EXTENDED REPORTS

Incidence of clinically manifest ulcers and their complications in patients with rheumatoid arthritis

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Abstract

***Background*—Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed in patients with rheumatoid arthritis (RA). Because of its frequency and severity, NSAID gastropathy is the most important side effect. The clinical spectrum of NSAID gastropathy includes gastrointestinal complaints, ulcers and their complications. To reduce NSAID gastropathy, rheumatologists in greater Amsterdam decided in January 1997 that prophylactic agents should be prescribed for patients with RA at high risk for NSAID gastropathy, defined as age 60 or older or a history of gastrointestinal (GI) ulcers, or both.**

***Objective*—To determine the incidence of clinically manifest ulcers and their complications in patients with RA at high risk for NSAID gastropathy during a period in which prophylaxis was recommended. Published reports show that the incidence of clinically manifest ulcers and their complications varies from 1.3% to 5%.**

***Patients and methods*—Within one year, three questionnaires were sent to all outpatients with RA of our clinic (n=2680). The patients were asked if they had had a gastroscopy and/or complication of an ulcer in the preceding months. When a GI event (ulcer or complication) had occurred an analysis was carried out to determine whether the event was possibly related to a compliance failure or a policy failure—for example, no prophylaxis prescribed when it was recommended.**

***Results*—The response rate for the three questionnaires was 88%, 76%, and 77%, respectively. All three questionnaires were returned by 1856 patients; NSAIDs were used in 1246 (67%) of them. Of the NSAID users 731 (59%) were in the high risk group. Clinically manifest ulcers occurred in seven high risk NSAID users (four gastric ulcers, two duodenal ulcers, and in one patient both types of ulcer). Complications of ulcers were diagnosed in eight (other) patients: seven (upper) GI bleedings and one perforation. Thus the incidence during one year of clinically manifest ulcers in the high risk group was 1.0% and of complications of ulcers 1.1%, together 2.1%. In the group of 15 patients with GI events, only one patient had not taken the adequately prescribed gastroprotective drugs (compliance failure). Misguidedly, gastroprotective drugs were not prescribed in seven patients (policy failure), but in the remaining seven patients gastroprotective drugs were adequately prescribed and used.**

***Conclusion*—The incidence of clinically manifest ulcers and of complications of ulcers in patients with RA at high risk for NSAID gastropathy is relatively low, and might be related to our strategy to prescribe prophylactic agents in these patients.**

(*Ann Rheum Dis* 2001;**60**:443–447)

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Accepted 26 September 2000

Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed in patients with rheumatoid arthritis (RA). The most important side effect is NSAID gastropathy, which includes the wide spectrum of dyspepsia, gastric and duodenal ulcers and their complications (bleeding and perforation).[1 2] It is estimated that dyspepsia occurs in 10–20% of NSAID users, though the prevalence may range from 5 to 50%.[2] In endoscopic studies, ulcers are seen in 10–25% of NSAID users,[2] while the incidence of complications of ulcers due to NSAID treatment varies from 1.3 to 5%.[2–7] Unfortunately, it is not possible to predict reliably in which NSAID users (complications of) ulcers will occur, because of the poor correlation between dyspepsia and ulcers and their complications.[8]

The most important risk factors for NSAID gastropathy are age 60 or older and a previous ulcer.[8] Other risk factors are concomitant use of corticosteroids and/or oral anticoagulants, high doses of NSAIDs, and cardiovascular disease.[9 10] Because of the frequency and severity of NSAID gastropathy, prophylaxis is advocated in high risk patients.

