The Second Generation of COX-2 Inhibitors: Clinical Pharmacological Point of View

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Abstract: Valdecoxib, parecoxib, etoricoxib and lumiracoxib represent the second generation of selective COX-2 inhibitors. In comparison to the first generation, they show an at least equivalent efficacy in the treatment of pain and inflammation. However, the postulated gain of safety is yet difficult to determine and seems to be, if any, small.

Keywords: Safety, efficacy, pain, inflammation, valdecoxib, parecoxib, etoricoxib, lumiracoxib

INTRODUCTION

A review of the second generation of selective cyclooxygenase (COX) -2 inhibitors from the clinical pharmacological point of view has to start with a clinical summary of the first generation of selective COX-2 inhibitors. This is because the intended progress by the development of new selective COX-2 inhibitors has to be compared with the already achieved goals in terms of efficacy and safety by the strategy of selective COX-2 inhibition.

The first generation of selective COX-2 inhibitors comprises in a strict sense only celecoxib and rofecoxib, which were purposely designed after the discovery of the COX-isoenzymes and description of their structure [1]. In a wider sense, nimesulide and meloxicam are included, too. These drugs are also COX-2 selective, though to a lesser degree than the so-called "coxibs", and not purposely, but by chance [1]. Furthermore, the oldest non-steroidal anti-inflammatory drug (NSAID), used by mankind since thousands of years, salicylic acid is COX-2 selective [2]. However, its mechanism of action is suggested to be rather a suppression of COX-2 expression than its weak inhibitory effects on the activity of preformed COX-2 and, even less, COX-1 [2, 3].

Clinically, the first generation of selective COX-2 inhibitors holds the promise of fewer side effects as far as the gastrointestinal tract, platelets and lung are concerned [4, 5]. However, there is still a considerable risk for serious gastrointestinal toxicity by selective COX-2 inhibitors [4]. With regard to the kidney as the second most frequent target of serious adverse effects of NSAIDs, selective COX-2 inhibitors seems to offer no clinically relevant advantage [6]. As a new problem, concerns over the cardiovascular risk of selective COX-2 inhibitors have been raised, which may outweigh any gain in gastrointestinal safety [4]. It must be stressed that despite these open questions selective COX-2 inhibitors are better described by large clinical trials than any other NSAID before. Moreover, most of the data on conventional NSAIDs, in particular ibuprofen, naproxen and diclofenac, stem from trials with selective COX-2 inhibitors where those drugs served as active comparators.

Now, the second generation of COX-2 inhibitors comes on the scene: valdecoxib (Bextra®, Pfizer-Pharmacia), parecoxib (Dynastat®, Pfizer-Pharmacia) and etoricoxib (Arcoxia® Merck). Moreover, lumiracoxib (COX189, Novartis; brand name presumably Prexige®), CS-502 (Sankyo) and others are in the pipeline. A number of reviews dealt already with the pharmacodynamics, pharmacokinetics, clinical efficacy and safety of these new drugs [7-11]. The present work will summarize and update the current knowledge on this field in the context of this special issue of *Mini-Reviews in Medicinal Chemistry* on the COX pathway.

PHARMACODYNAMICS

Using the human whole blood assay, which is generally accepted to be the gold standard for *in vitro* testing of COX inhibitors [12], Riendeau *et al*. reported a COX-2 selectivity of 30 for valdecoxib (the same applies for its water soluble prodrug parecoxib), and 106 for etoricoxib; the values assessed for celecoxib and rofecoxib were 7.6 and 35, respectively [13]. For lumiracoxib Marshall *et al*. showed 700-fold COX-2 selectivity in the human whole blood assay, in the same experiment the COX-2 selectivity of rofecoxib and celecoxib was 100 and 50, respectively [14]. Obviously, the human whole blood assay is not sufficiently standardised to compare data from different laboratories number by number, only the obtained rank orders are comparable.

In animal models of pain and inflammation, such as carrageenan-induced hyperalgesia, carrageenan-induced paw edema and adjuvant arthritis, valdecoxib, parecoxib, etoricoxib and lumiracoxib, demonstrated consistently an efficacy similar to the COX-unselective NSAIDs indomethacin, diclofenac and naproxen, respectively [10, 13, 15, 16].

Clinically, the sparing of the exclusively COX-1 dependent platelet aggregation and thromboxane production in humans *in vivo* by a NSAID in supratherapeutic dosage is the relevant and ultimate proof a high COX-2 selectivity. Valdecoxib, parecoxib, etoricoxib as well as lumiracoxib passed this test as summarized in table 1. These results fit well in the description of preclinical pharmacodynamics, however, it must be stressed that this proof *in vivo* is possible only after the therapeutic dose range is defined by phase II and III trials.

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Table 1. Effects of Valdecoxib, Parecoxib, Etoricoxib and Lumiracoxib on Platelet Aggregation and Thromboxane B_2 (TXB_2) Production in Humans *In vivo*. Naproxen and Ibuprofen for Comparison

	Dose	Platelet aggregation (% inhibition)	TXB_2 production (% inhibition)	Ref.
Valdecoxib	40 mg BID for 7 days	No inhibition	No decrease	[17,18]
Parecoxib	40 mg BID for 8 days	No inhibition	No decrease	[19]
Etoricoxib	120 mg OD for 6 days	No inhibition	No decrease	[20]
Lumiracoxib	Dose escalation 50 mg BID up to 300 mg BID over 9 days	No inhibition	?	[21]
Naproxen	500 mg BID	>90 % inhibition	>90%	[18]
Ibuprofen	800 mg TID	Max. 90 % inhibition	>90%	[17]

PHARMACOKINETICS

Valdecoxib, etoricoxib and lumiracoxib are rapidly absorbed after oral ingestion with a bioavailability of >80% in man, each [22-24]. Parecoxib is the water-soluble inactive prodrug of valdecoxib; after intravenous or intramuscular injection it is rapidly hydrolysed by the liver esterase with a half-life ($t_{1/2}$) of 0.3-0.7 h to its active metabolite valdecoxib [25]. All above-mentioned drugs are subjected to an extensive hepatic metabolism and excreted as inactive metabolites in the urine. Detailed data on the pharmacokinetics of each compound are given in table 2.

