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Original article

GOAL: multicenter, open-label, post-marketing study of flavocoxid, a novel dual pathway inhibitor anti-inflammatory agent of botanical origin

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Abstract

Objectives:
GOAL (Gauging Osteoarthritis [OA] with Limbrel*), an open-label, post-marketing study was performed to determine the overall efficacy and gastrointestinal (GI) tolerability of flavocoxid, a novel, plant-based, anti-inflammatory medication, in a 'real world' clinical practice setting. To this end, the study enrolled several unique patient types including nonsteroidal anti-inflammatory drug (NSAID) naïve patients, those who had used NSAIDs in the past, regardless of outcome (positive or negative), and those who had previously taken a gastroprotective medication to improve GI tolerability or continued to take it as a precautionary measure to prevent NSAID-associated GI damage.

Methods:
A total of 1067 individuals at 41 rheumatology practices were enrolled and prescribed flavocoxid, 500 mg b.i.d., for 60 days. The Physician Global Assessment of Disease (PGAD) visual analog scale (VAS) was used as a global measure to assess the signs and symptoms of OA, including joint discomfort, functional stiffness, functional mobility and quality of life. In addition, overall tolerability and upper GI tolerability were assessed by individual questions scored on a 5-part Likert scale. The physicians also monitored any interruption in, or cessation of use of flavocoxid due to a GI issue as well as changes in the use of gastroprotective medications. Adverse event (AE) monitoring was also conducted.

Results:
Of the 1005 patients who completed all follow-up visits, physicians recorded an average improvement in VAS scores from 60.1 ± 18.8 at baseline to 42.5 ± 21.9 at 8 weeks ($p < 0.001$) in 65.8% of patients. The PGAD VAS noted the most significant improvement in those patients with moderate to severe OA (baseline VAS [0 = least severe, 100 = most severe]: 0–25mm, -3.5 ± 6.9; 26–50 mm, -10.1 ± 17.0; 51–75 mm, -19.3 ± 19.5; 76–100 mm, -29.6 ± 23.6; $p < 0.001$) and in those patients who were historically non-responders to NSAIDs (40.3 ± 21.1 vs. 66.3 ± 17.7 at baseline; $p < 0.001$). Patients who had previously responded well to NSAIDs had VAS scores of 42.6 ± 19.8 vs. 58.0 ± 18.0 ($p < 0.001$) and NSAID naïve subjects showed improvement in VAS scores from 60.5 ± 18.0 at baseline to 46.3 ± 23.7 ($p < 0.001$). The study recorded a low incidence (~10%) of AEs reported to physicians and good overall tolerability to flavocoxid. Flavocoxid showed improved upper GI tolerability in almost 50% of previous NSAID users ($p < 0.001$) and reduced therapy interruption in ~90% of previous NSAID users with a history of GI-related therapy interruptions ($p < 0.0001$). Finally, the use of flavocoxid resulted in a >30% reduction in or cessation of the use of gastroprotective medications such as proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2s) in subjects ($p < 0.001$).

*Limbrel is manufactured by Primus Pharmaceuticals, Inc., Scottsdale, AZ, USA.

Conclusions:
Within a 'real world' clinical rheumatology practice setting, flavocoxid demonstrated significant efficacy in the management of OA in multiple patient types and displayed significant potential for reducing the possibility of adverse GI side-effects and use of gastroprotective agents associated with more traditional OA medications. A limitation of this study was that it was open-label and not rigorously controlled. The large population may compensate for this lack of control.

