

COX-2

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=Abstract=

Korean cost-effectiveness analysis of NSAIDs, NSAIDs with co-treatments to prevent gastrointestinal toxicity, and COX-2 specific inhibitors in the treatment of rheumatoid arthritis

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Background : Nonsteroidal anti-inflammatory drugs (NSAIDs) are used in nearly every patient with rheumatoid arthritis (RA) but their use can be associated with gastrointestinal (GI) side effects, which may be prevented with prophylactic prescription of misoprostol and omeprazole. Recently marketed COX-2 specific inhibitor (COX-2) affords protection against gastropathy. This study was performed to assess Korean cost-effectiveness of NSAIDs, NSAIDs with co-treatments to prevent GI toxicity, and COX-2 in the treatment of RA, and compare it with American cost-effectiveness analysis.

Methods : Markov (state-transition) models were used to simulate a cohort of RA patients with approximately 2.5:1 female to male ratio and 50 years, taking disease modifying antirheumatic drugs, low dose steroid (prednisone 10 mg/day) and one of the following strategies: 1) NSAIDs without prophylaxis, 2) NSAIDs with misoprostol, 3) NSAIDs with proton pump inhibitor (PPI), or 4) COX-2. Data on incidence, USA cost and consequences of adverse events from treatments were taken from the literature. Treatment costs of adverse events in Korea were calculated based on each disease code. Health effects were expressed as quality-adjusted life years (QALYs). Sensitivity analyses of probability of GI complication and cost were performed. Costs and health outcomes were discounted at a rate of 3% per year.

Results : Among the strategies to prevent GI toxicity, PPI was the most cost-effective strategy in Korea and COX-2 was in USA, respectively. The incremental C/E (cost/effectiveness) ratio between PPI and no prophylaxis was 38,068 × 10³ ₩/ QALY (32,044\$/QALY) in Korea. The incremental

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C/E ratio between COX-2 and no prophylaxis was 53,228\$/QALY in USA. The base case analysis results were sensitive to cost of NSAIDs and COX-2 in Korea, and cost of NSAIDs in USA, respectively, and adverse event rates of NSAIDs, misoprostol, and PPI in Korea. The medical cost of NSAID side effects in Korea is 11% of USA, but the sensitivity analyses varying medical costs were robust. The sensitivity analyses using age, discount rate and utility were robust.

Conclusions : Although PPI in Korea and COX-2 in USA are the best option among the strategies to prevent GI toxicity, the incremental C/E ratios between PPI versus no prophylaxis in Korea and COX-2 versus no prophylaxis in USA are over 30,000 and 50,000\$/QALY, respectively. However, it appears that the prescription of COX-2 in the group of higher cost NSAIDs users in Korea was the best option.(Korean J Med 60:574- 588, 2001)

Key Words : Cost-effectiveness Analysis; NSAIDs; Misoprostol, PPI;, Cox-2; Arthritis, Rheumatoid

1-2% (14-17)

가 가 PG analogue misoprostol¹⁸⁻²⁵⁾ proton pump inhibitor (PPI) omeprazole (OMP)²⁶⁻²⁸⁾

cyclooxygenase (COX) arachidonic acid prostaglandin (PG) COX (PGE2, PGI2), (PGI2, thromboxane A2), COX-2 COX-2 (PGF2), (dyspepsia), (PGE2), (PGD2) 가 COX isoenzyme COX-1 COX-2가 PG³⁻⁶⁾ COX-1 COX-2 가²⁹⁻³²⁾ COX-2 COX-1 COX-2 가 PG 가 가⁷⁻¹³⁾ 가 PG misoprostol^{21-23, 25)} 15-30%

3 : COX-2

Table 1. Base case probabilities of adverse events

Markov states	Annual Probabilities	Probabilities
Dyspepsia	0.29 ⁴⁰⁾	
Serious GI* complication		
A. NSAID	0.0190 ¹⁸⁾	
B. NSAID + Misoprostol	0.0118 ¹⁸⁾	
C. NSAID + PPI †	0.0053 ²⁴⁾	
D. COX-2	0.0020 ³⁰⁾	
Post-GI complication	Serious GI complication rate x 1.48	
Admission due to GI complication		0.67 ²³⁾
Surgery among admission		0.39 ²³⁾
GI complication death among admission		0.12 ⁷⁾
Acute hepatic failure	0.00005 ^{8, 47)}	
Acute renal failure	0.00006 ¹⁰⁾	