Rheumatologists in greater Amsterdam, the Netherlands, decided in January 1997 to prescribe a prophylactic agent to patients with RA at high risk for NSAID gastropathy, defined

Table 1 Characteristics of patients with rheumatoid arthritis (RA) using non-steroidal anti-inflammatory drugs (NSAIDs), who returned all three questionaires within one year. Comparison between high risk and low risk patients with RA. Results are shown as No (%)

	Patients with RA, NSAID users					
	Low risk (n=515)	*High risk (n=731)*			*Total 1246 (100%)*	*Odds ratio (95% confidence interval)*
	Age <60 years	*Age ≥60 years*				
Ulcer in medical history, No (%)	Absent (A) 506 (41) or 9 unknown	Present (B) 48 (4)	Absent (C) 570 (46) or 5 unkown	Present (D) 108 (9)		
Events	1 (0.2)	0	10 (1.8)	5 (5)	16 (1.3)	10.8 (1.42 to 81.8)
Ulcers	1 (0.2)	0	5 (0.9)	2 (2)	8 (0.6)	4.97 (0.61 to 40.5)
Complications	0 (0)	0	5 (0.9)	3 (3)	8 (0.6)	p<0.05
Gastroprotection	149 (29)	26 (54)	249 (44)	79 (73)	508† (41)	1.66 (1.42 to 1.93)
GI complaints*						
Epigastric pain	61 (12)	11 (23)	47 (9)	17 (16)		0.85 (0.60 to 1.22)
Heartburn	62 (12)	7 (15)	47 (9)	22 (20)		0.82 (0.58 to 1.18)
Nausea	52 (10)	6 (13)	31 (6)	9 (8)		0.60 (0.40 to 0.90)
Vomiting	14 (3)	3 (6)	11 (2)	5 (5)		0.96 (0.47 to 1.92)
Belching	60 (12)	11 (23)	56 (10)	18 (17)		1.00 (0.70 to 1.42)
Puffy feeling in the stomach	66 (13)	16 (33)	52 (9)	14 (13)		0.86 (0.61 to 1.21)
Current treatment						
DMARDs*	424 (84)	38 (79)	408 (72)	67 (62)	944 (76)	0.62 (0.47 to 0.82)
Corticosteroids	74 (15)	9 (19)	111 (20)	25 (23)	219 (18)	1.47 (1.09 to 2.00)
Anticoagulants	8 (2)	0	14 (3)	6 (6)	28 (2)	1.78 (0.78 to 3.92)
Cardiovascular drugs	66 (13)	10 (21)	149 (26)	37 (34)	263 (21)	2.49 (1.84 to 3.38)

*GI = gastrointestinal complaints: moderate, severe, or very severe (versus absent or mild); DMARDs = disease modifying antirheumatic drugs.
†For five patients it was unknown whether or not they were treated with gastroprotection.

as age 60 years or older or a previous ulcer, or both. The choice of the type of prophylaxis was open, though there was a slight preference for a proton pump inhibitor, because of its effectiveness in prevention[11 12] and treatment[13] of NSAID related ulcers, as well as good tolerance of its use.

The objective of this observational study was to determine the incidence of clinically manifest ulcers and their complications in patients with RA at high risk for NSAID gastropathy during the recommended administration of a prophylactic agent, to compare the percentage of upper gastrointestinal (GI) events with data from the literature, and to obtain an impression of the reasons for failure of prophylaxis.

Patients and methods

In greater Amsterdam, the Netherlands, patients with rheumatic diseases are treated at the outpatient clinics of the Jan van Breemen Institute or the departments of rheumatology of the Academic Hospital Vrije Universiteit or Slotervaart Hospital. In January 1997, agreement was reached among rheumatologists in greater Amsterdam that prophylaxis of NSAID gastropathy was warranted in high risk patients with RA, defined as age above 60 or previous ulcer, or both. The choice of the type of prophylactic agent to be prescribed was open, with a slight preference for proton pump inhibitor.

Three subsequent questionnaires, each referring to the previous four months, were sent to all 2680 patients with RA, of whom the diagnosis RA was documented in the database containing data derived from the Standard Diagnosis Registration forms. In these questionnaires patients were asked about NSAID use, previous ulcer(s), and whether they had had a gastroscopy and/or complication of an ulcer during the preceding months. Because it is difficult, if not impossible, to obtain reliable data on the exact use of NSAIDs in a large group of patients during an observation period of one year, because of the use of different daily doses and because controlling compliance is complicated, patients were divided into NSAID users or non-users, depending on their response to the questionnaire.