Introduction

Osteoarthritis (OA) is a multifactorial disease often caused by injury or repetitive trauma to joints and involves both immunological and metabolic pathogenic mechanisms. It has been shown that the production of arachidonic acid (AA)-derived fatty acid metabolites generated via cyclooxygenase (COX-1, COX-2) and 5-lipoxygenase (5-LOX) enzyme pathways contribute to inflammation, pain and eventual joint damage[1]. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), used to treat the pain and inflammation associated with OA, favor inhibition of COX-1 over COX-2 while selective COX-2 inhibitors favor inhibition of the COX-2 enzyme. This selective inhibition of either the COX-1 or COX-2 pathways results in significant adverse events (AEs), including gastric ulceration and bleeding, cardio- and reno-vascular events as well as impaired platelet function resulting in prolonged bleeding time[2–4]. In addition, long-term use of selective COX-2 inhibitors has been found to increase gastric toxicity[5]. The removal of specific selective COX-2 inhibitors from the market has focused attention on the potential cardiodynamic AEs that may result from inhibiting one metabolic pathway in excess of another[6].

When COX-1 is inhibited by traditional NSAIDs, gastroprotective prostaglandin levels are reduced in the mucosa, predisposing it to ulceration[7,8]. Although selective COX-2 inhibitors were designed to spare the stomach and reduce the incidence of ulceration, patients with a history of peptic disease may still experience significant exacerbation of gastric damage while using these agents[9,10]. This effect is also aggravated in the presence of low-dose aspirin taken for cardioprotective purposes[7,8]. Prostaglandins produced by both COX-1 and COX-2 contribute to the healing responses in the stomach after minor ulcerations[7,8]. Selective COX-2 inhibitors have been reported to reduce initial short-term incidence of ulceration[7,8,11]. However, there is also evidence to suggest that, after prolonged use of selective COX-2 inhibitors, there is no difference in the incidence of ulceration compared to patients on NSAIDs[12]. In fact, these agents may actually delay ulcer healing[12–15].

Inhibition of COX-1 and/or COX-2 by NSAIDs or selective COX-2 inhibitors can also 'shunt' AA metabolism down the 5-LOX pathway. This 'shunt' increases production of potent chemoattractive and vasoconstrictive leukotrienes[16,17] and can promote or aggravate systemic side-effects such as asthma, gastric ulceration, renal insufficiency, hypertension and other cardiovascular complications. COX enzyme inhibition has specifically been shown to increase the level of leukotriene B_4 (LTB_4), a potent chemoattractant agent of white blood cells (WBC) present in synovial fluid[18]. Studies in patients taking NSAIDs have also shown higher levels of LTB_4 in gastric mucosa[19] and in the walls of NSAID induced gastric ulcers[20] as well as higher levels of neutrophils in mesenteric venules[21]. It is estimated that up to a third of long-term NSAID users develop duodenal ulcers and/or other mucosal damage which may be asymptomatic[22]. These data have significant clinical and pharmacoeconomic importance. The estimated average annual costs of direct and indirect NSAID-related toxicities to each patient is in the hundreds of dollars and almost $7.5 billion total in the United States alone[11]. It is clear, therefore, that an anti-inflammatory agent with a more 'balanced' mechanism of action across the COX and LOX enzyme pathways[23] that could effectively manage the inflammatory processes associated with OA[1,24] while maintaining a desirable safety profile would be a welcome addition to the available therapeutic regimens.

Flavocoxid (Limbrel*), a prescription medical food composed of a specially formulated, proprietary blend of the bioflavonoids, (+)-catechin and baicalin, manages the metabolic processes that underlie OA. Flavocoxid possesses a unique 'dual-inhibition' mechanism of action inhibiting COX-1 and COX-2 equally with additional 5-LOX enzyme inhibition[1,23]. In addition, flavocoxid has significant antioxidant activity which down-regulates the production of inducible inflammatory proteins whose expression is regulated by reactive oxygen species (ROS) (e.g., tumor necrosis factor alpha [TNFα], COX-2, 5-LOX, inducible nitric oxide synthase [iNOS]) and their corresponding metabolites[25]. Flavocoxid also inhibits the direct conversion of AA by ROS to oxidized lipids such as malondialdehyde[25]. The mixture of bioflavonoids in flavocoxid has also been shown to actively reduce the level of ROS in the synovial fluid of OA patients[26]. Both catechin and baicalin are 'Generally Recognized as Safe' (GRAS) ingredients, a statutory FDA requirement for medical foods based on expert panel review of preclinical and human toxicity data of both compounds. Flavocoxid has demonstrated a favorable safety profile in prospective clinical trials[27,28]. Other studies have established efficacy of flavocoxid in managing the signs and symptoms of OA in a controlled clinical trial environment[24,29]. This observational, open-label, post-marketing study was designed to assess the overall efficacy and tolerability of flavocoxid in managing OA in 'real world' rheumatology clinical