For the prescribing physician it is important to realise, that in the elderly and patients with hepatic impairment plasma concentrations of these new NSAIDs are expected to be increased, as demonstrated for valdecoxib and etoricoxib [9, 22]. Since hepatic clearance cannot be predicted accurately, the only way to deal with this problem is a cautionary "go low, go slow" approach. Renal impairment does not affect elimination of valdecoxib, parecoxib or etoricoxib, for lumiracoxib are no data available [9, 22]. However, preexisting renal impairment is a major risk factor for NSAID-induced renal failure, thus NSAIDs, including selective COX-2 inhibitors (see safety, below), must be used, if any, with extreme caution and at the lowest therapeutic dose [6].

THERAPEUTIC EFFICACY

The efficacy of the second generation of COX-2 inhibitors was evaluated for the classic NSAID indications, comprising pain (postoperative pain, dysmenorrhea, back pain), osteoarthritis and rheumatoid arthritis, initially in dose finding studies, later in larger trials with active comparators.

Pain

The analgesic efficacy of valdecoxib was tested in several double blind, controlled and randomised studies including oral surgery, orthopedic, gynecologic and general surgery. Single and multiple doses of 10 mg to 40 mg valdecoxib were compared to standard treatments including ibuprofen, diclofenac, ketorolac, tramadol or oxycocodone/acetaminophen. These pain studies suggest an analgesic dosage of 20 to 40 mg valdecoxib as single dose or repeatedly, which turned out to be as effective or superior to the active comparators [27-30]. For treatment of primary dysmenorrhea valdecoxib 20 to 40 mg BID was found to be effective in two randomised, controlled trials [31, 32].

The efficacy of parecoxib for treatment of acute postoperative pain has been evaluated in comparison to placebo, morphine or ketorolac. Intravenous or intramuscular parecoxib 20 mg or 40 mg was more effective than placebo and as effective as intramuscular ketorolac 60 mg in 304 patients with postoperative dental pain [8]. After abdominal hysterectomy or myomectomy intravenous parecoxib 20 mg or 40 mg demonstrated similar efficacy as ketorolac 30 mg intravenously in 202 patients [33]. A bolus of parecoxib 40 mg, but not parecoxib 20 mg, appeared to be as effective as ketorolac 30 mg in a smaller study, including 72 women after elective gynecological surgery [34]. In treatment of pain following orthopedic surgery, intravenous parecoxib 40

Table 2. Pharmacokinetics of Valdecoxib, Parecoxib, Etoricoxib and Lumiracoxib. CYP = Cytochrome P450

Bioavailability p.o. (%)		t_{max} (h)	Hepatic metabolism	$t_{1/2}$ (h)	Excretion	Ref.
Valdecoxib	83%	2-3 h, p.o.	CYP3A4, CYP2C9 Glucuronidation	8 h	Inactive metabolites in urine	[22]
Parecoxib	parenteral only[1]	0.5 h, i.v.[2] 1.5 h, i.m.[2]	Hydrolyzation by liveresterase to valdecoxib	0.5 h[1]	Inactive metabolites in urine	[8, 25]
Etoricoxib	100%	1 h, p.o.	CYP3A4, CYP2C9, CYP2D6, CYP1A2 (CYP2C19) Glucuronidation	22 h	Inactive metabolites in urine	[23, 26]
Lumiracoxib	>80%	2-3 h, p.o	?	3-6 h	Inactive metabolites in urine	[21, 24]

[1] Metabolism to valdecoxib
[2] t_{max} of valdecoxib after parecoxib i.v./i.m.

Table 3. Therapeutic Doses of Valdecoxib, Parecoxib, Etoricoxib and Lumiracoxib for *Approved or Claimed Indications

	Postoperative Pain	Primary dysmenorrhea	Osteoarthritis	Rheumatoid arthritis	Ref.
Valdecoxib	20-40 mg once daily or BID[1]	*20 mg BID or 40 mg once daily	*10 mg once daily	*10 (-20) mg once daily	[46]
Parecoxib	*20-40 mg once daily or BID[1]	–	–	–	[47]
Etoricoxib	120 mg once daily[1]	120 mg once daily	60-90 mg once daily	90-120 mg once daily	[9]
Lumiracoxib	400 mg once daily?	?	400 mg once daily	?	[11]

[1] Short term (1-2 days) only

mg was more effective than intravenous morphine 4 mg and as effective as intravenous ketorolac 30 mg [35].

In several controlled trials the efficacy of etoricoxib for treatment of chronic low back pain, postoperative dental pain and primary dysmenorrhea was studied. Etoricoxib 60 mg and 90 mg provided better relief of chronic low back pain than placebo [9]. For postoperative dental pain, a single dose of etoricoxib 120 mg was as effective as higher etoricoxib doses and showed comparable efficacy to naproxen sodium 550 mg [9]. Also for treatment of primary dysmenorrhea, single doses of etoricoxib 120 mg provided rapid and sustained analgesia that was superior to placebo and similar to that of naproxen sodium 550 mg [36].

Regarding lumiracoxib, the published results are very scarce. Available data show that a single dose of 400 mg lumiracoxib was superior to ibuprofen 400 mg for dental pain relief [11].

Osteoarthritis

Three double blind, randomised studies compared valdecoxib with naproxen for 6 to 12 weeks. Based on the WOMAC index, the standard measure for clinical response [37], valdecoxib 10 or 20 mg once daily improved pain, stiffness and functional status comparable to naproxen 500 mg BID [38, 39].

Etoricoxib 5 mg, 10 mg, 30 mg, 60 mg and 90 mg demonstrated significantly greater efficacy, assessed by the WOMAC VA 3.0 pain subscale, and patient and investigator global assessment of disease status, than placebo in a randomised, double blind trial including 617 patients with osteoarthritis of the knee [40]. A clear dose-response relationship was observed with etoricoxib 30 mg being superior to 5 and 10 mg; the 60 mg and 90 mg treatments exerted about double the effect size of 30 mg [40]. The treatment effect of etoricoxib was maintained over 52 weeks; again the 60 mg and 90 mg treatments were more effective than 30 mg with respect to pain, patient and investigator global assessment of disease status [40].