Dyspepsia (epigastric pain, heartburn, nausea, vomiting, puffy feeling in the stomach, and belching) was scored on a five point scale (1 = no complaints; 2 = mild; 3 = moderate; 4 severe; and 5 = very severe or unbearable complaints). Questions about other drugs and smoking habits were also asked.

GI events were divided into clinically manifest ulcers and complications. A clinically manifest ulcer was defined as dyspeptic symptoms leading to a gastroscopy, in which an endoscopic ulcer was observed; bleeding and perforation were regarded as complications of ulcers. In the case of a gastroscopy or an ulcer complication, or both, the results of the endoscopy were checked in the patient's record; if necessary, these patients were telephoned to complete the questionnaire.

For all patients with a GI event it was assessed whether there was a policy failure, compliance failure, or none of these (rest group). A GI event in a patient without gastroprotection, but who should have been prescribed a prophylactic agent according to the above described guidelines, was defined as a policy failure; an event in a patient who did not take the prescribed prophylactic drugs was regarded as a compliance failure. Events not related to policy or compliance were categorised as the rest group.

A comparison was made between demographic and disease characteristics between patients at high risk versus low risk for NSAID gastropathy and between high risk patients with and without gastroprotection.

Moreover, a (small) case-control study was performed between patients with RA with and without a GI event. For each index patient (with a GI event) we selected (derived from our database) three or four patients with RA of the

Table 2 Comparison of 731 high risk patients with rheumatoid arthritis (age >60 years and/or previous ulcer), with and without gastroprotection. Results are given as No (%) unless otherwise stated

	With gastroprotection	*Without gastroprotection*	*Odds ratio (95% confidence interval)*
Total number	357 (49)	374 (51)	
Female	245 (69)	253 (68)	
Age (mean, range)	69.9 (41.2–90.0)	69.1 (23.9–89.6)	
Gastrointestinal events			
Total	10 (3)	5 (1)	2.1 (0.7 to 6.3)
Ulcers	2 (0.6)	5 (1)	0.4 (0.1 to 2.2)
Complications	8 (2)	0 (0)	p<0.01
History of GI ulcer			
Known	354	372	
Present	105 (30)	51 (14)	2.2 (1.6 to 2.9)
Absent	249 (70)	321 (86)	0.8 (0.75 to 0.88)
Unknown	3	2	
GI complaints*			
Epigastric pain	52 (15)	23 (6)	2.6 (1.6 to 4.4)
Heartburn	48 (13)	28 (7)	1.9 (1.2 to 3.1)
Nausea	30 (8)	16 (4)	2.1 (1.1 to 3.8)
Vomiting	12 (3)	7 (2)	1.8 (0.7 to 4.7)
Belching	59 (17)	26 (7)	2.7 (1.6 to 4.3)
Puffy feeling in the stomach	55 (15)	28 (7)	2.3 (1.4 to 3.6)
Current treatment			
DMARDs*	267 (75)	249 (67)	1.5 (1.1 to 2.1)
Corticosteroids	90 (25)	53 (14)	2.0 (1.4 to 3.0)
Anticoagulants	8 (2)	8 (2)	1.0 (0.4 to 2.7)
Cardiovascular drugs	129 (36)	113 (30)	1.3 (1.0 to 1.8)

*GI = gastrointestinal complaints: moderate, severe, or very severe (versus absent or mild); DMARDs = disease modifying antirheumatic drugs.