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practices in a large, diverse population over a wide geographic area in the United States. Participating physicians made a clinical decision to start their OA patients on flavocoxid therapy and agreed to evaluate patients responses to treatment based on improvement in symptoms, reduction in discomfort, tolerability (particularly GI), change in the use of concomitant gastroprotective medications and AEs. By intent, minimal external inclusion or exclusion criteria were imposed on physicians, the decision of whether or not to start flavocoxid being left entirely to physician and patient judgment.

Patients and methods

This multicenter, open-label, post-marketing study was carried out at 41 rheumatology practices throughout the United States. Flavocoxid was prescribed for 1067 individuals drawn from the physicians' patient populations. Subjects all had a prior diagnosis of OA established by various methods including clinical examination and radiography and who, in the physician's judgment, were in need of either new, or a change in prior, anti-inflammatory therapy and for whom the physician had recommended flavocoxid as the therapy of choice. Patients had the study explained to them and if they agreed to participate were placed on flavocoxid 500 mg b.i.d. for 60 days.

Inclusion and exclusion criteria were kept to a minimum and were intended to reflect 'real world' decision making allowances for physicians and patients. Major inclusion criteria included: osteoarthritis of any joint(s), as previously diagnosed by the physician; use of NSAIDs at baseline allowed; use of gastro-protective medications at baseline allowed. Major exclusion criteria included: use of flavocoxid at baseline and any specific contraindication to the use of flavocoxid such as potential allergy to one of the product components.

Major endpoints of the study included: VAS for physician global assessment of disease activity (PGAD), based on a 0–100 mm point scale, with 0 representing disease of least severe and 100, most severe activity, and a 5-part Likert scale with physician evaluations of joint discomfort/pain, stiffness, mobility, quality of life and upper GI tolerability. Physicians also assessed therapy discontinuation due to GI issues, change in the use of gastroprotective medications (specifically PPIs or H2s) and recorded all AEs.

Comparisons between groups with respect to change in OA severity between baseline and 2-month visits were done using a one-way ANOVA. All p-values are reported as two-tail. A paired t-test was used to analyze PGAD VAS scores between baseline and 2-month visits. A chi-square test was used to analyze comparative change at 2 months in OA status (improved/worsened/same) of baseline NSAID users and non-users. Individual endpoint comparisons to baseline between patients based on their response to NSAID at baseline and/or on their baseline NSAID use were also recorded at 2 months. A McNemar test was used to compare the proportion of patients who stopped using flavocoxid due to GI tolerability issues to those who had stopped their NSAID use prior to entry into the study and to those who discontinued upon entry into the study. A multivariate linear regression was also done with OA severity change being the dependent variable.

Results

Out of 1067 individuals initially enrolled in the study, 1005 persons completed all scheduled visits. Six dropped out because of an adverse event [bladder burning (1), sour stomach (1), increased pain (1), severe diarrhea (1), and unspecified (2)] while 56 individuals were lost to follow-up. Of those who completed all study visits, 20% were males ($n=199$), 74% females (748) and 6% were not reported ($n=58$). The average age of the study population was 64 years (±12.3) and the average baseline PGAD VAS score for females was 59.7 ± 19.3 and for males, 60.9 ± 17.1 (combined average 60.1 ± 18.8). Of those individuals using anti-inflammatory medication prior to entry into the study ($n=646$), 61% reported using an NSAID for an average of 15 months. Of the entire enrolled population, 30% ($n=304$) reported no use of NSAIDs and 6% ($n=55$) did not report on NSAID use.

