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COST EFFECTIVENESS OF REPLACING DICLOFENAC WITH A FIXED COMBINATION OF MISOPROSTOL AND DICLOFENAC IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective. **To estimate the costs and health consequences of replacing treatment with diclofenac 50 mg with a fixed combination of diclofenac 50 mg and misoprostol 0.2 mg 3 times a day in patients with rheumatoid arthritis (RA).**

Methods. **A decision tree was developed to simulate 6 months of nonsteroidal antiinflammatory drug (NSAID) treatment for RA. The probabilities of the clinical outcomes were based on a literature review. A survey of Norwegian rheumatologists was undertaken to explore their clinical management of dyspepsia in RA patients taking NSAIDs. Valuation of health states was based on results of the Short Form 36 health survey.**

Results. **In female RA patients without any risk factors associated with serious gastrointestinal (GI) complications, the incremental cost of replacing diclofenac with the fixed misoprostol/diclofenac combination therapy was $72,700 per quality-adjusted life-year gained. For patients with 1 risk factor, the cost was less than $16,000. With 2 or 3 risk factors, the use of misoprostol was cost saving. The cost-effectiveness ratios in males were ~20% higher than in females.**

Conclusion. **Replacing diclofenac with a fixed diclofenac/misoprostol combination is cost effective when restricted to RA patients at increased risk of serious GI events.**

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Nonsteroidal antiinflammatory drugs (NSAIDs) are in widespread use, but can cause peptic ulcers and gastrointestinal (GI) bleeding and perforation (1–3). The risk of such complications in rheumatoid arthritis (RA) patients taking NSAIDs may be 6 times that in RA patients not taking NSAIDs (4). According to Fries, the annual risk of death or hospitalization due to upper GI disease is 1.3–1.6% in RA patients taking NSAIDs, while the rate may be as high as 4–5% in certain high-risk groups (5).

Misoprostol is a synthetic prostaglandin analog that when taken along with NSAIDs, is shown to reduce the occurrence of endoscopically proven gastric and duodenal ulcers (6–11). However, the use of misoprostol is itself associated with minor GI symptoms, foremost of which are diarrhea and abdominal pain (6–10,12–14). This somewhat limits the usefulness of this drug. Additional costs, which should to be justified by its *net* health benefits, are also incurred. The many economic analyses addressing this issue vary widely in their conclusions (15–22), mainly because the investigators have different assumptions about the risk of upper GI complications among persons who take NSAIDs (23). The uncertainty about this risk stems from the design of the first major randomized trial that used *endoscopically* detected ulcer as the end point (6). Since a considerable proportion of upper GI ulcers are asymptomatic (24–27), the *clinical* benefit of misoprostol remained unresolved.

In a later study by Silverstein and coworkers (12) (the Misoprostol Ulcer Complications Outcome Safety Assessment [MUCOSA] trial), a significant reduction in the occurrence of gastric bleeding and perforation in RA patients taking NSAIDs was shown. Whether society ought to fund the use of misoprostol will depend on the *net* costs and benefits of using it, however. The side effects detract from the health benefit of reduced ulcer

risk and may call for diagnostic scrutiny. A crucial factor in the analysis may therefore be the clinical management of dyspepsia.

In the present study, we combined the results of various clinical trials, data on costs, and data on quality of life with information about the management of patients taking NSAIDs. Our aims were 1) to compare the cost effectiveness of 6 months of treatment with a fixed combination of diclofenac 50 mg and misoprostol 0.2 mg 3 times a day with that of diclofenac alone in a population similar to that in the MUCOSA study, 2) to examine the cost effectiveness of the same drug regimen in patients with lower or higher risk of serious GI events compared with those of the MUCOSA population, and 3) to examine the cost effectiveness of replacing NSAIDs other than diclofenac with the fixed misoprostol/diclofenac combination or adding misoprostol in separate tablets to diclofenac or other NSAIDs.

PATIENTS AND METHODS

The model. A deterministic decision-analysis model incorporating the relevant decisions and outcomes was developed using Data software version 3.0 (28). In Figure 1, square boxes represent decisions, circles represent chance nodes, and triangles represent end points. In 1 main branch of the decision tree, the patient received the fixed misoprostol/diclofenac combination, while in the other, diclofenac alone. The structure of the 2 main branches was identical, but the probabilities and pay-offs were not. Possible events were relief of rheumatic symptoms ("well"), dyspepsia, other side effects (abdominal cramping, diarrhea, etc.) with or without withdrawal of the medication, and GI bleeding or perforation with a risk of immediate death (Figure 1). The patient was followed up for 180 days. A societal perspective was adopted (i.e., all costs and all benefits were included).

