treatment	Week	ACR responders (%)	ACR non responders (%)	p
AMG	0	1.2	98.8	
Celecoxib	0	2.1	97.9	1.0000
AMG	4	24.7	75.3	
Celecoxib	4	26.3	73.7	0.8649
AMG	12	34.1	65.9	
Celecoxib	12	37.9	62.1	0.6428
AMG	24	43.5	56.5	
Celecoxib	24	51.6	47.4	0.2950

Fisher's exact test.

Table VI. Drug-related adverse events in patients with rheumatoid arthritis given AMG or celecoxib for 24 weeks.

Parameter	AMG	Celecoxib
N° of patients with adverse events	32	34
N° of patients with gastrointestinal adverse events	25	31
N° of total adverse events	57	68
N° of gastrointestinal adverse events	45	57

Table VII. Number of gastrointestinal adverse events in patients with rheumatoid arthritis given AMG or celecoxib for 24 weeks.

Adverse event	AMG n	Celecoxib n
Heartburn	7	13
Epigastric pain	7	7
Abdominal pain	4	5
Nausea	6	3
Vomiting	0	2
Dyspepsia	3	6
Flatulence	7	6
Diarrhoea	1	3
Lost of appetite	1	1
Esophagitis	0	1
Esophageal ulcer	1	2
Gastric petechiae	3	1
Gatric erosions	1	1
Gastric ulcer	1	1
Duodenal petechiae	0	2
Duodenal erosions	0	1
Duodenal ulcer	2	1
Other	1	1
Total	45	57

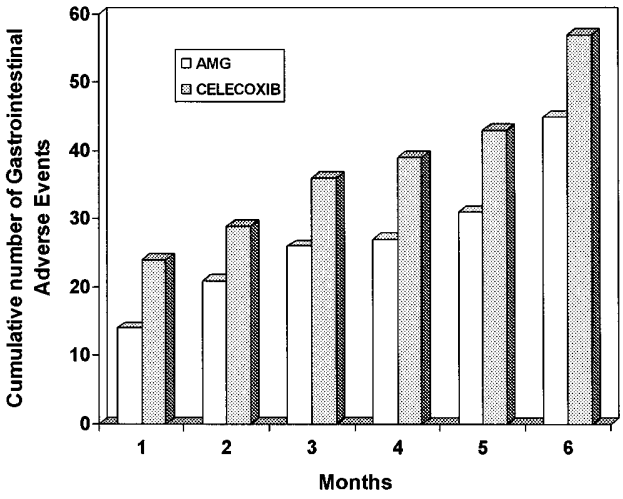

Fig. 2. Cumulative incidence of GI adverse events in patients with rheumatoid arthritis given AMG or celecoxib for 24 weeks.

1) for AMG; those reported for celecoxib were gastrointestinal complaints (n = 2) and allergic reactions (n = 2).

Discussion

Gastrointestinal toxicity induced by NSAIDs represent one of the most common serious adverse drug events in the industrialized world, with a significant impact both on public health and costs related to the management of side effects. Different strategies have been adopted in order to reduce the NSAID-associated gastro-duodenal damage: the addition of a gastroprotective agent, such as proton pump inhibitor or misoprostol, a synthetic PGE_1 derivative, or the use of cyclooxygenase-2 selective inhibitors which, while maintaining the same activity of traditional NSAIDs in reducing arthritis pain and inflammation, markedly improves the disease-related quality of life (38,39) as a result of their better gastrointestinal tolerability. A prospective study (40) that compared conventional NSAIDs alone with NSAIDs plus misoprostol reported that 0.95% of patients with rheumatoid arthritis who were taking a NSAID alone had upper gastrointestinal complications over a period of 6 months; the combined treatment determined a 40% reduction in the risk.

Along the same lines, studies carried out with selective COX-2 inhibitors, like celecoxib (22) and rofecoxib (23), showed on average a 50% reduction in the incidence of clinically significant upper gastrointestinal events and ulcer complications, in comparison with non-selective NSAIDs. Amongst the different COX-2 inhibitors so far developed and available on the market, the selectivity ratio towards the two isoenzymes varies greatly depending on the methodology employed (*in vivo, ex-vivo* or *in vitro* assays, intact cells or purified enzyme as drug target, variations in substrate concentration and incubation time) (41,42). As a consequence, classification of these agents clinically is difficult because there are insufficient data to predict the correlations between biochemical and pharmacological properties and the clinical effect of a given agent. In any case, from a clinical standpoint selectivity, COX-2 selectivity should translate in effective anti-inflammatory and analgesic activities while sparing COX-1

Table VIII. Reasons for withdrawal among patients with rheumatoid arthritis given AMG or celecoxib.

Reason	AMG (n = 33)	Celecoxib (n = 21)
Did not cooperate/withdrew consent	39.4%	52.4%
Adverse events	21.2%	19.0%
Intercurrent illness	15.2%	4.8%
Loss of follow-up	9.1%	9.5%
Lack of compliance/poor compliance	3.0%	0
Lack of safety	3.0%	0
Other protocol violations	3.0%	0
Other reasons	6.1%	14.3%

associated physiological functions like, for instance, mucosal PG synthesis and platelet aggregation (42, 43). Although in some assays, celecoxib displayed a low selectivity ratio (44, 45), it fulfills the "clinical definition" of selective COX-2 inhibitor and large clinical trials (19, 20) and meta-analyses (22) have provided strong evidence for its gastrosparing activity.