Table 3 Case-control comparison between 69 rheumatoid patients with and without a gastrointestinal event—that is, a clinically manifest ulcer and/or complication. Results are given as No (%) unless otherwise stated

	Clinical manifest ulcer and/or complication		
	Present	*Absent*	*Odds ratio (95% confidence interval)*
Number	15	54	
Ulcer	7 (47)	0	
Complication	8 (53)	0	
Age (mean, range)	73.6 (61.5–89.4)	72.4 (60.4–90.0)	
History of ulcer	5 (33)	7 (13)	3.4 (0.9 to 12.8)
GI complaints*			
Epigastric pain	8 (53)	5 (9)	11.2 (2.9 to 4.4)
Heartburn	4 (27)	4 (8)	4.6 (1.0 to 21.0)
Nausea	5 (33)	1 (2)	24.5 (2.6 to 23.3)
Vomiting	3 (20)	1 (2)	13.2 (1.3 to 13.9)
Belching	4 (27)	6 (11)	2.9 (0.7 to 12.1)
Puffy feeling in the stomach	4 (27)	1 (2)	19.3 (2.0 to 189)
H pylori			
Positive	10 (67)	27 (50)	2.0 (0.6 to 6.6)
Negative	4 (27)	26 (48)	0.4 (0.1 to 1.4)
Unknown	1 (7)	1 (2)	
DMARDs*	7 (47)	46 (85)	0.2 (0.04 to 0.5)
Corticosteroids	7 (47)	12 (22)	3.1 (0.9 to 10.2)
Anticoagulants	2 (13)	1 (2)	8.2 (0.7 to 97.0)
Cardiovascular drugs	6 (40)	17 (31)	1.5 (0.5 to 4.7)
(Any) gastroprotection	10 (67)	30 (56)	1.6 (0.5 to 5.3)

*GI = gastrointestinal complaints: moderate, severe, or very severe (versus absent or mild); DMARDs = disease modifying antirheumatic drugs.

same sex aged within five years above or below the index patient. We compared demographic data, dyspeptic symptoms, *H pylori* status, and use of drugs in all 15 index patients and 54 control patients with RA. Demographic data, dyspeptic symptoms, and drug use were derived from the questionnaires. In patients with GI events, screening for *H pylori* was done by culture, after endoscopy, or by serological testing; in the controls, only serological tests were performed.

STATISTICAL METHODS

Odds ratios with 95% confidence interval (CI) were computed to express relations between variables. Additionally, χ^2 or exact tests were used to judge significance.

Results

The response rate for the three questionnaires was 88%, 76%, and 77%, respectively. All three questionnaires were returned by 1856 patients with RA; NSAIDs were used in 1246 (67%) of them. Of these 1246 NSAID treated patients, 683 (55%) were at high risk for NSAID gastropathy because of age above 60 years (and a previous ulcer in 108 (9%)). Additionally, 48 (4%) patients younger than 60 years with a history of an ulcer were also regarded as high risk. Ulcer history was unknown in five elderly and nine younger patients: these were regarded, arbitrarily, as patients with a negative history for GI ulcers. Thus the high risk group comprised 731 (683+48) (59%) of the patients with RA who used NSAIDs. Table 1 shows the characteristics of the 1246 patients with RA who used NSAIDs and who returned all three questionnaires.

After one year, 15 patients in the high risk group (n=731) had developed a GI event. In seven patients clinically manifest ulcers were diagnosed (four gastric ulcers, two duodenal ulcers, and one patient with both types of ulcer). Complications of ulcers occurred in eight (other) patients: seven (upper) GI bleedings and one perforation of the stomach. Thus the incidence of clinically manifest ulcers was 1.0% and of complications of ulcers 1.1%, together 2.1%.

We compared the frequency of GI events in high risk (n=15) versus low risk patients (n=1): the difference was statistically significant, with more events occurring in the high risk than in the low risk group (odds ratio 10.8; 95% CI 1.4 to 81.8). Both ulcers (odds ratio 5.0; 95% CI 0.6 to 40.5) and their complications (p<0.05) occurred more frequently in the high risk patients, though the difference was not statistically significant for ulcers (table 1).