Management of dyspepsia in NSAID-treated patients. Taking into account the wide variation in medical practice (29), we modeled dyspepsia management as a stochastic process. Opinions on the clinical management of dyspepsia in NSAID-treated patients were obtained from a mail survey of the members (n = 135) of the Norwegian Society of Rheumatology (67% response rate). The respondents were presented with 3 scenarios (low, medium, and high risk of ulcer complications) of RA patients who develop dyspepsia during treatment with either diclofenac or a combination of diclofenac and misoprostol. The physicians were asked to choose between the following actions: 1) discontinue current NSAID medication (yes/no), 2) start additional medication (yes/no), and 3) refer for gastroscopy (yes/no). The responses (Table 1) were subsequently used in the decision model (Figure 1).

Costing. Treatment costs were based on utilization of various types of health services and their unit costs (Table 2). The cost of inpatient care (GI bleeding and perforation) was

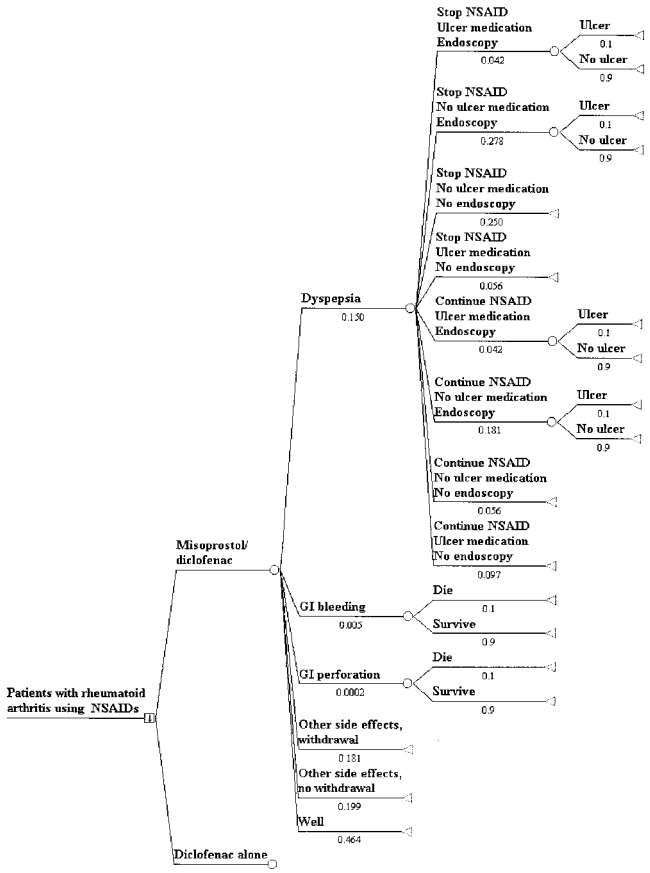

Figure 1. Structure of the decision tree using the responses shown in Table 1. Square boxes represent decisions, circles represent chance nodes, and triangles represent end points. NSAIDs = nonsteroidal antiinflammatory drugs; GI = gastrointestinal.

based on diagnosis-related group charges (30,31), while the costs of physician visits, endoscopy, and laboratory tests were assigned according to the fee schedules for medical services (32,33).

Market prices were used for pharmaceuticals (Table 2). The incremental cost of the misoprostol/diclofenac combination compared with diclofenac alone was $0.67 (Table 2). The use of ulcer medication was set according to treatment guidelines (34), assuming that omeprazole is most frequently used. All costs were measured in 1996 Norwegian Crowns ($1 = NOK7) and have been converted to 1996 United States dollars for this report.