* GI; gastrointestinal, † PPI; proton pump inhibitor

Table 2. Cost estimates

	Korea		USA	Korea/USA ratio
	× 10 ³ Won	US dollars*	1999 US dollars	
RA treatment/year	942	793	1,988 ⁴⁸⁻⁵⁰⁾	0.40
NSAID/year	250 ¹⁾	210	820 ³⁸⁾	0.26
Misoprostol (400 µg/day)/year	246 ¹⁾	207	656 ³⁸⁾	0.32
PPI† (20 mg/day)/year	471 ¹⁾	396	1,232 ³⁸⁾	0.32
COX-2 (celecoxib 400mg/day, rofecoxib 50mg/day)/year	1,027 ¹⁾	864	1,767 ³⁸⁾	0.49
Dyspepsia/event	11	9	74 ⁶⁾	0.12
Outpatient visit/care due to GI complication/event	95	80	328 ⁶⁾	0.24
Inpatient medical treatment due to GI complication/event	745	627	6,233 ⁶⁾	0.10
Inpatient surgical treatment due to GI complication/event	3,102	2,611	29,606 ⁶⁾	0.09
Acute hepatic failure/event	1,054	887	13,205 ⁵¹⁾	0.07
Acute renal failure/event	3,945	3,321	17,5105 ²⁾	0.19

* Korean Won : US dollar = 1,188:1²⁾, † PPI; proton pump inhibitor

2000 3 5
 50
 가
 , 가
 , 3 2 , ,
 가 30% 가 4
 (Table 2). 2000 3 7

가

1)

Consumer Price Index³⁷⁾ 0.019²⁰⁾,
 1999 US , 0.028³⁰⁾, 0.29⁴⁰⁾ . Miso-
 , 1999 Red Book³⁸⁾ 가 ,
 가 (Table 2). Misoprostol
 가 400g ,
 , 11 Silverstein the Misoprostol Ulcer Complications
 (aceclofenac: 100 mg bid, talniflumate: 370 mg tid, Outcome Safety Assessment (MUCOSA) study
 etodolac: 200 mg tid, piroxicam: 10 mg bid, ibuprofen: 0.0118²⁰⁾ 246,010
 800 mg tid, nabumetone: 500 mg bid, loxprofen: 60 mg 1¹⁾(207 , 1999 1 1,188
 bid, lonazolac calcium: 200 mg tid, sulindac: 100 mg 2²⁾), 656 38³⁾ . PPI 20
 tid, tiaprofenic acid: 200 mg tid, naproxen: 500 mg bid mg Ekstrm
 per day)¹⁾, 10 Scandinavian Collaborative Ulcer Recurrence
 (ibuprofen: 800 mg tid, naproxen: 500 mg bid, (SCUR) study 0.0053²⁶⁾,
 diclofenac: 75 mg bid, piroxicam: 10mg bid, etodolac: 471,580 1¹⁾(396)²⁾, 1,232 38³⁾
 300 mg bid, sulindac: 150 mg bid, oxaprozin: 600 mg (Table 2).
 bid, ketoprofen: 75 mg bid per day)³⁸⁾ COX-2
 (Table 2), celecoxib . Rofecoxib
 가 가
 (QALYs, quality- 가
 adjusted life years) 400 1,027,110 1¹⁾
 time-trade off standard gamble (864)²⁾, 1,767 38³⁾
 (utility) (Table 3). meta- analysis³²⁾ 0.002 .
 (0.92, 0.65) Misoprostol 가 가
 (0.12)
 가 Health Utility Index II³⁹⁾ , PPI

Table 3. Quality-of-life adjustments

Event	Quality-of-Life Adjustment
<u>No medical problems</u>	
Controlled rheumatoid arthritis	0.92 ³⁹⁾
Uncontrolled rheumatoid arthritis	0.65 ³⁹⁾
<u>Short-term complication</u>	
Dyspepsia	0.79 ^{53, 54)} for 2 weeks
GI complication	
Outpatient	0.79 ⁵³⁾ for 4 weeks
Inpatient	0 for 2 weeks, 0.79 ⁵³⁾ for 2 weeks
Hepatic failure	0 for 2 weeks*
Renal failure	0 for 4 weeks*