There was no statistically significant difference in dyspeptic symptoms between the high risk and the low risk group. The high risk patients used gastroprotective drugs more commonly, but also used corticosteroids, oral anticoagulants (not statistically significant), and cardiovascular drugs more often. In contrast, in the high risk group the percentage of patients treated with disease modifying antirheumatic drugs (DMARDs) was lower.

To get an impression as to whether the use of gastroprotective drugs had influenced the occurrence of GI events in the high risk group we compared the characteristics of the patients with (n=357 (49%)) and without gastroprotection (n=374 (51%); (table 2)). GI events occurred more often in the group with gastroprotection than without gastroprotection (odds ratio 2.1; 95% CI 0.7 to 6.3), though the difference was not statistically significant. In particular, complications occurred more often in patients with gastroprotection (8 *v* 0; p<0.01). Patients with gastroprotection had more previous GI ulcers (odds ratio 2.2; 95% CI 1.6 to 2.9), and used DMARDs, corticosteroids, and cardiovascular drugs more frequently, and had more dyspeptic symptoms.

Table 3 shows the demographic and disease characteristics of the 15 patients with RA with

GI events and 54 control patients with RA (matched for age and sex).

In the group with events, more patients had a history of previous ulcer (odds ratio 3.4; 95% CI 0.9 to 12.8), and more patients had GI complaints. Moreover, there was an increased tendency for the presence of *H pylori* infection (odds ratio 2.0; 95% CI 0.6 to 6.6), though not statistically significant, and for the use of corticosteroids, oral anticoagulants, and cardiovascular drugs.

Policy failures occurred in seven of 15 patients with a GI event; a compliance failure was seen in only one patient; in seven patients none of these types of failure occurred.

Discussion

The main conclusion of this observational study is that there is a relatively low incidence of clinically manifest ulcers of 1.0% and of complications of ulcers of 1.1%, together 2.1%, in patients with RA at increased risk for NSAID gastropathy, defined as age above 60 or a previous ulcer, or both. In comparison with other studies,[2–7] these incidence values are relatively low, especially taking into account that our group comprised high risk patients with RA.

Comparison of the results of our study with the results of other studies is difficult because patient groups, underlying diseases, and doses of NSAIDs may vary between different studies. Apart from this, comparing data on clinically manifest ulcers is hampered by the fact that the number of clinically manifest ulcers is also dependent on indications for, and number of, endoscopies. Therefore, we will focus on the complications of ulcers, which are more objective end points.

In the placebo arm of the MUCOSA trial, which compared placebo with misoprostol, the complication rate was 1% after six months of observation.[4] According to the ARAMIS database, the observed complication rate was 13 out of 1000 patients with RA a year (1.3%).[5] Because in other studies complication rates range from 2 to 5% a year,[3 6 7] it can probably be presumed from the available reports that the complication rate in NSAID users generally varies from 1.3% to 5%.[2–7]

The relatively low complication rate (1.1%) in our study may be related to our agreement to prescribe prophylactic drugs for high risk patients. Of course it might be argued that the design of our (observational) study has some limitations that are absent in randomised controlled clinical trials. Randomised controlled trials are better than observational studies in certain circumstances—for example, to examine the effects of new drugs. On the other hand, clinical trials are generally performed in a selected group of patients. Therefore, it can always be questioned whether results of randomised, double blind trials can be generalised to clinical (daily) practice. The results of our observational study give insight into the magnitude of NSAID gastropathy in daily practice.

Another drawback of the present study is the limited information on the time frame of drug exposure. Detailed information might be important because, for example, NSAID gastropathy might be different in chronic (daily) NSAID users than in patients who use NSAIDs only if necessary—for example, three to four times a week. To solve the issue about the time frame, one should have exact data on prescription, and, probably more important, about compliance. As in most other studies, we do not have these data: the patients were enrolled if they used NSAIDs, more or less as an intention to treat design.