Probabilities. In this analysis, dyspepsia means symptoms from the upper GI tract that are consistent with an ulcer (i.e., *not* diarrhea or abdominal cramping). Here, we used data from the MUCOSA study (12) (Table 3), and for the sensitivity analyses, we adopted extreme low or high values (lower bound and upper bound, respectively) from other trials (6,7,13,35). Withdrawal rates vary considerably across the studies (7,8,12,36,37). The rates from the MUCOSA study were adopted because they reflect medication withdrawal during a relatively long period of use (Table 3). Additionally, since the

Table 1. Management of RA patients taking NSAIDs who develop dyspepsia, by physician's choice of strategy*

Strategy	Misoprostol plus diclofenac			Diclofenac alone		
	Scenario 1	Scenario 2	Scenario 3	Scenario 1	Scenario 2	Scenario 3
Discontinue NSAID						
Start ulcer medication; perform endoscopy	4.2	0.0	27.1	7.4	0.0	41.9
Start ulcer medication; no endoscopy	5.6	4.3	1.7	11.1	6.6	0.0
No ulcer medication; perform endoscopy	27.8	18.6	52.5	22.2	13.2	43.5
No ulcer medication; no endoscopy	25.0	52.9	5.1	29.6	55.3	4.8
Continue NSAID						
Start ulcer medication; perform endoscopy	4.2	4.3	5.1	9.9	5.3	4.8
Start ulcer medication; no endoscopy	9.7	8.6	3.4	16.0	15.8	3.2
No ulcer medication; perform endoscopy	18.1	7.1	5.1	3.7	3.9	1.6
No ulcer medication; no endoscopy	5.6	4.3	0.0	0.0	0.0	0.0

* Opinions on the clinical management of dyspepsia in rheumatoid arthritis (RA) patients taking nonsteroidal antiinflammatory drugs (NSAIDs) were obtained from a mail survey of the members (n = 135) of the Norwegian Society of Rheumatology (67% response rate). The respondents were presented with 3 scenarios representing low (scenario 2), medium (scenario 1), and high (scenario 3) risk of ulcer complications in RA patients developing dyspepsia during treatment with either diclofenac or a combination of diclofenac and misoprostol. Scenario 1 was a 67-year-old woman with moderate RA who had no risk factors associated with gastrointestinal (GI) complications; scenario 2 was a 52-year-old woman with mild RA who had no risk factors associated with GI complications; and scenario 3 was a 79-year-old woman with severe RA who was taking prednisolone 5 mg/day and had previously had a bleeding gastric ulcer. Physicians were asked to choose between the following actions: discontinue current NSAIDs (yes/no), start additional medication for ulcer (yes/no), and refer for gastroscopy (yes/no). Values are percentages.

design of this study was of high-quality scoring, 4 of 5 on the Jadad scale, the reported rates would be expected to be accurate.

The rate of detected ulcers depends on referrals for endoscopy among patients with dyspepsia. Among patients taking diclofenac, 28% of those with dyspepsia had ulcer at endoscopy (Searle: data on file). A study of diclofenac versus diclofenac/misoprostol (8) showed a 64% reduction in the prevalence of ulcer. Assuming similar reductions among patients with dyspepsia, 10% of patients with dyspepsia who are taking misoprostol will have an ulcer.

The fatality rate for patients with GI bleeding or perforation varies from 3% to 33% across various studies (12,38–46). Our study population was at increased risk because the patients were relatively old and had RA. The MUCOSA study was not designed to study fatality rates, but the observed rate (3%) was lower than that of most other studies. We chose to assume a 10% fatality rate for those with upper GI bleeding or gastric perforation (Table 3), which is lower than the 19% observed in the Arthritis, Rheumatism, and Aging Medical Information System database (47). We used extreme estimates from other studies in the sensitivity analyses.

In the MUCOSA study, 53% in the misoprostol group and 46% in the control group reported moderate or severe side effects (including dyspepsia), while the rates of *any* event were 74% and 67%, respectively (Searle: data on file). The latter rates were applied in the sensitivity analyses. Age ≥75 years, a history of GI bleeding, a history of peptic ulcer disease, and a history of heart disease were identified as risk factors for developing bleeding or perforation in the MUCOSA study (12). Based on the prevalence of these factors and their relative effect, the estimated risk of serious events in an RA population without any risk factors present would be ~47% lower than in the MUCOSA population. Table 4 shows the occurrence of events relative to this population, assuming additive as well as multiplicative effects of the risk factors. Conservatively, we used the additive risk estimates in the cost-effectiveness model.