*Authors best estimates

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COX-2 49% 가
 가 75% 50% 0.5, 0.6, 0.7, 0.8, 0.9 가
 가
 (discount rate) 3%
 41)
 가 11%
 가 2 9
 3. (sensitivity analysis)
 47가 20 40
 COX-2 - 가 , 0% 9%
 4가 TreeAge Software (3.5), Inc. Decision Analysis Software⁴²⁾
 0.013¹⁶⁾
 0.038, misoprostol 0.007¹⁸⁾ 0.017, PPI
 0.004²⁷⁾ 0.011, COX-2 0.001
 0.009³⁰⁾
 가 47가
 가 가 가 가 가 QALY 11.45, misoprostol
 가 가 가 가 가 11.54, PPI 11.66, COX-2 11.74
 , sulindac (110 × 17,569
 10³ ¹⁾, 92 ²⁾ nabumetone (496 × 10³ ¹⁾, 418 × 10³ ¹⁾(14,789 ²⁾, misoprostol 21,379 × 10³ ¹⁾
²⁾, ibuprofen (86 ³⁸⁾ oxaprozin ((17,996 ²⁾, PPI 25,456 × 10³ ¹⁾(21,428
 1,095 ³⁸⁾)²⁾, COX-2 31,170 × 10³ ¹⁾(26,237
 COX-2)²⁾ (Table 4- 1). 43,921 ,

Table 4-1. Base case analysis, Korea

Strategy	QALY*	Cost		C/E ratio [‡]	
		(× 10 ³ ₩)	(US dollars [†])	(× 10 ³ ₩/QALY)	(\$/QALY)
NSAID	11.45	17,569	14,789	-	-
Misoprostol	11.54	21,379	17,996	Extended dominated	Extended dominated
PPI [§]	11.66	25,456	21,428	38,068	32,044
COX-2	11.74	31,170	26,237	68,930	58,022

* QALY; quality-adjusted life year, † Korean Won : US dollar = 1,188:1²⁾, ‡ C/E ratio: incremental cost/effectiveness ratio, § PPI; proton pump inhibitor

Table 4-2. Base case analysis, USA

Strategy	QALY*	Cost (\$)	C/E ratio [†] (\$/QALY)
NSAID	11.45	43,921	-
Misoprostol	11.54	53,268	Extended dominated
COX-2	11.74	59,361	53,228
PPI [‡]	11.66	63,088	Dominated

* QALY; quality-adjusted life year, † C/E ratio; incremental cost/effectiveness ratio, ‡ PPI; proton pump inhibitor

53,268 , 63,088 , 59,361 (Table 4-2). 가
 , misoprostol (Table 4-1). COX-2
 - 가 PPI misoprostol 가 46,900 × 10³
 - 가 /QALY (39,478 /QALY) .
 (extended dominated). PPI , misoprostol
 - 가 38,068 × 10³ - 가 COX-2
 /QALY (32,044 /QALY) , COX-2 - 가
 PPI - 가 68,930 × 10³ . PPI COX-2
 /QALY (58,022 /QALY) . QALY
 , COX-2 (dominated), COX-2
 PPI 53,228 /QALY - 가

Table 5-1. Sensitivity analysis: probability of GI complication of NSAID, Korea

	QALY*	Cost		C/E ratio [‡]	
		(× 10 ³ ₩)	(US dollar [†])	(× 10 ³ ₩/QALY)	(\$/QALY)
pGI complication [§] of NSAID: 0.013 ¹⁴⁾					
NSAID	11.53	17,635	14,845	-	-
Misoprostol	11.58	21,490	18,089	Extended dominated	Extended dominated
PPI	11.68	25,540	21,498	51,254	43,143
COX-2	11.74	31,170	26,237	88,652	74,623
pGI complication of NSAID: 0.038					
NSAID	11.22	17,406	14,651	-	-
Misoprostol	11.40	21,070	17,736	20,267	17,060
PPI	11.60	25,206	21,217	20,606	17,345
COX-2	11.74	31,170	26,237	41,054	34,557