Patients generally had multiple sites of OA with the majority diagnosed with OA of the knee (64%), hand (55%) and spine (44%) (Table 1). Of those individuals who were taking NSAIDs at the time of the baseline visit, most were using the COX-2 inhibitor, celecoxib (16.4%, $n=165$), followed by meloxicam (14%, $n=137$) and then various NSAIDs (Table 3). NSAID users were stratified according to their response to the use of these medications at baseline. Almost half (44.7%) of NSAID users had a positive response to these medications ($n=289$) (Table 2). However, a third (33.1%) of these previous NSAID users had to interrupt or discontinue their NSAID use due to a GI issue ($n=214$). Almost half of the patients (48%) taking NSAIDs were concomitantly using a gastroprotective

Table 1. Sites of OA as assessed at baseline.

OA site*	% of Patients
Knee ($n=643$)	64
Hand ($n=556$)	55
Spine ($n=441$)	44
Hip ($n=305$)	30
Feet ($n=194$)	19
Other ($n=414$)	41

*Total exceeds 100% due to multiple OA sites per patient.

Table 2. Stratification of responses from baseline nonsteroidal anti-inflammatory drug (NSAID) users to this class of medication.

Positive response to NSAID at baseline patients (%)	
Yes	44
No	36
Not reported	20
Stopped NSAID due to GI issue	
Yes	33
No	51
Not reported	9
Not applicable	7
Used PPI or H-2 therapy due to NSAID-dependent GI concern	
PPI	42
H-2	5
None	49
Other	1
Not reported	3

A large percentage of the study population did not have a positive response to NSAIDs in the past, either due to a gastrointestinal (GI) related event or because of the concomitant use of gastroprotective medications.

Table 3. Nonsteroidal anti-inflammatory drugs (NSAIDs) used by patients at baseline.

	% of Patients
Celecoxib ($n=165$)	16
Meloxicam ($n=137$)	14
Ibuprofen ($n=119$)	12
Naproxen ($n=100$)	10
Diclofenac ($n=66$)	7
Other NSAIDs ($n=59$)	6
Other ($n=5$)	0.5
None ($n=299$)	30
Not reported ($n=55$)	5.5

medication such as a PPI or H2 antagonist ($n=310$) (Table 2).

The PGAD VAS scores for each OA site were relatively the same at baseline ranging from 59.7 ± 19.4 in the feet to 62.2 ± 18.5 for the spine and showed similar improvement at 8 weeks by reduction in severity ([-15.5 ± 20.5 in feet] to [-18.6 ± 22.0 for the hip]; $p=0.37$). Upon completion of the study, physicians recorded an improvement in the signs and symptoms of OA after flavocoxid therapy in the majority of patients (65.8%). Physician Global Assessment of Disease VAS evaluation of the total patient population noted a significant average improvement of 30% over the 2-month period (VAS scores; 60.1 ± 18.8 at baseline and 42.5 ± 21.9 at 8 weeks; $p<0.001$) (Figure 1). The physician evaluations for other parameters as interpreted from patient reports at the time of study visits confirmed the global assessments in that more than half the patients had an improvement in their joint discomfort ($n=588$, 59%), stiffness ($n=564$, 56%), physical function ($n=543$; 54%) and perhaps most importantly, overall quality of life ($n=556$; 55%) (Table 4).