Health states (quality of life). Quality of life weights were first estimated for RA patients who tolerate the medication well, and then secondly for other patient groups, by

Table 2. Unit costs (in dollars) based on utilization of various types of health services*

Type of cost	Type of valuation (ref.)	Cost (lower and upper bound)
Inpatient care for upper GI surgery	DRG (31)	17,338 (13,870–20,805)
Inpatient care for upper GI bleeding	DRG (31)	3,620 (2,896–4,344)
Physician visit	Physician fee schedule (32)	44 (33–51)
Daily cost of ulcer medication	Market price	3.60 (2.60–5.70)
Daily cost of diclofenac	Market price	1.12
Daily cost of misoprostol + diclofenac	Market price	1.79 (1.79–2.90)
Cost of endoscopy (gastroscopy)	Outpatient clinic fee schedule (33)	150 (97–180†)

* GI = gastrointestinal; DRG = diagnosis-related group.
† Base case estimate plus 20%.

Table 3. Probabilities used in the decision tree*

Variable	Base case (lower and upper bound)		Ref.
	Misoprostol plus diclofenac	Diclofenac alone	
Dyspepsia	0.15 (0.083–0.23)	0.13 (0.044–0.19)	7, 12, 13
Ulcer in patients with dyspepsia	0.10 (0.047–0.137)	0.28 (0.13–0.38)	Searle, data on file
GI bleeding	0.00545 (0.00436†–0.00750)	0.00720 (0.00577†–0.01149)	12
GI perforation	0.000227 (0.000182†–0.000272†)	0.00225 (0.0018†–0.0027†)	12
Fatality from GI bleeding	0.10 (0.03–0.33)	0.10 (0.03–0.33)	39, 40, 45
Fatality from GI perforation	0.10 (0.07–0.33)	0.10 (0.07–0.33)	39–41
Withdrawal from therapy	0.275 (0.10–0.324)	0.202 (0.10–0.242)	7, 12
Any side effect	0.53 (0.42†–0.74)	0.46 (0.37†–0.67)	12

* In this analysis, dyspepsia means symptoms in the upper gastrointestinal (GI) tract consistent with ulcer (i.e., *not* diarrhea or abdominal cramping).
† Base case estimate ± 20%.

subtracting the losses incurred by the different events. Estimates for the first group was based on a survey of ~1,600 RA patients in Oslo, Norway (48). Based on these data and guidelines developed at the National Institute of Public Health of Norway (49), a value of 0.94 was assigned to RA patients who tolerate the medication well (Table 5). The guidelines reflect the person trade-offs that members of society wish to make between health care outcomes (50–52).

Patients surviving a GI bleed will be weak and bedridden due to the blood loss, and patients with GI perforation are usually more ill, and emergency surgery may be undertaken on vital indication, justifying a greater health status reduction. Values were set at 0.6 and 0.5, respectively (0.34 and 0.44 below those who are well).

All other events imply much smaller health state reductions. We assigned values such that the difference between the states would reflect trade-offs in choosing between curing the various disease states in a traditional "person trade-off" manner (53). Patients withdrawing from NSAID treatment usually develop increasing pain or stiffness. We assumed that the additional suffering because of withdrawal of NSAIDs was markedly smaller (0.02) than the suffering from the RA itself (0.06).

For dyspepsia, we assumed a 0.01 reduction and a somewhat greater reduction in the presence of ulcer (0.03). Diarrhea and abdominal pain are usually mild to moderate, and a 0.01 reduction was assumed. In the sensitivity analyses, we used 0.005 as the lower bound and 0.02 as the upper bound for the reductions.

Durations. The estimation of drug costs and of health consequences was partly based on the duration of various conditions. In the MUCOSA study, GI bleeding and perforations were evenly distributed across the study period, and time until onset of such complications was set at 90 days. The median duration from the start of medication until the onset of side effects is 2–3 days, while the median duration of side effects is 2 days (54). Dyspepsia is likely to occur within 4 weeks of beginning NSAID/misoprostol medication (41).

In line with guidelines for the treatment of ulcers, we assumed 4 weeks of medication for the treatment of ulcers, while 2 and 8 weeks were chosen as the upper and lower limits.