In 583 patients with osteoarthritis, lumiracoxib 50 mg, 100 mg and 200 mg BID for 4 weeks were superior to placebo, but less effective than diclofenac 75 mg BID in pain relief and improvement of mobility and stiffness [41].

Rheumatoid Arthritis

Valdecoxib in a dose range from 10 to 40 mg once daily for 12 weeks produced symptomatic improvement of arthritis comparable with 500 mg naproxen BID and superior to placebo [42].

In a dose finding study in 581 RA patients etoricoxib 90 mg and 120 mg once daily showed significant improvements of patient and investigator global assessment of disease activity as compared to placebo [43]. In two active-comparator studies, etoricoxib 90 mg once daily was more effective than naproxen 500 mg BID [44, 45].

Altogether, the therapeutic doses of the second generation of selective COX-2 inhibitors for the various approved or claimed indications are well established by the clinical trials (table 3).

SAFETY

Gastrointestinal damage is the most frequent and most serious side effect of NSAIDs. Also renal safety, interference with platelet function, NSAID-induced asthma and cardiovascular safety must be considered. Apart from these NSAID typical adverse effects, other adverse effects unrelated to the mechanism of action, such as allergy must be included in analysis.

GASTROINTESTINAL SAFETY

Gastroduodenal Ulcer

The incidence of gastroduodenal ulcers in patients with osteoarthritis or rheumatoid arthritis receiving valdecoxib in the therapeutic dosages of 10 and 20 mg once daily for 12-14 weeks was comparable with placebo and significantly lower than observed with naproxen 500 mg BID, ibuprofen 800 mg TID or diclofenac 75 mg BID [38, 48]. Also in supratherapeutic doses of 20 and 40 mg BID for 14 weeks valdecoxib had a significantly lower risk for gastroduodenal ulcers than naproxen 500 mg BID [49].

As expectable, the same holds true for valdecoxib´s prodrug parecoxib. In a randomised, double blind study, 92 healthy elderly volunteers received intravenously for 7 days the high dose of parecoxib 40 mg BID, ketorolac 15 mg QID or placebo. Parecoxib as well as placebo produced no endoscopic ulcers, whereas ketorolac was associated with a 23% ulcer rate [50].

A 12 week study in osteoarthritis and rheumatoid arthritis patients demonstrates an incidence of endoscopic ulcers of 1.4% with placebo, 7.4% with etoricoxib 120 mg once daily and 25.3% with naproxen 500 mg BID ($p<0.001$ vs. etoricoxib and placebo) [51]. Similar results were seen in a 12 week study comparing again the high dose of etoricoxib

Table 4. Incidence of Endoscopic Ulcer in Patients With and Without Risk Factors for NSAID-Induced Gastroduodenal Ulcer. Descriptive Comparison of Pooled Data from Placebo or Active Comparator Controlled Trials with Valdecoxib. Please Note, that Statistical Conclusions cannot be Drawn from this Comparison. Data from [54]

Risk factor		Placebo controlled trials		Active comparator controlled trials			
		Placebo	Valdecoxib 10-20 mg/d	Valdecoxib 10-80 mg/d	Ibuprofen 800 mg TID	Naproxen 500 mg BID	Diclofenac 75 mg BID
History of ulcer	**No**	4.4%	3.4%	4.1%	13.8%	13.3%	14.7%
	Yes	5.1%	7.1%	11.1%	12.5%	29.2%	17.1%
Age ≥ 65 years	**No**	3.7%	3.5%	3.7%	8.2%	12.8%	13.2%
	Yes	5.8%	4.6%	7.6%	21.6%	22.0%	18.2%
Low dose aspirin	**No**	4.4%	3.2%	3.8%	9.8%	16.0%	12.8%
	Yes	5.2%	8.3%	13.3%	32.3%	11.4%	31.8%

120 mg (8.1%) with ibuprofen 800 mg TID (17%) and placebo (1,9%) [52].

Finally, in 1042 patients with osteoarthritis treated with lumiracoxib 200 mg or 400 mg once daily for 13 weeks, the cumulative incidence of gastroduodenal ulcer of lumiracoxib (4.3% and 4.0%, respectively) was significantly lower than with ibuprofen 800 mg TID (15.7%) and similar to celecoxib 200 mg once daily (3.2%) [53].

It must be stressed that the influence of major risk factors for NSAID-induced gastroduodenal ulcer – history of ulcer, elderly age, treatment with low dose aspirin or glucocorticoids – remains to be determined by adequately designed and powered studies. For valdecoxib as the new coxib with the largest database, a descriptive comparison of the pooled results of placebo and active comparator controlled trials indicates a higher baseline risk with a still present, but narrower safety advantage over COX-unselective NSAIDs (table 4) [54]. Remarkably, in presence of a risk factor, it appears that there is an otherwise unrecognisable dose related effect of valdecoxib at supratherapeutic doses on ulcer incidence, pointing to an interplay between risk factors and the potential to develop gastroduodenal ulcer in patients treated with valdecoxib (Fig. (**1**)) [55].

Just one decade ago, clinicians and drug agencies would have been satisfied by the lack of gastric damage observed in the endoscopic studies. Since then, as for evaluation of drug efficacy and safety in general, conclusions based on surrogate parameters became regarded rightly as unreliable. “Endoscopic ulcer" is still such a surrogate parameter, because its clinical relevance is doubtful. Relevant, “hard” endpoints are perforation, symptomatic ulcer and bleeding (PUB) or even more strictly perforation, obstruction and