*QALY; quality-adjusted life year, † Korean Won : US dollars = 1,188:1²⁾, ‡ C/E ratio; incremental cost/effectiveness ratio, § pGI complication; probability of gastrointestinal toxicity, PPI; proton pump inhibitor

Table 5-2. Sensitivity analysis: probability of GI complication of misoprostol co-treatment, Korea

	QALY*	Cost		C/E ratio [‡]	
		(× 10 ³ ₩)	(US dollar [†])	(× 10 ³ ₩/QALY)	(\$/QALY)
pGI complication [§] of misoprostol: 0.007 ¹⁶⁾					
NSAID	11.45	17,569	14,789	-	-
Misoprostol	11.60	21,522	18,117	27,629	23,257
PPI	11.66	25,456	21,428	61,371	51,659
COX-2	11.74	31,170	26,237	68,930	58,022
pGI complication of misoprostol: 0.017					
NSAID	11.45	17,569	14,789	-	-
Misoprostol	11.48	21,235	17,875	Extended dominated	Extended dominated
PPI	11.66	25,456	21,428	38,068	32,044
COX-2	11.74	31,170	26,237	68,930	58,022

*QALY; quality-adjusted life year, † Korean Won : US dollars = 1,188:1²⁾, ‡ C/E ratio; incremental cost/effectiveness ratio, § pGI complication; probability of gastrointestinal toxicity, PPI; proton pump inhibitor

3 : COX-2

COX-2 5-3) misoprostol 가

(Table 4-2). 가 ().

2. , PPI , COX-2 (

0.038 가 (Table 5-1) misoprostol , 11 가 가

0.007 (Table 5-2), sulindac 가 . 가

PPI 0.011 가 (Table 가 nabumetone misoprostol

Table 5-3. Sensitivity analysis: probability of GI complication of PPI co-treatment, Korea

	QALY [†]	Cost		C/E ratio [‡]	
		(× 10 ³ ₩)	(US dollar [†])	(× 10 ³ ₩/QALY)	(\$/QALY)
pGI complication [§] of PPI: 0.004 ²⁵⁾					
NSAID	11.45	17,569	14,179	-	-
Misoprostol	11.54	21,379	17,996	Extended dominated	Extended dominated
PPI	11.68	25,522	21,483	35,754	30,096
COX-2	11.74	31,170	26,237	83,495	70,282
pGI complication of PPI: 0.011					
NSAID	11.45	17,569	14,789	-	-
Misoprostol	11.54	21,379	17,996	43,861	36,920
PPI	11.59	25,189	21,203	Extended dominated	Extended dominated
COX-2	11.74	31,170	26,237	48,180	40,556

* QALY: quality-adjusted life year; † Korean Won : US dollars = 1,188:1²⁾; ‡ C/E ratio: incremental cost/effectiveness ratio; § pGI complication: probability of gastrointestinal toxicity; PPI: proton pump inhibitor

Table 6. Sensitivity analysis of cost of NSAID, Korea

	QALY [†]	Cost		C/E ratio [‡]	
		(× 10 ³ ₩)	(US dollar [†])	(× 10 ³ ₩/QALY)	(\$/QALY)
Lowest cost of NSAID (sulindac 100 mg tid): 110 × 10 ³ ₩/year ¹⁾					
NSAID	11.45	15,512	13,058	-	-
Misoprostol	11.54	19,257	16,209	Extended dominated	Extended dominated
PPI[§]	11.66	23,196	19,526	38,068	32,044
COX-2	11.74	31,170	26,237	68,930	58,022
Highest cost of NSAID (nabumetone 500 mg bid): 496 × 10 ³ ₩/year ¹⁾					
NSAID	11.45	21,183	17,831	-	-
Misoprostol	11.54	25,109	21,135	Extended dominated	Extended dominated
PPI	11.66	29,428	24,771	Extended dominated	Extended dominated
COX-2	11.74	31,170	26,237	34,427	28,979

* QALY; quality-adjusted life year, † Korean Won : US dollars = 1,188:1²⁾, ‡ C/E ratio; incremental cost/effectiveness ratio, § PPI; proton pump inhibitor