The increased mortality rates observed in RA (55–59) are likely to vary with the severity of the disease. In the MUCOSA study, the mean age was 72 years among patients

Table 4. Risk of complications relative to the MUCOSA population (12), by presence of risk factors*

Risk factor present	Additive model	Multiplicative model
None	0.53	0.60
MUCOSA population	1.00	1.00
CHD	0.98	0.98
History of peptic ulcer	1.21	1.21
Age ≥75 years	1.31	1.31
History of GI bleeding	1.36	1.36
Peptic ulcer and CHD	2.19	2.23
Age and CHD	2.29	2.42
Age and peptic ulcer	2.53	3.00
Age and GI bleeding	2.67	3.36
All risk factors	4.90	16.02

* In an additive model, the risk of complications in the presence of ≥2 risk factors is the sum of the risk associated with each factor. In a multiplicative model, the individual risks are multiplied. MUCOSA = Misoprostol Ulcer Complications Outcome Safety Assessment trial; CHD = coronary heart disease; GI = gastrointestinal.

Table 5. Reduction in health states (quality of life), by specific event*

QOL loss due to	Base case (lower and upper bound)
RA that is well treated	0.06† (0.048‡–0.072‡)
GI bleeding	0.34 (0.28‡–0.40‡)
GI perforation	0.44 (0.35‡–0.53‡)
Dyspepsia	0.01 (0.005–0.03)
Ulcer	0.03 (0.005–0.05)
Withdrawn NSAID treatment	0.02 (0.005–0.04)
Diarrhea or abdominal pain	0.01 (0.005–0.03)

* QOL = quality of life; RA = rheumatoid arthritis; GI = gastrointestinal; NSAID = nonsteroidal antiinflammatory drug.
† Defining perfect health by convention as 1.00, QOL for patients with RA is 0.94 (1.00–0.06).
‡ Base case ± 20%.

Table 6. Cost (in dollars) per gained life-year and per gained QALY, by the presence of risk factors associated with GI complications and by sex*

Patient group	Cost per life-year gained		Cost per QALY gained	
	Males	Females	Males	Females
RA, risk of GI complications as in the MUCOSA population	13,700	11,800	18,100	15,100
RA, no risk factors	45,900	39,400	95,900	72,700
RA and coronary heart disease	14,400	12,400	19,300	16,000
RA and a history of peptic ulcer	7,400	6,300	9,100	7,700
RA and age ≥75 years	7,000	5,800	8,900	7,100
RA and a history of GI bleeding	4,100	3,500	4,900	4,100
RA and ≥2 risk factors	Cost saving	Cost saving	Cost saving	Cost saving

* QALY = quality-adjusted life-year; GI = gastrointestinal; RA = rheumatoid arthritis; MUCOSA = Misoprostol Ulcer Complications Outcome Safety Assessment trial.

with serious upper GI complications (Searle: data on file). When estimating life-year gains from avoiding such potentially fatal complications, we used Norwegian life tables but increased the annual mortality rates by 5% (zero and 10% in sensitivity analyses) to account for the presence of RA. This implies life expectancies of 7.6 years for males and 9.2 years for females, respectively, and 5.4 and 6.3 when discounted at 5%.

Sensitivity analyses. Sensitivity analyses were undertaken to explore to what extent the results were sensitive to changes in the assumptions upon which they were based. The lower and upper bounds for the parameters were taken from various studies (see Tables 1–5). When we had no empirical studies, the bounds were set 20% under and over the base case value.

Further details of the model and the parameter estimates, as well as details from the MUCOSA study, are presented in a technical report that can be obtained from the University of Southern Denmark World Wide Web site (http://www.sam.sdu.dk/dept/chs/RESEARCH/Index.htm) or from the authors.

RESULTS

Costs, health consequences, and cost effectiveness. For a female patient group with a risk of GI complications similar to that in the MUCOSA study (some patients having risk factors, some not), the expected (average) cost per patient prescribed the fixed diclofenac/misoprostol combination was $327, while it was $298 for diclofenac alone. Replacing diclofenac with the fixed combination generated gains of 0.0016 quality-adjusted life-years (QALYs) in males and 0.0019 QALYs in females, and 0.0021 and 0.0025 life-years, respectively.

The estimated 6-month mortality rate among those taking misoprostol/diclofenac was 0.057%, while it was 0.095% for those taking diclofenac alone. According to the base case probabilities, the prescription of misoprostol to 10,000 patients would mean, on the one hand, the saving of 4 lives and the prevention of severe episodes of bleeding and perforation in 15 and 19 patients, respectively. On the other hand, it would mean some additional discomfort (dyspepsia, diarrhea, and lower abdominal cramping) in 454 of the 10,000 patients.