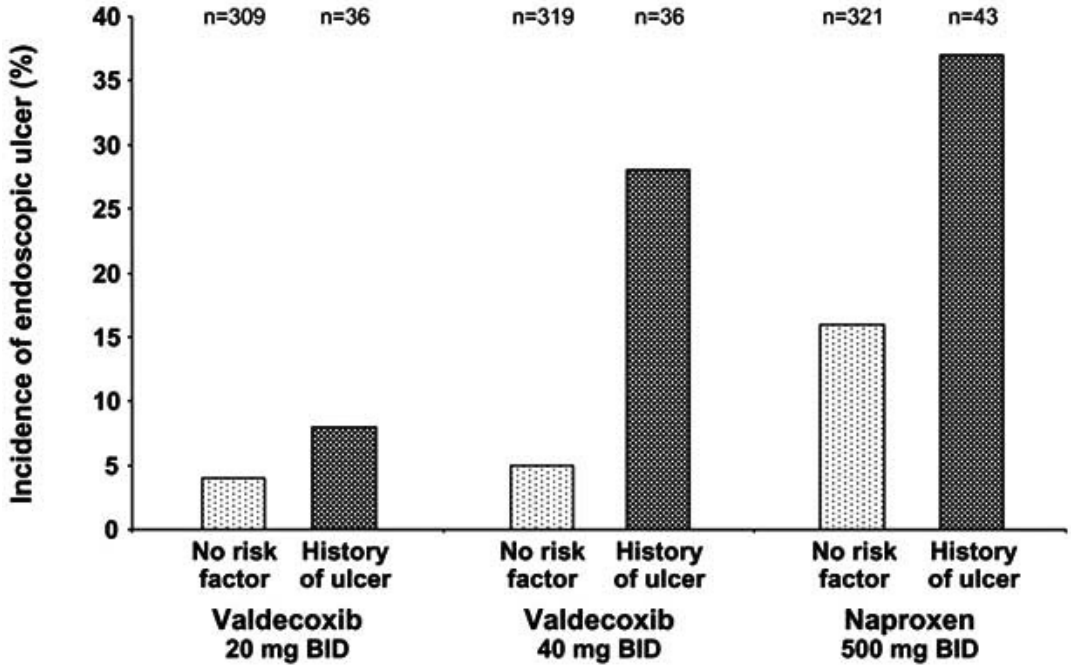

Fig. (1). Effect of the gastroduodenal risk factor "history of ulcer" on the incidence of endoscopic ulcer in patients with osteoarthritis or rheumatoid arthritis treated for 14 week with valdecoxib 20 mg BID, valdecoxib 40 mg BID, or naproxen 500 mg BID [55].

bleeding (POB). For the new COX-2 inhibitors few about PUBs or POBs is known and so far no full papers on this topic are published. However, a prospectively designed analysis of 8 randomised controlled arthritis trials presented on the EULAR meeting 2003, demonstrated significantly less POBs in patients treated with valdecoxib (Fig. (**2**)) [56]. Accordingly, a combined analysis of 10 clinical trials reported a risk reduction of 50% for the incidence of PUBs by use of etoricoxib 60 to 120 mg/d in comparison with ibuprofen 800 mg TID, diclofenac 50 mg TID and naproxen 500 mg BID [9].

Unfortunately, the influence of gastroduodenal risk factors (see above) on the incidence of PUBs or POBs deserves even larger prospective studies to produce robust data; thus, this important topic is not addressed yet.

Subjective Gastrointestinal Symptoms

Dyspepsia and other subjective gastrointestinal complaints should not be neglected. Although they are harmless and not related to development of ulcer and its complications, of which 80% occur without antecedent dyspepsia [57], subjective gastrointestinal symptoms are a major cause for cessation of treatment. Selective COX-2 inhibitors of the second generation are not free of these side effects but show significantly less dyspepsia and led to less drop outs due to gastrointestinal complaints than conventional NSAIDs [9, 38, 39, 42, 58].

Small Bowel and Colon Toxicity

Most studies and reviews on the gastrointestinal safety of NSAIDs were focused on the stomach and the duodenum and spent less, if any attention, on the small bowel and colon. This region merits more attention, since the rate of mucosal damage, ulcer and its complications is nearly as high as in the upper gastrointestinal tract [59]. In a valuable Finish study 37% of all fatal adverse effects of NSAIDs were located in the lower gastrointestinal tract, 57% in the stomach and duodenum, 3% in the kidney and 3% of fatal side effects were allergic reactions [60]. This issue becomes now recognized and was already addressed in studies with etoricoxib and lumiracoxib: Fecal blood loss by etoricoxib 120 mg/d, ibuprofen 800 mg TID and placebo for 28 days was assessed in a double-blind study in 62 healthy volunteers. In result, etoricoxib caused no more fecal blood loss than placebo, whereas ibuprofen led to a 3fold increase [51]. The Cr51 excretion as indicator for small bowel toxicity was compared between lumiracoxib, naproxen and placebo in a cross-over study in 25 healthy volunteers [61]. Cr51 excretion was markedly increased by naproxen (1.22%), whereas the percentage excreted after lumiracoxib (0.74%) did not differ from placebo (0.60%) [61]. While these results are encouraging, one have to keep in mind that fecal blood loss and Cr51 excretion are still surrogates and future studies have to investigate the incidence of intestinal perforation, bleeding and obstruction in the small bowel and colon.

Renal Safety

The renal side effects of NSAIDs caused by COX inhibition comprise reduction in renal blood flow and glomerular filtration rate, sodium and water retention and hyperkalaemia. Analgesic nephropathy by habitual use of NSAIDs is probably also related to COX inhibition as pathomechanism chronic reduction in perfusion of the renal medulla and subsequently ischemic damage is suggested [6].