The present study shows that both AMG and celecoxib are similarly effective in controlling the symptoms of rheumatoid arthritis. Like the therapeutic efficacy, the GI safety and tolerability of both drugs are also similar, confirming the results of previous endoscopic studies where AMG was compared to traditional NSAIDs (27, 28, 46).

The lack of correlation between symptoms and mucosal damage after NSAID administration has been repeatedly shown in clinical trials and the lack of symptoms cannot therefore be considered a mirror of the lack of mucosal damage; in fact, a large proportion of serious NSAID induced gastrointestinal complications can be asymptomatic (47, 48). In this study, both symptoms and mucosal damage have been investigated by specific questionnaires and GI endoscopy, respectively; the subjective and objective evaluations highlight the remarkable gastroduodenal tolerability of AMG and celecoxib, with a similar incidence of adverse events possibly or probably related to treatment; in particular, gastrointestinal events resulted for both drugs comparable in frequency, intensity and type.

Despite COX inhibition and prostanoid depletion, AMG does not damage the gastroduodenal mucosa but rather protects it from noxious stimuli. Mucosal protection is achieved *via* the inhibition of acid secretion, increase of bicarbonate production and stimulation of mucosal blood flow, mechanisms all driven by the increase of CGRP and NO production (26, 49-51).

It is now clearly established that microvascular damage represents the earliest event following NSAID administration (52), preceding and contributing to the development of epithelial lesions. In a recent experimental study (53), electron microscopic examination of gastric mucosa did show that even the selective COX-2 inhibitor celecoxib induced, like conventional NSAIDs, marked endothelial damage. However, under the same experimental conditions, both acute and chronic AMG administration produced very limited damage, most likely thanks to the release of the vasodilator and endothelial protective NO.

Both COX isoforms (COX-1 and COX-2) are constitutively expressed in the adult mammalian kidney and contribute to the biosynthesis of prostanoids. Inhibition of COX activity in the kidney by NSAIDs has relatively mild consequences in healthy individuals, but can lead to serious adverse events in patients whose renal function is PG dependent. Most studies have reported transient decreases in sodium excretion upon initiation of therapy with either traditional NSAIDs or coxibs that, in patients whose renal function is dependent on prostanoids, can affect the glomerular filtration rate (GFR). Changes in renal function may result in hypertension and edema; as a consequence, patients who are at risk for adverse renal events (e.g. patients with congestive heart failure, renal or hepatic disease, as well as those of advanced age receiving therapy with diuretics or angiotensin-converting enzyme (ACE) inhibitors) should be monitored with the same caution when receiving selective COX-2 inhibitors as when receiving treatment with conventional NSAIDs. It is therefore evident that COX-2 selective NSAIDs do not offer any advantage over non-selective drugs in terms of renal safety (54). On the contrary, AMG does not impair renal function, evaluated with clinical and biochemical parameters after repeated administration (55). Here again, maintenance of renal blood flow by the released NO is likely to be the underlying mechanism of AMG renal safety.

Although the use of selective COX-2 inhibitors in place of conventional NSAIDs for the treatment of arthritis appears to reduce the risk of serious gastrointestinal toxicity, the role played by these inhibitors in the generation or exacerbation of ischaemic cardiovascular disease is less clear. Clinical studies demonstrate that hypertension can be induced or aggravated by COX-2 inhibitors to a degree similar or higher than that which occurs with non-selective drugs (56). Endothelial dysfunction, an indicator of cardiac ischaemia, may also be exacerbated by COX-2 inhibition (57) and there is much debate as to whether these changes lead to an absolute increase in ischaemic cardiac events (58). These effects on cardiovascular risk factors appear all more important in patients with rheumatoid arthritis where there is an increase in the incidence of ischaemic heart disease (59).

Soon after the introduction of celecoxib and rofecoxib into the market, it was reported that both drugs suppressed the formation of prostacyclin I_2 (PGI_2) in healthy volunteers (60). PGI_2 had previously been shown to be the predominant COX product in endothelium, inhibiting platelet aggregation, causing vasodilatation and preventing the proliferation of vascular smooth muscle cells *in vitro* (61). However, it was assumed that PGI_2 was derived mainly from COX-1, the only isoform expressed constitutively in endothelial

cells. This assumption later proved to be incorrect, since studies in mice and humans showed that COX-2 was the dominant source (62, 63). The individual cardiovascular effects of PGI_2 *in vitro* contrast with those of thromboxane A_2 (TXA_2), the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction and vascular proliferation (64). Whereas traditional NSAIDs inhibit both TXA_2 and PGI_2, the coxibs leave TXA_2 generation unaffected, reflecting the absence of COX-2 in platelets, and thus increase thrombotic risk, predisposing patients to heart attack and stroke (64). As a matter of fact, a series of epidemiologic analyses (65, 66) have also raised questions about the cardiovascular safety of the coxibs and both the US FDA and EMEA(67, 68), followed by the Italian Drug Agency [AIFA (69)], have issued warnings about the cardiovascular risk of COX-2 selective inhibitors as well as non-selective NSAIDs and given guidance on their use in patients with cardiovascular risk factors. Conversely from COX-2 selective NSAIDs which do not affect platelet aggregation (70-72), AMG displays both *in vitro* and *ex vivo* an antiplatelet activity comparable to that of aspirin (25). This pharmacological action should render the drug more suitable than selective COX-2 inhibitors for patients with one or more CV risk factors.

Taken together, all these data allow the conclusion that AMG is an effective anti-inflammatory drug, with a safety profile encompassing the GI tract, the kidney and the CV system. Due to these properties and its peculiar mechanism of action, this compound seems to be particularly suitable for long-term use, especially in older subjects and patients with renal or CV disease.

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