The incremental cost of replacing diclofenac with the fixed misoprostol/diclofenac combination was $13,700 per life-year saved and $18,100 per QALY gained in males, and $11,800 and $15,100, respectively, in females (Table 6). In the following, most cost-effectiveness ratios will be presented for women only because RA is more prevalent in women. The ratios for men are ~20% higher because of their shorter life expectancy.

For a group of female patients without any risk factors for GI complications, the estimated cost per QALY was $73,700 (Table 7). While the cost effectiveness in patients with heart disease was about the same as that for the average MUCOSA patient, the cost per QALY was $4,100 in female patients with a history of GI bleeding (Table 6). In both male and female patients with a risk of complications that was more than ~1.6 times the risk in the MUCOSA population, i.e., ≥2 risk factors present, the use of the fixed misoprostol/diclofenac regimen was cost saving (Table 6). Despite the shorter life expectancy in individuals >80 years, the use of misoprostol was slightly more cost effective than in younger patients because of the higher risk of complications.

The cheaper the "NSAID-alone tablet," the higher the cost of replacing it with the fixed combination tablet. If the fixed misoprostol/diclofenac combination were replacing the least expensive NSAID on the Norwegian market, the incremental cost of the fixed combination would be $66,600 per QALY, while it would be $4,900 if it replaced the most expensive NSAID (risk of

Table 7. Sensitivity analysis for cost (in dollars) per gained life-year and gained QALY in female RA patients, according to different assumptions*

Variable	Range of the variable		Cost per QALY gained		Cost per life-year gained	
	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Cost, in dollars						
Inpatient care for GI complications						
Without surgery	13,870	20,805	19,300	10,800	15,100	8,500
With surgery	2,896	4,344	15,600	14,600	12,200	11,400
Physician visit	33	51	14,800	15,300	11,600	11,900
Ulcer medication	2.60	5.70	15,700	13,700	12,300	10,700
Endoscopy	97	180	14,700	15,300	11,400	12,000
Probability						
Dyspepsia						
Misoprostol + diclofenac	0.083	0.23	8,900	21,900	46,700	125,000
Diclofenac	0.044	0.19	23,500	8,800	19,000	6,700
Ulcer						
Misoprostol + diclofenac	0.047	0.137	14,600	15,400	11,500	12,000
Diclofenac	0.13	0.38	16,200	14,400	12,700	11,300
Bleeding						
Misoprostol + diclofenac	0.00436	0.00750	8,300	72,600	6,900	37,800
Diclofenac	0.00577	0.01149	38,900	70	25,200	57
Perforation						
Misoprostol + diclofenac	0.000182	0.000272	14,400	15,900	11,300	12,200
Diclofenac	0.0018	0.0027	23,100	9,400	17,000	7,600
Dying						
From bleeding	0.03	0.33	25,900	5,500	18,300	4,800
From perforation	0.07	0.33	18,600	6,100	14,000	5,300
Any side effect						
Misoprostol + diclofenac	0.42	0.74	12,500	20,000	9,800	15,500
Diclofenac	0.37	0.67	17,200	10,200	13,400	8,000
Quality of life						
Survive bleeding	0.28	0.40	15,200	15,000	–	–
Survive perforation	0.35	0.53	15,400	14,800	–	–
Experience dyspepsia	0.005	0.03	14,800	16,300	–	–
Experience ulcer	0.005	0.05	15,900	14,500	–	–
Well	0.928	0.952	15,300	14,900	–	–
Any side effect	0.005	0.03	15,100	15,100	–	–
Duration						
Life expectancy of females	4.7 years	8.8 years	21,300	10,200	15,500	8,400

* QALY = quality-adjusted life-year; RA = rheumatoid arthritis; GI = gastrointestinal.

GI complications as in the MUCOSA study). The cost per QALY for adding misoprostol in *separate* tablets to any NSAID would be $93,900.