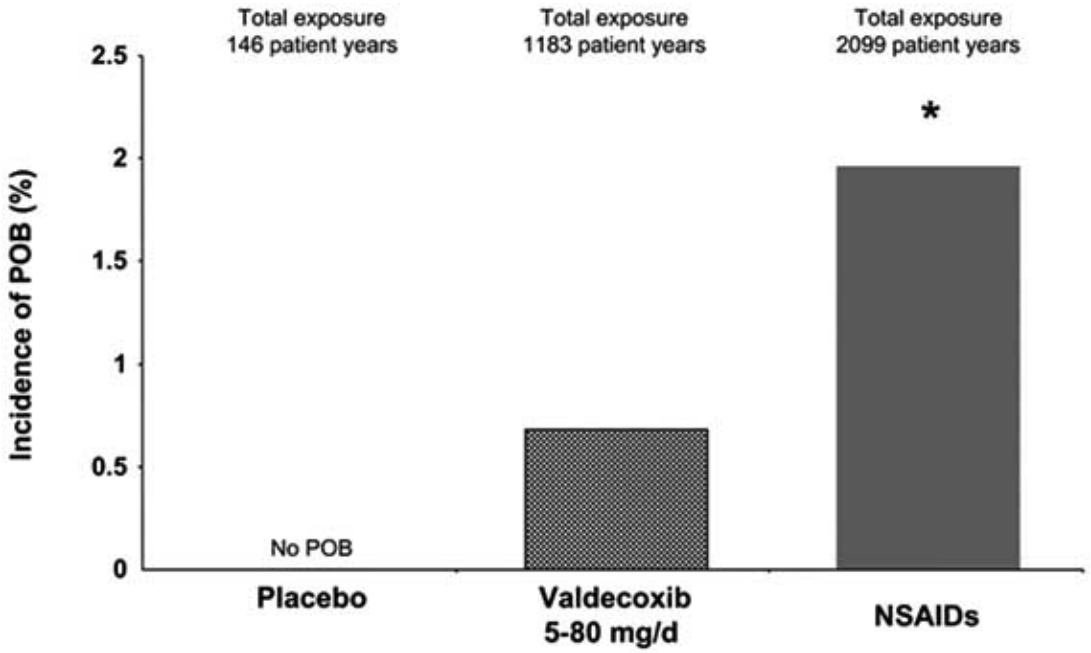

Fig. (2). Incidence of gastrointestinal perforation, obstruction and bleeding (POB) in patients with osteoarthritis or rheumatoid arthritis treated for 12-26 weeks with placebo (n=973), valdecoxib 5-80 mg/d (n=4362), or COX- unselective NSAIDs (naproxen 500 mg BID, n=1181; diclofenac 75 mg BID n=711; ibuprofen 800 mg TID, n=207).* =$p<0.05$ versus placebo and valdecoxib, respectively. Data from 8 randomized, controlled arthritis trials were evaluated by a blinded, independent external adjudication committee in a prospectively designed analysis plan [56].

In contrast, acute interstitial nephritis is an allergic reaction and is induced by many drugs other than NSAIDs [6].

The only well described renal adverse effects of the new coxibs are sodium retention and oedema. Closely related is the risk for arterial hypertension; however, one has to keep in mind, that this side effect is dependent on the interference of selective COX-2 inhibitors with the thromboxane-prostacyclin system, too (see below).

The incidence of peripheral oedema with valdecoxib, etoricoxib or lumiracoxib in therapeutic dosage is 2-3%, thus similar to naproxen, ibuprofen or diclofenac; the same applies for the onset or aggravation of hypertension [9, 54, 58]. All other potential renal side effects are not sufficiently characterised and remain to be assessed by specific studies in populations at risk.

Cardiovascular Safety

As a class effect, selective COX-2 inhibitors completely spare thromboxane synthesis and markedly inhibit prostacyclin formation as shown repeatedly for celecoxib and rofecoxib [62-64]. This shift of the thromboxane/prostacyclin ratio towards thromboxane by selective COX-2 inhibition could pose a thrombogenic risk.

The analysis of the cardiovascular risk of valdecoxib is given in Fig. (**3**) [55]. No additional risk by valdecoxib is perceivable so far. Also the limited data for lumiracoxib, including 1101 patients treated with lumiracoxib 400 mg/d for at least 4 weeks, revealed no cardiovascular risk [footnote: Novartis, data on file]. However, given the biochemical findings, adequately powered prospective studies must address this important issue.

Allergy

Valdecoxib, parecoxib, etoricoxib and lumiracoxib cause apparently no more allergic reactions than other NSAIDs. However, the short history of valdecoxib provides a valuable lesson on the cautionary use of new drugs: Valdecoxib and parecoxib contain a sulfonamide moiety, but there were no problems in clinical trials with patients with history of sulfonamide allergy. Surprisingly, after approval of valdecoxib severe systemic and cutaneous allergic reactions, including anaphylaxis and Lyell syndrome were observed [11]. For parecoxib, the injectable prodrug of valdecoxib, this problem was not reported so far, probably due to the shorter duration of treatment courses. In consequence, the warning that valdecoxib and parecoxib should not be used in patients with history of sulfonamide allergy was added to the product label [11].

To avoid cross reactions in patients with a history of allergy, physicians also need some elementary knowledge of the drugs chemical structure. The term "coxibs" is a functional one, the coxibs share no uniform structure. As described by *de Leval* in the preceding review of this special issue of *Mini-Reviews in Medicinal Chemistry*, valdecoxib and parecoxib are closely related with celecoxib, which is a