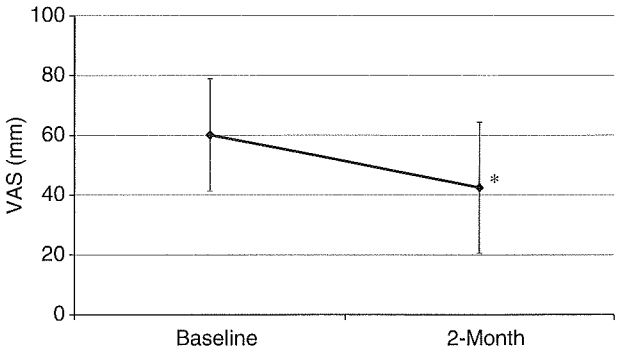

Figure 1. Improvement in Physician Global Assessment of Disease (PGAD) visual analog scales (VAS). 65.8% ($n=661$) of patients reported an average improvement of 30%, (VAS scores; 60.1 ± 18.8 at baseline and 42.5 ± 21.9 at 8 weeks; $^*p<0.001$).

Table 4. Physician evaluation of subscales.

Month 2 vs. baseline	Somewhat or much better	About the same	Somewhat or much worse
Joint discomfort	59% ($n=588$)	32% ($n=326$)	8% ($n=75$)
Stiffness	56% ($n=564$)	36% ($n=357$)	7% ($n=65$)
Mobility	54% ($n=543$)	38% ($n=386$)	6% ($n=58$)
Quality of life	55% ($n=556$)	38% ($n=379$)	5% ($n=54$)

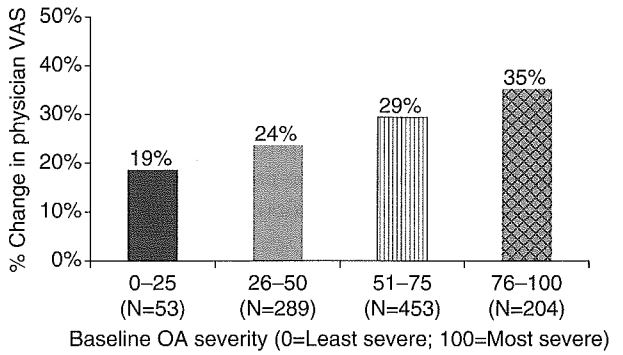

Figure 2. Percent improvement in Physician Global Assessment of Disease (PGAD) visual analog scales (VAS) stratified by baseline OA severity. All between-group differences and each group's improvement over baseline was significant, $p<0.001$.

An important observation was that patients diagnosed with more clinically severe OA at baseline responded better to flavocoxid therapy than those with milder disease (Figure 2). From the least to the most severe OA as judged by PGAD VAS scores, flavocoxid showed a corresponding increase in improvement of VAS scores grouped at baseline in the following ranges: the 0–25 mm group improved -3.5 ± 6.9; the 26–50 mm group improved -10.1 ± 17.0; the 51–75 mm group improved -19.3 ± 19.5; and the 76–100 mm group improved -29.6 ± 23.6; $p<0.001$) (Figure 2). By ANOVA,

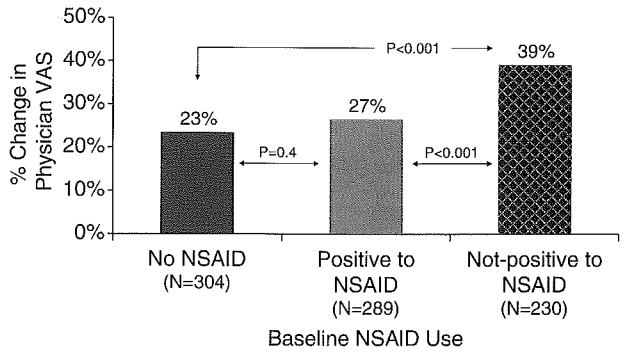

Figure 3. Percent improvement in Physician Global Assessment of Disease (PGAD) visual analog scales (VAS) based on baseline nonsteroidal anti-inflammatory drug (NSAID) use and response to this prior use. All groups also reported a significant improvement over baseline, $p<0.001$.