Results of sensitivity analyses. The consequences of changing the assumptions upon which the analysis was based are shown in Table 7 and Figure 2. Uncertainty with respect to some of variables (e.g., probability of dyspepsia and other side effects, probability of GI complications, mortality from complications, life expectancy) had a considerable influence on the results. For example, changing the probability of dyspepsia when using misoprostol from the lowest estimate to the highest estimate would change the cost per QALY from $8,900 to $21,900. As shown above, the risk of GI complications and the incremental cost of misoprostol are most crucial for the outcome of the analyses. For the majority of the parameters, including the life quality estimates, uncertainties were of limited importance. However, if an NSAID has the same arthritis effectiveness as diclofenac, but only half the risk of bleeding and perforation, then that drug would have lower costs and greater net benefits than the fixed misoprostol/diclofenac combination.

DISCUSSION

The results of this study indicate that the cost of using the fixed misoprostol/diclofenac combination is almost $100,000 per QALY in RA patients at minimal risk of GI complications, while it is lower than $20,000 or is even cost saving in high-risk groups. Several earlier studies concluded that misoprostol is generally cost

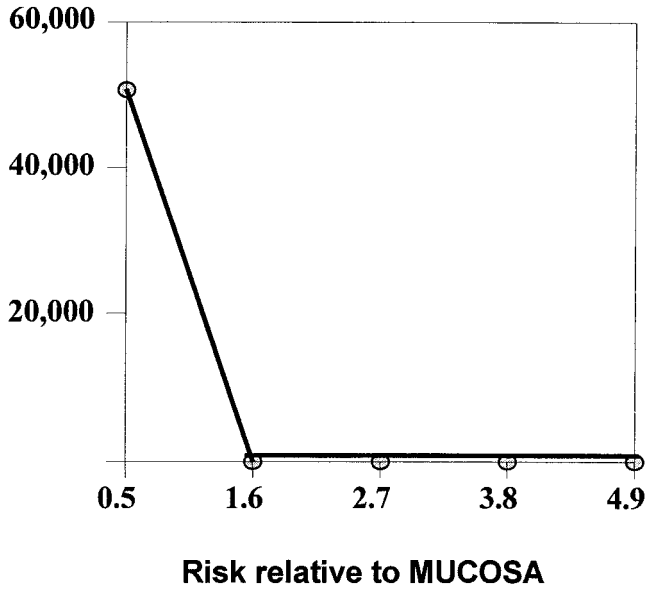

Figure 2. Sensitivity analysis. Cost (in dollars) per quality-adjusted life-year by risk of serious complications relative to the Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) population.

saving (i.e., incurs lower net costs *and* greater health benefits than not using misoprostol) (17–20). In contrast, Edelson et al (16) assumed that a small fraction of ulcers are symptomatic and concluded that misoprostol represents a costly prevention of NSAID complications. Variation in assumptions about clinical ulcers is likely to explain the divergence (23). While ulcers can be endoscopically detected in a considerable proportion of patients taking NSAIDs (7,8), the MUCOSA study indicates that the majority of such ulcers are asymptomatic. Therefore, the health benefit of using misoprostol ought to be based on clinical, rather than endoscopic, end points, as presented in a recent publication reporting the cost per avoided GI complication (22). Our study brings the issue one step further by presenting the cost per QALY, thus making comparisons with competing health care programs easier.

The cost effectiveness of misoprostol depends heavily on the risk of serious GI complications. A 6-month risk of 0.95% as observed in the MUCOSA study (12) is somewhat higher than the 0.65% (1.3% during 1 year) observed by Fries (5). Differences in the presence of risk factors may explain this discrepancy. We used age ≥75 years and a history of peptic ulcer, GI bleeding, and/or cardiac disease as risk factors (12). In a study by Fries et al (38), similar risk factors were identified, as well as the concomitant use of corticosteroids, higher doses of NSAIDs, and increased disability. It seems reasonable to assume that, for example, age, cardiac disease, and disability are not causal factors, but rather are variables that are associated with biologic phenomena that lead to serious GI complications. While corticosteroid use apparently was not a risk factor in the MUCOSA study (12), this does not mean that such medication is "safe." Therefore, risk factors other than those detected in the MUCOSA study may be relevant when physicians are targeting patients for GI prophylaxis.

The occurrence of minor side effects (abdominal pain, etc.) from diclofenac or misoprostol/diclofenac treatment varies considerably across studies. This variation is likely to be due to the length of the study period, the type of patients included in the trials, and the way reports of side effects were elicited and recorded. The dyspepsia rates in the MUCOSA study were higher than those in several other studies whether the patients received misoprostol or not. By using the MUCOSA data, we avoided bias in favor of misoprostol.