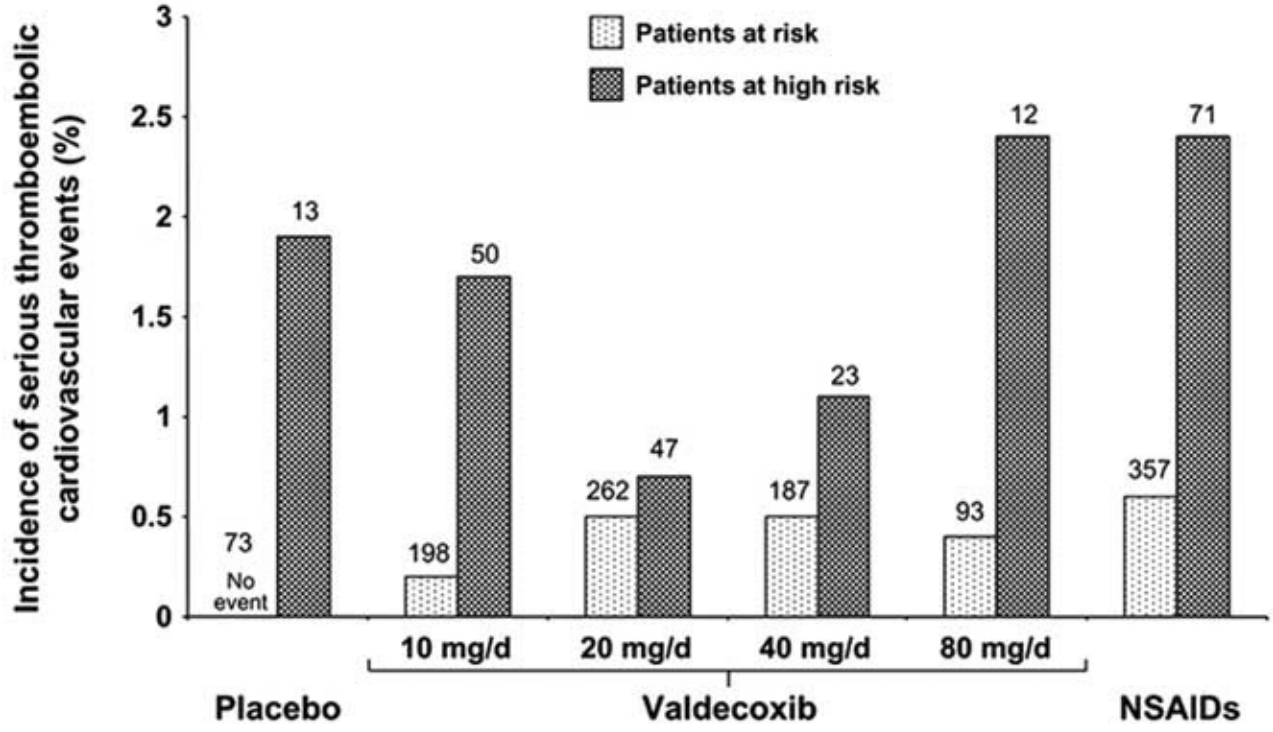

Fig. (3). Incidence of serious thromboembolic cardiovascular events (myocardial infarction, myocardial ischemia, cardiac arrest, stroke, transitory ischemic attack, venous thrombosis, peripheral ischemia) in patients at risk (history of hypertension, hyperlipidemia, smoking) or at high risk (manifest ischemic cardiovascular disease) treated with placebo, valdecoxib 10 mg/d, valdecoxib 20 mg/d, valdecoxib 40 mg/d, valdecoxib 80 mg/d or COX-unselective NSAIDs (naproxen 500 mg BID, diclofenace 75 mg BID, ibuprofen 800 mg TID). Total exposure in patient years is indicated on top of each column. Please note, that statistical conclusions cannot be drawn from this comparison. Data from [55].

sulfonamide, too. Rofecoxib and etoricoxib are quite similar, both containing a methylsulfone moiety. In contrast, lumiracoxib is different to all other coxibs and belongs like diclofenac to the heteroaryl acetic acid group.

Interactions

Due to their cytochrome P450 (CYP) dependent metabolism and weak inhibition of these enzymes (see table 2), the interactions of valdecoxib, parecoxib and etoricoxib with important other drugs were scrutinized in several studies.

Valdecoxib and its prodrug parecoxib had no interactions with propofol, glyburide, glibenclamide, midazolam, methotrexate, oral contraceptives or fentanyl [8, 22, 54]. Vice versa, inhibitors of CYP3A4 and CYP2C9 like fluconazole and ketoconazole are known to increase valdecoxib plasma concentrations by 30-70% [54].

No relevant interactions were found between etoricoxib and prednisolone or oral contraceptives. Divergent results with no effects and a 30% increase of methotrexate´s AUC, respectively, were obtained for the interaction with methotrexate [9]. Also for digoxin mixed results were found, showing an unchanged AUC but a 33% increase of the digoxin peak plasma concentration [9]. Conversely, ketoconazole increased etoricoxib plasma concentrations by 43%, whereas rifampicin decreased it by 65% [9].

Like other NSAIDs, valdecoxib, parecoxib and etoricoxib led to slight increases of warfarin serum levels and its anticoagulant activity [9, 22]. To deal with this moderate and time-limited problem, more frequent INR controls within the first weeks after start of NSAID therapy are recommended. Notably, the lack of platelet inhibition, by selective COX-2 inhibitors is a clear advantage in this situation.

Another typical NSAID interaction is the elevation of lithium plasma level, as described for valdecoxib [54]. Lithium is handled like sodium by the kidney, thus the inhibition of COX-2 dependent tubular sodium excretion cause reduction of lithium excretion, too [6]. In consequence, this interaction is expected for all selective COX-2 inhibitors as well as COX-unselective NSAIDs.

A newly recognized interaction of some NSAIDs is their ability to block the inactivation of COX-1 by aspirin, thereby antagonising the irreversible inhibition of platelet aggregation [65, 66]. The clinical relevance of this finding was recently underlined by the results of an epidemiological study, suggesting an attenuation of the cardioprotective effect of low dose aspirin by concomitant treatment with ibuprofen [67]. Fortunately, selective COX-2 inhibitors at therapeutic doses do not interfere with the antiplatelet effect of aspirin [66]. As a rule, Ouellet et al. found that the higher the selectivity for COX-2, the lower is the potential to block inhibition of platelet COX-1 by aspirin, as demonstrated for etoricoxib as well as valdecoxib and rofecoxib [68].

CONCLUSIONS

The strategy of selective COX-2 inhibition postulates equivalent efficacious but safer NSAIDs. Regarding efficacy, the second generation of selective COX-2 inhibitors exerts antiphlogistic and analgesic effects similar to COX-unselective NSAIDs. With exception of a study comparing valdecoxib with rofecoxib in postoperative dental pain [28], no head to head comparisons with the first generation of selective COX-2 inhibitors are published. In the aforementioned study by Fricke et al., a single dose of valdecoxib 40 mg had a higher efficacy and a more rapid onset of action than rofecoxib 50 mg [28]. However, since the formulation of rofecoxib was altered for blinding purpose, the validity of these findings remains to be confirmed. From my personal, not evidence based point of view, the new coxibs are slightly more efficacious than celecoxib, meloxicam and nimesulide, which appear in daily routine somewhat underdosed.

Regarding safety, it is still too early to draw valid conclusions for all new coxibs, because the current body of evidence resembles an unfinished patchwork. With certainty it can be concluded that in comparison to COX-unselective NSAIDs, the second generation of COX-2 inhibitors have (1) a significantly reduced risk of dyspepsia and endoscopic ulcer, (2) no effect on platelet aggregation, (3) a similar risk for oedema and hypertension. In addition, parecoxib has the potential to replace conventional NSAIDs for treatment of postoperative pain. After surgery, parecoxib´s lack of antiaggregatory actions, its superior gastrointestinal safety, the rapid onset of action, and the parenteral application in patients unable to swallow are clearly advantageous.