improvement in OA severity for individuals with baseline VAS scores >50 mm was significantly better compared to individuals with milder baseline VAS scores 26–50 mm ($p<0.001$). Improvements in OA severity for baseline VAS scores >25 mm were also statistically significant compared to the improvement observed in individuals with less severe OA at baseline (VAS scores <25 mm; $p<0.001$). Finally, males ($n=199$) showed significantly greater improvement after flavocoxid therapy compared to females (change in VAS scores of -21.5 ± 21.4 vs. -17.1 ± 21.4 for females; $p=0.013$). No statistically reliable factors were identified that could account for this difference. The use of NSAIDs between genders, prior response (either positive or negative) to NSAID use, and severity of OA at baseline were all comparable. Of interest, a similar result was noted in a recent 3-month, well-controlled, double-blind, clinical trial of 220 patients comparing flavocoxid to naproxen in OA of the knee[29].

The response of patients to flavocoxid based on whether they used an NSAID at baseline and their responses to prior treatments was also examined (Figure 3). Patients who had not responded positively to an NSAID ($n=230$, 23%) recorded an improvement of 39% in PGAD VAS scores while on flavocoxid (40.3 ± 21.1 vs. 66.3 ± 17.7 at baseline) while patients who had responded positively to NSAIDs in the past ($n=289$, 29% of individuals) showed a 27% PGAD VAS score improvement (42.6 ± 19.8 vs. 58.0 ± 18.0 at baseline). The NSAID naïve patients ($n=304$, 28.5%) were reported as having an average improvement of 23% on flavocoxid therapy based on physician VAS scores (46.3 ± 23.7 vs. 60.5 ± 18.0 at baseline). The improvement of the previous NSAID non-responders was significant over patients who previously responded to NSAIDs and to those patients who were NSAID naïve at baseline ($p<0.001$) compatible with the better response seen in patients with more severe disease. Improvement in PGAD VAS scores for all three patients types was significant over baseline ($p<0.001$).

Based on physician evaluations, most patients (85%, $n=855$) defined their tolerability of flavocoxid as 'very well' or 'well.' Physicians also reported that a large number of baseline NSAID users (48%, $n=313$) had upper GI tolerability to flavocoxid that was 'much better' or 'somewhat better' than what they had previously experienced with an NSAID. Further comparisons of GI tolerability indicated that 9% of patients ($n=88$) stopped flavocoxid because of an upper GI-related issue, compared to 33% ($n=214$) of baseline NSAID users who reported that they had discontinued use of an NSAID because of upper GI intolerance. Importantly, 90% ($n=184$) of the upper GI-intolerant population ($n=214$) on NSAIDs or COX-2 inhibitors did not discontinue flavocoxid therapy during the study. These results are consistent with data indicating that 31% ($n=96$) of those previous NSAID users, who were on PPI or H2 antagonists at baseline ($n=310$), either completely discontinued or significantly decreased their use of these gastroprotective medications after beginning flavocoxid therapy.

The overall incidence and distribution of AEs reported in the study is shown in Table 5. Most of the AEs reported were mild with the most common being lower GI disturbances (7.4% of total AEs). It is interesting to note that the total number of GI AEs reported here is lower than the number of patients who discontinued use of flavocoxid due to a GI issue. This phenomenon has been described in the literature and appears to be due to discrepancies in reporting that exist when physicians ask patients a general query such as 'what side-effects were experienced during the study' versus a symptom specific question related to stopping flavocoxid because of a GI tolerability issue[30–33]. Only six AEs resulted in study drop-out. The nature and severity of AE's reported here are very similar to those seen in other well-controlled clinical studies[24,28] and to what has been reported in post-marketing surveillance.

Discussion

In this study, approximately 66% of patients ($n=661$) reported an average improvement of 30% in the signs and symptoms of OA while on flavocoxid therapy, as judged by PGAD VAS and specific Likert scores. Importantly, those patients who had failed prior NSAID treatment and those with more severe OA at baseline showed the best response to flavocoxid. These results may reflect patient expectations which were met with flavocoxid therapy, (but not by previous therapies) rather than measurable improvements. In a real-world setting, however, this type of result needs to be taken into account. A low incidence of total AEs (10%) was also reported in

Table 5. Incidence of adverse events.