We report the cost effectiveness of using misoprostol 0.2 mg 3 times daily. In the MUCOSA study, patients were advised to take 0.2 mg *4* times daily, while in practice, the mean daily dose was reported to be 0.6 mg (12). In a study of the dose-response relationship of misoprostol, Raskin et al (36) found that misoprostol 0.2 mg 3 times a day was equally effective as 0.2 mg 4 times a day in preventing endoscopic gastric ulcers (36). Consequently, it seems justified to adopt effectiveness data from the MUCOSA study even though we assumed a daily dose of 0.2 mg 3 times a day.

Ideally, costs should be based on market prices rather than charges. However, market prices were available for pharmaceuticals only because Norway has a publicly financed health care system, and, unlike in some other countries, physicians and hospitals rarely discount the announced charges.

The quality of life estimates are important because misoprostol induces dyspepsia, abdominal pain, and diarrhea. The weakness of using Short Form 36 scores and guidelines (49) in estimating these effects is that they are to some extent based on judgments rather than on public preference for the health states in our study. The sensitivity analyses, however, indicate that only major changes in the health state assessments will invalidate our conclusions.

Whether the use of misoprostol is warranted is basically a question about the trade-off of additional side effects (~500 in 10,000 misoprostol users) and monetary costs against preventing 4 fatal and 34 nonfatal serious

GI events. Cost-effectiveness analyses aim at assisting such decisions by ranking health care programs according to their cost per unit of health benefit. There is hardly any well-defined limit between programs that are "cost effective" and those that are not. Rather, the use of misoprostol ought to be compared with other, competing programs, for example, antihypertensive and lipid-lowering treatments or coronary bypass surgery. Here, the results will vary considerably (60–64). In general, the use of a fixed misoprostol/diclofenac combination appears to compete favorably when administered in patients at increased risk of GI complications. For patients without any risk factors, the use of the combined treatment is questionable.

In the United States, the unit costs of health care, such as physician visits, endoscopy, and hospital admissions, can be much higher than in Norway. Some of the cost differences will make the use of misoprostol more cost effective than in Norway, some of them will make it less cost effective. On balance, the cost effectiveness is likely to be about the same in the two countries if the price of misoprostol and diclofenac is the same.

The fixed misoprostol/diclofenac combination treatment can replace NSAIDs other than diclofenac. Such replacement will be less cost effective than discussed above if the alternative were less expensive, more effective, or less toxic than diclofenac. In high-risk patients, clinicians may well choose other NSAIDs such as ibuprofen, which has been shown to have lower GI toxicity than diclofenac (65). Assessment of the cost effectiveness of such alternatives faces 2 problems, however. First, clinical data to support an alternative analysis are scarce, and second, it is difficult to define toxicity in relation to equipotent doses. As indicated in the sensitivity analysis, the results of this study would be very different if there were an NSAID with the same arthritis effectiveness as diclofenac, but with much lower toxicity.

The incremental cost of misoprostol is much higher when prescribed as individual tablets than as combination tablets. For such prescriptions, misoprostol is not cost effective unless it is prescribed in patients who have 2 or more risk factors.

We do not have the proper data to estimate the cost effectiveness of misoprostol in osteoarthritis patients. However, the MUCOSA population was composed of patients with overall mild disease, in that most patients were seronegative and the average Health Assessment Questionnaire score was favorable (12). The cost effectiveness in osteoarthritis patients may not necessarily be very different from our results in RA patients.

The choice of treatment for patients at high risk of GI complications is challenging for clinicians. In addition to diclofenac/misoprostol, other antiinflammatory therapeutic options may be considered, among which are ibuprofen, nonacetylated salicylic acid, low-dose corticosteroids in RA, and acetaminophen in osteoarthritis. In the near future, specific cyclooxygenase 2 inhibitors with lower GI toxicity but higher price will be available (66). Before this new class of drugs is widely adopted, their cost effectiveness ought to be determined. This, however, will require data about the impact on rheumatic symptoms as well as about *clinical* GI side effects.

We conclude that the cost effectiveness of misoprostol depends heavily on the risk of GI complications, the cost of misoprostol/diclofenac compared with diclofenac alone, as well as on the cost, effectiveness, and toxicity of alternative drugs. In high-risk patients, the fixed misoprostol and diclofenac combination appears to be cost effective or even cost saving.

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