With caution it can be stated, that the incidence of PUBs and POBs, respectively, is reduced by valdecoxib (implying its prodrug parecoxib) and etoricoxib. Furthermore, there is no evidence for an excess of cardiovascular events by these drugs so far. For lumiracoxib the incidence of ulcer complications and cardiovascular events is evaluated in the TARGET study, which is scheduled to be completed at the end of the year 2003.

Nothing can be said about the safety of the new coxibs in patients with asthma and in patients with risk factors for NSAID-induced renal failure. Undetermined is also, whether their high COX-2 selectivity translates into further reduction of NSAID-typical side effects in comparison with celecoxib and rofecoxib. Again, it may be allowed to give my personal opinion, that the gastrointestinal safety data of the new coxibs are more convincing than the corresponding results for celecoxib. As far as renal safety is concerned, it is prudent to speculate that the second generation of COX-2 inhibitors offers no clinical relevant advantage over the first generation or the COX-unselective NSAIDs.

For most of the open issues studies are underway. The results are expected to shed more light on the second generation of COX-2 inhibitors and overall on the so far successful strategy of selective COX-2 inhibition.

REFERENCES

[1] Hawkey, C.J. *Lancet*, **1999**, *353*, 307.
[2] Frölich, J.C. *Trends Pharmacol. Sci*., **1997**, *18*, 30.
[3] Cieslik, K.; Zhu, Y.; Wu, K.K. *J. Biol. Chem*., **2002**, *277*, 49304.
[4] Fitzgerald, G.A.; Patrono, C. *N. Engl. J. Med.*, **2001**, *345*, 433.
[5] Szczeklik, A.; Stevenson, D.D. *J. Allergy Clin. Immunol*., **2003**, *111*, 913.
[6] Stichtenoth, D.O.; Frölich, J.C. *Curr. Pharm. Des*., **2000**, *6*, 1737.