Although it was advocated that prophylactic drugs should be prescribed in the high risk group, GI events occurred more often in the high risk than in the low risk group (2.1% *v* 0.2%). This does not imply that the strategy to prescribe prophylactic drugs is ineffective, but reflects the increased background risk of GI events in the high risk group. Patients in the high risk group were older and had a history of more ulcers (by definition), and used corticosteroids and cardiovascular drugs more often, which are all well known risk factors for GI events in NSAID users.[3 4] The observation that corticosteroids and cardiovascular drugs were more (and DMARDs less) often used in high risk patients is probably related to their age.

The relatively low frequency of GI events in the low risk group indicates that increasing the prescription of prophylactic drugs in low risk patients will not be cost effective.

It is important to discuss whether it is possible to lower the complication rate further. In the near future, COX-2 selective inhibitors will probably be useful, because early data on efficacy and safety seem promising.[14] However, long term safety of these drugs has to be proved, and their prescription may be limited by costs in certain countries.

It is interesting to divide the events into compliance failure, policy failure, and neither of these. It should be mentioned that the word "failure" does not imply that the event can be fully explained by the particular type of failure. If most GI events are related to policy failures it would be important to spend energy in better implementation of the agreement between the prescribing doctors; on the other hand, if most events are related to compliance, it would be useful to try to improve that. Complications occurred in seven patients who should have been prescribed a prophylactic agent according to the above described consensus (policy failure), and in only one patient could the complication be related to compliance failure, which suggests that improvement of patient compliance is probably not the most useful strategy towards further lowering of the complication rate.

Prophylactic drugs were not prescribed for almost half of the high risk patients. These patients may be regarded as policy failures and an increased rate of GI events could be expected. However, in comparison with patients for whom gastroprotective drugs were adequately prescribed, a lower number of GI events was seen in the group without gastroprotection. This does not prove that gastroprotective drugs are ineffective, but it reflects the

fact that patients treated with gastroprotective drugs have a higher baseline risk for GI events. In comparison with patients for whom gastroprotective drugs have been adequately prescribed, the patients without gastroprotection had previous ulcers and dyspeptic symptoms less often, and were treated with corticosteroids and cardiovascular drugs less frequently.

These findings probably illustrate that rheumatologists can make an adequate selection within the high risk group, based on the above described differences in medical history, dyspeptic symptoms, drug treatment and, also very importantly, their clinical experience as rheumatologists.

It also suggests that extension of prophylactic measures to all high risk patients would lead to only a small decrease in the number of GI events, which is almost certainly not cost effective.

Finally, we compared the data of the 15 patients with GI events with those for 54 NSAID treated, control patients with RA, matched for age and sex . As expected, the percentage of patients with previous ulcers, dyspeptic symptoms, the use of corticosteroids and cardiovascular drugs, including oral anticoagulants, is higher in the group of patients with GI events. We also looked for *H pylori* infection, because the correlation between *H pylori* infection and peptic ulcers in non-NSAID users has been proved.[15] So far, the role of *H pylori* in NSAID users is far from clear, because data on interaction of *H pylori* and NSAIDs are conflicting.[16 17] We found a higher incidence of *H pylori* infection in patients with a GI event, though the difference was not significant (67% *v* 50%). In our opinion, additional data on the relation between *H pylori* and ulcers in NSAID users are urgently needed.

In summary, we found a relatively low incidence of clinically manifest ulcers (1%) and complications of ulcers (1.1%) in NSAID treated high risk patients with RA, defined as age above 60 or a previous ulcer, or both. In our opinion, this may be, at least partly, related to our strategy of prescribing prophylactic drugs for high risk patients. It was shown that further lowering of the incidence of GI events—for example, by prescribing gastroprotective drugs for patients with low(er) baseline risk, with the currently available gastroprotective drugs and current knowledge of risk factors, will probably not be cost effective. Other strategies for (further) lowering of the complication rate are discussed: eradication of *H pylori* is one of the possibilities, which needs to be investigated further.

This study was financially supported by a grant from Astra.

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