Events	Incidence (%)	Events	Incidence (%)
Body as a whole	0.4	Gastrointestinal	7.4
Fever/chills (3)		Nausea/upset stomach (24)	
Fatigue (1)		Dyspepsia/heartburn/reflux (14)	
Cardiovascular	0.3	Diarrhea (11)	
Hypertension (2)		Abdominal pain/cramps (8)	
Fluid retention (1)		Flatulence (3)	
Central nervous system	1.0	Constipation (2)	
Headache (4)		GI issues, NFS (12)	
Dizziness (2)		Gynecologic	0.1
Insomnia (2)		Breast soreness (1)	
Sedation (2)		Musculoskeletal	0.4
Ear, nose, throat	0.1	Leg pain (2)	
Oral ulcers (1)		Joint pain/stiffness (2)	
		Respiratory system	0.2
Eye	0.1	Scratchy throat (1)	
Blurred vision (1)		Wheezing (1)	
		Skin	0.4
Hepatic	0.1	Rash/red bumps (3)	
Increased liver function test (1)		Itching (1)	
Total			10.4

this study. Drop-out rates were much lower (0.6%) compared to a similar post-marketing study of diclofenac (18%)[34] and celecoxib (13% total withdrawals with 4% withdrawing due to GI AEs)[35]. In particular, upper GI tolerability improved in almost half of previous NSAID users. Of those patients who had previously paused or interrupted their use of an NSAID due to upper GI-related issues, ~90% finished the study on flavocoxid. Published studies suggest that 65–90% of patients with a GI risk factor are not prescribed a gastroprotective agent along with their NSAID, while those who are prescribed one often do not take it[36]. This contributes to a high rate of non-compliance with as many as 2–10% of patients discontinuing their NSAID therapy because of UGI toxicity[37]. Switching among drugs or discontinuation of therapy continues to be an issue with NSAID use, often resulting from undesired side-effects or less than optimal efficacy[34,35,38,39]. A number of studies have investigated the issue of under- or non-utilization with NSAIDs[34–36,38–40] with GI intolerance reported as the primary reason[37,41]. Patients are more likely to persist with a treatment regimen with a medication that is well-tolerated as well as being effective.

GI toxicity associated with NSAID use is also an important socioeconomic problem. Up to 2% of all patients taking an NSAID will suffer a serious GI complication, resulting in up to an estimated 107 000 hospitalizations and 16 500 deaths each year in arthritis patients alone. This results in an annual cost approximately $7.5 billion in the United States[42–45]. The American College of Rheumatology (ACR) has defined patients who are age 65 or older, having comorbid medical conditions, taking oral glucocorticoids, with a history of peptic ulcer disease, having a history of upper GI bleeding and/or taking anticoagulants or low dose aspirin for cardioprotection as *at risk* for upper GI bleeding while being treated for OA with anti-inflammatory agents[46]. In these types of patients, the ACR recommends that PPIs be co-administered with traditional NSAIDs. The justification for these standards is well intentioned, but the data regarding safety and efficacy are mixed. A meta-analysis of clinical trials where PPIs or H2 antagonists were included in NSAID therapy found poor compliance among patients being treated[36] and questionable long-term benefit even with good compliance[47–51]. In addition, a strong dose- and duration-dependent association has been noted between the use of PPIs and the risk of osteoporosis-related fractures, presumably due to calcium malabsorption resulting from induced hypochlorhydria[52–54]. Several investigations have also found that PPIs are over-utilized in many medical settings[55–57] and may be an independent risk factor for many nosocomial bacterial infections[58]. Although specific criteria have been defined by the ACR and suggested by various investigators, some studies have shown that they are over-utilized in at least one-quarter of patients with no risk factors for GI bleeding while being treated with NSAIDs for OA[59]. In this study, flavocoxid therapy was associated both with increased compliance among patients with past GI issues and reduced use and need for an gastroprotective medications suggesting this may be due to inherent properties of the molecules in this formulation.