PPI 가 COX-2
 PPI 가 2 9 가
 , COX-2가
 $34,427 \times 10^3$ /QALY (28,979 /QALY) ().
 가 가 (Table 6).
 8 가 가
 ibuprofen misoprostol - ().
 가 PPI , PPI
 51,239
 /QALY - 가 PPI 가 가
 . 가 가 oxaprozin
 가 ().
 COX-2 가
 , 가 0.8 가
 PPI COX-2 , 가
 - 가 , 가
 COX-2 가 가 . COX-2
 가 0.8
 - 가 $34,904 \times 10^3$
 /QALY (29,380 /QALY) COX-2 가
 가 0.9
 (Figure 1).

COX-2 가
 , 가 0.9 가
 - 가 50,000 /QALY 가 ()
).

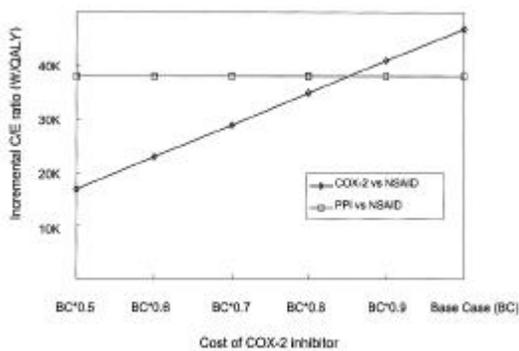


Figure 1. Sensitivity analysis of cost of COX-2 inhibitor, Korea. The sensitivity analysis varying cost of COX-2 inhibitor showed that the incremental cost-effectiveness ratio between COX-2 and NSAID was lower than that of PPI and NSAID when if the cost was less than 0.8 of base case (822103W/year).

misoprostol PPI
 COX-2
¹⁸⁻³¹⁾ Edelson ²¹⁾
 misoprostol (years
 of life saved) 95,600
 misoprostol 40,000
 , Gabriel
²²⁾ misoprostol
 misoprostol
 Kristiansen
 diclofenac 75 mg bid celecoxib 200 mg bid
 36,000\$/QALY - 가
⁵⁵⁾ misoprostol
 - 가
 49,195 /QALY, COX-2
 - 가 53,228 /QALY -

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 가
 가
 가
 PPI
 38,068 × 10³ /QALY (32,044 /QALY)
 가
 25%²⁾
 가 12,500
 /QALY 가 , PPI가 가 가 가
 가
 가 가 가
 가
 COX-2
 가 ^{20, 55)}
 가 COX-2 1 1
 가 가 2 1
 가
 COX-2 가
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 가
 cyclooxygenase (COX)- 1
 , miso-
 , prostol proton pump inhibitor (PPI) , COX-2
 가
 가
 3 COX-2

3 : COX-2

가 , PPI

: Markov (state transition) COX-2 가 QALY가

2.5:1 : 가 50 (dominated). COX-2 53,228 /QALY -

1) , 2) 가 COX-2

, misoprostol , 3) 가 가

PPI , 4) COX-2 4가 COX-2 가 , NSAID,

misoprostol PPI

. Markov state (outcome) , 가

(, , ,), , 11%

1966 가 2 9 가

2000 Medline COX-2

Consumer Price Index : misoprostol

1999 US (QALYs, , PPI , COX-2

Quality-adjusted life years) PPI , COX-2 가

3% , 30,000 50,000\$/ QALY

가 , 가 - 가

가

: 4가 QALY

11.45, misoprostol 11.54, PPI 11.66, 가

COX-2 11.74 . COX-2

$17,569 \times 10^3$ (14,789), miso- . 1 1

prostol $21,379 \times 10^3$ (17,996), PPI COX-2 2

$25,456 \times 10^3$ (21,428), COX-2 31,170 1

$\times 10^3$ (26,237) , 43,921 , 가

53,268 , 63,088 , 59,361 .

, misoprostol

- 가 PPI -

가 (extended

dominated), PPI

- 가 $38,068 \times 10^3$ /QALY (32,044

/QALY), COX-2 PPI -

가 $68,930 \times 10^3$ /QALY (58,022 /QALY)

PPI 가

, misoprostol

- 가 COX-2 -

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