[7] Chavez, M.L.; DeKorte, C.J. *Clin. Ther*., **2003**, *25*, 817.
[8] Cheer, S.M.; Goa, K.L. *Drugs*, **2001**, *61*, 1133.
[9] Cochrane, D.J.; Jarvis, B.; Keating, G.M. *Drugs*, **2002**, *62*, 2637.
[10] Ding, C.; Jones, G. *Idrugs*, **2002**, *5*, 1168.
[11] Stichtenoth, D.O.; Frölich, J.C. *Drugs*, **2003**, *63*, 33.
[12] Warner, T.D.; Pairet, M.; Van Ryn, J. In *Therapeutic roles of selective COX-2 inhibitors*; Vane, J.R.; Botting, R.M., Eds. William Harvey Press: London, **2001**; pp. 76-94.
[13] Riendeau, D.; Percival, M.D.; Brideau, C.; *et al. J. Pharmacol. Exp. Ther*., **2001**, *296*, 558.
[14] Marshall, P.J.; Berry, C.; Wasvary, J. *Ann. Rheum. Dis*., **2002**, *61 (Suppl. 1),* 259.
[15] Talley, J.J.; Brown, D.L.; Carter, J.S.; *et al. J. Med. Chem*., **2000**, *43*, 775.
[16] Talley, J.J.; Bertenshaw, S.R.; Brown, D.L.; *et al. J. Med. Chem*., **2000**, *43*, 1661.
[17] Leese, P.T.; Recker, D.P.; Kent, J.D. *J. Clin. Pharmacol*., **2003**, *43*, 504.
[18] Leese, P.T.; Talwalker, S.; Kent, J.D.; Recker, D.P. *Am. J. Emerg. Med*., **2002**, *20*, 275.
[19] Noveck, R.J.; Laurent, A.; Kuss, M.; Talwalker, S.; Hubbard, R.C. *Clin. Drug Invest.*, **2001**, *21*, 465.
[20] Wagner, J.A.; Kraft, W.; Burke, J.; *et al. Arthritis Rheum*., **2001**, *44* (Suppl. 9), S135.
[21] Rordorf, C.; Scott, G.; Milosavljev, S.; Blood, P.; Branson, J.; Greig, G. *Ann. Rheum. Dis*., **2002**. *61* (Suppl. 1), 420.
[22] Ormrod, D.; Wellington. K.; Wagstaff. A.J. *Drugs*, **2002**, *62*, 2059.
[23] Agrawal, N.G.; Porras. A.G.; Matthews, C.Z.; *et al. J. Clin. Pharmacol*., **2003**, *43*, 268.
[24] Scott, G.; Rordorf, C.; Blood, P.; Branson, J.; Milosavljev, S.; Greig, G. *Ann. Rheum. Dis.*, **2002**, *61* (Suppl. 1), 244.
[25] Hubbard, R.; Kuss, M.; Talwalker, S.; *et al. Ann. Emerg. Med*., **2000**, *36*, S69.
[26] Kassahun, K.; McIntosh, I.S.; Shou, M.; *et al. Drug Metab. Dispos*., **2001**, *29*, 813.
[27] Camu, F.; Beecher, T.; Recker, D.P.; Verburg, K.M. *Am. J. Ther*., **2002**, *9*, 43.
[28] Fricke, J.; Varkalis, J.; Zwillich, S.; *et al. Am. J. Ther*., **2002**, *9*, 89.
[29] Desjardins, P.J.; Shu, V.S.; Recker, D.P.; Verburg, K.M.; Woolf, C.J. *Anesthesiology*, **2002**, *97*, 565.
[30] Daniels, S.E.; Desjardins, P.J.; Talwalker, S.; Recker, D.P.; Verburg, K.M. *J. Am. Dent. Assoc*., **2002**, *133*, 611.
[31] Torri, S.; Kuss, M.E.; Talwalker, S.C.; Daniels, S.; Snabes, M.C. *Fertil. Steril*., **2001**, *76*, S95.
[32] Daniels, S.E.; Talwalker, S.; Torri, S.; Snabes, M.C.; Recker, D.P.; Verburg, K.M. *Obstet. Gynecol*., **2002**, *100*, 350.
[33] Barton, S.F.; Langeland, F.F.; Snabes, M.C.; LeComte, D.; Kuss, M.E.; Dhadda, S.S.; Hubbard, R.C. *Anesthesiology*, **2002**, *97*, 306.
[34] Kenaan, C.A.; Bikhazi, G.B.; Deepika, K.; Calfa, C.I.; Ortiz, K. *Anesth. Analg*., **2001**, *92* (Suppl.), S257.
[35] Rasmussen, G.L.; Steckner, K.; Hogue, C.; Torri, S.; Hubbard, R.C. *Am. J. Orthop.*, **2002**, *31*, 336.
[36] Malmstrom, K.; Kotey, P.; Cichanowitz, N.; Daniels, S.; Desjardins, P.J. *Gynecol. Obstet. Invest*., **2003**, *Aug 04*, Epub.
[37] Bellamy, N.; Buchanan, W.W.; Goldsmith, C.H.; Campbell, J.; Stitt, L.W. *J. Rheumatol.*, **1988**, *15*, 1833.
[38] Kivitz, A.; Eisen, G.; Zhao, W.W.; Bevirt, T.; Recker, D.P. *J. Fam. Pract*., **2002**, *51*, 530.
[39] Makarowski, W.; Zhao, W.W.; Bevirt, T.; Recker, D.P. *Osteoarthritis Cartilage,* **2002**, *10*, 290.
[40] Gottesdiener, K.; Schnitzer, T.; Fisher, C.; *et al. Rheumatology*, **2002**, *41*, 1052.
[41] Moore, A.; Della Casa Alberghi, O.; Gitton, X.; Sloan, V.; Limona, A. *Ann. Rheum. Dis*., **2002**, *61* (Suppl. 1), 137.
[42] Bensen, W.; Weaver, A.; Espinoza, L.; Zhao, W.W.; Riley, W.; Paperiello, B.; Recker, D.P. *Rheumatology*, **2002**, *41*, 1008.
[43] Curtis, S.P.; Maldonado-Cocco, J.; Losada, B.R.; Gallagher, A.E.; Ng, J.; Mukhopadhyay, S. *Ann. Rheum. Dis*., **2001**, *60 (Suppl. 1),* FRI0030.
[44] Matsumoto, A.K.; Melina, A.; Mandel, D.R.; *et al. J. Rheumatol*., **2002**, *29*, 1623.
[45] Collantes, E.; Curtis, S.P.; Lee, K.W.; *et al. BMC Fam. Pract*., **2002**, *3*, 10.
[46] Product information Bextra®. Pharmacia Europe EEIG, High Wycombe, Great Britain, *March*, **2003**.
[47] Product information Dynastat®. Pharmacia Europe EEIG, High Wycombe, Great Britain, *March,* **2003**.
[48] Sikes, D.H.; Agrawal, N.M.; Zhao, W.W.; Kent, J.D.; Recker, D.P.; Verburg, K.M. *Eur. J. Gastroenterol. Hepatol*., **2002**, *14*, 1101.
[49] Agrawal, N.; Paperiello, B.; Zhao, W.W.; *et al. Arthritis Rheum*., **2001**, *44 (Suppl.)*, Abstract 1917.
[50] Stoltz, R.R.; Harris, S.I.; Kuss, M.E.; *et al. Am. J. Gastroenterol*., **2002**, *97*, 65.
[51] Hunt, R.H.; Harper, S.; Callegari, P.; *et al. Aliment. Pharmacol. Ther*., **2003**, *17*, 201.
[52] Hunt, R.H.; Harper, S.; Watson, D.J.; *et al. Am. J. Gastroenterol*., **2003**, *98*, 1725.
[53] Hawkey, C.J.; Karateev, D.; Codreanu, C.; *et al. Ann. Rheum. Dis*., **2002**, *61,* (Suppl. 1)*,* 126.
[54] Product Information Bextra®. Searle, Pharmacia Corporation, Chicago, IL, *October,* **2003**.
[55] FDA-Review NDA 21-341. www.fda.gov/cder/foi/nda/2001/21-341_Bextra.htm. May 30, **2002**.
[56] Goldstein, J.L.; Stenson, W.; Agrawal, N.; *et al.* EULAR, Lissabon, **2003**, AB 0113.
[57] Singh, G.; Ramey, D.R.; Morfeld, D.; Shi, H.; Hatoum, H.T.; Fries, J.F. *Arch. Intern. Med*., **1996**, *156*, 1530.
[58] Schnitzer, T.; Geusens, P.; Hasler, P.; *et al. Arthritis Rheum*., **2000**, *43* (Suppl.), S336.
[59] Allison, M.C.; Howatson, A.G.; Torrance, C.J.; Lee, F.D.; Russell, R.I. *N. Engl. J. Med*., **1992**, *327*, 749.
[60] Myllykangas-Luosujärvi, R.; Aho, K.; Isomäki, H. *J. Rheumatol*., **1995**, *22*, 2214.
[61] Atherton, C.T.; Jones, J.I.W.; McKaig, B.C.; *et al. Ann. Rheum. Dis*., **2002**, *61* (Suppl. 1), 245.
[62] McAdam, B.F.; Catella-Lawson, F.; Mardini, I.A.; Kapoor, S.; Lawson, J.A.; FitzGerald, G.A. *Proc. Natl. Acad. Sci. USA*, **1999**, *96*, 272.
[63] Catella-Lawson, F.; McAdam, B.; Morrison, B.W.; *et al. J. Pharmacol. Exp. Ther*., **1999**, *289*, 735.
[64] Dilger, K.; Herrlinger, C.; Peters, J.; Seyberth, H.W.; Schweer, H.; Klotz, U. *J. Clin. Pharmacol.*, **2002**, *42*, 985.
[65] Catella-Lawson, F.; Reilly, M.P.; Kapoor, S.C.; *et al. N. Engl. J. Med*., **2001**, *345*, 1809.
[66] Baigent, C.; Patrono, C. *Arthritis Rheum.*, **2003**, *48*, 12.
[67] MacDonald, T.M.; Wei, L. *Lancet*, **2003**, *36*, 573.
[68] Ouellet, M.; Riendeau, D.; Percival, M.D. *Proc. Natl. Acad. Sci. USA*, **2001**, *98*, 14583.