It was initially thought that uncoupling of the COX enzymes by selective inhibition of COX-2 would result in a reduced incidence of ulceration[7,8,11]. However, short- as well as long-term use of these products has led to systemic side-effects including a high incidence of ulceration with long-term usage[60]. The balance of fatty acid metabolism has become critical to understanding these

side-effects and planning strategies for future therapies. Both traditional NSAIDs and selective COX-2 inhibitors have been shown to have similar side-effects on the stomach. Strong down-regulation of either COX-1 or COX-2 enzymes gives specific side-effect profiles that have been shown to be related to the lowering of protective fatty acid metabolites and shunting toward metabolic production of damaging leukotrienes from the 5-LOX pathway[19–21]. Leukotrienes contribute to gastric mucosal damage by inducing microvasculature injury and promoting a breakdown of the mucosal barrier and by attracting leukocytes to the point of tissue injury[17,61]. By balancing the inhibition of AA metabolism across the two major COX enzymatic pathways[23] and inhibiting the inducible pathways of inflammation[25], flavocoxid may only modulate rather than deplete the production of prostaglandin F_1 and E_2 (PGF_1 and PGE_2), which are required for maintenance of gastric mucosal integrity[62]. In addition, through inhibition of the 5-LOX pathway, flavocoxid may prevent the enhanced synthesis of cysteinyl leukotrienes thereby preventing the shunt of AA metabolism toward this pathway consequent upon COX inhibition.

It is thought that increased liberation of free radicals derived from peroxidation of cell membrane derived polyunsaturated fatty acids is another mechanism by which NSAID-induced neutrophil attraction contributes to the pathogenesis of gastric mucosal damage[8]. Flavocoxid has a significant antioxidant activity as demonstrated by the inhibition of malondialdehyde production in culture[25], a physiological activity shared by PPIs[63,64]. This antioxidant property may prevent direct oxidative damage as well as induction of other inflammatory factors from immune cells which may be present in the gastric mucosa, thus preventing further damage to tissue.

Conclusion

In the 'real world' context of this study, patients encompassing a wide range of demographic and clinical parameters appeared to derive benefit in efficacy and/or tolerability from flavocoxid. Those who had not responded positively to an NSAID in the past, those with moderate-to-severe OA and males are likely to derive a substantial benefit from flavocoxid therapy. Patients who had a positive response to NSAIDs in the past also showed significant improvement, possibly related to enhanced compliance. Safety aspects of the study included a low incidence of overall AEs, good tolerability to flavocoxid, improved upper GI tolerability in half of previous NSAID users, reduced therapy interruption in NSAID users with a history of GI-related therapy issues and decreased concomitant use of gastroprotective medications in previous NSAID users. On the basis of this open-label, post-marketing study, flavocoxid appears to be a viable first-line OA therapeutic option particularly in patients with upper GI toxicity or compliance issues. This study was designed to reflect the consequences of 'real-world' clinical decisions when a physician decides to prescribe an anti-inflammatory therapy to an OA patient, with minimal interference from the parameters of a clinical study. The limitations of this study are those inherent to any post-marketing study without a control group or rigorous inclusion and exclusion criteria including all potential bias based on patients' and physicians' expectations. These met expectations may explain why some patients who previously did not feel relief with NSAIDs did well on flavocoxid. Still, the large and diverse number of investigative sites and sizable study population allows for meaningful, generalized conclusions favoring flavocoxid as a viable option for OA therapy.

Transparency

Declaration of funding

Primus Pharmaceuticals, Inc. was the financial sponsor of this study.

Declaration of financial/other relationships

L.P., B.P.B. and R.M.L. have disclosed that they are employees of, and have stock options with Primus. Dr. McLain is a stockholder in Primus Pharmaceuticals, Inc.

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