Cost-Effectiveness of Treatment Strategies for Osteoarthritis of the Knee in Taiwan

ZUI-SHEN YEN, MEI-SHU LAI, CHEN-TI WANG, LI-SHU CHEN, SHYR-CHYR CHEN, WEN-JONE CHEN, and SHENG-MOU HOU

ABSTRACT. ***Objective***. To evaluate the cost-effectiveness of 3 treatment strategies for osteoarthritis (OA) of the knee: naproxen, celecoxib, and hyaluronan.

Methods. We developed a decision model to estimate the costs and effectiveness of 3 treatment strategies: 250 mg naproxen 3 times daily for 26 weeks, 100 mg celecoxib twice daily for 26 weeks, and 25 mg hyaluronan by intraarticular injection once per week for 5 weeks followed by conventional treatment for 21 weeks. The probabilities and utility data were obtained by surveying the literature and consulting experts. Cost data were obtained from insurance reimbursement data of National Taiwan University Hospital and were converted to 2002 US dollars. The timeframe of the decision tree was 26 weeks. Outcomes were expressed in aggregated costs, quality-adjusted life-years (QALY), and the incremental cost-effectiveness ratio (ICER). Sensitivity analyses were performed on most variables.

Results. The expected total costs for the naproxen, celecoxib, and hyaluronan strategies were US$498.98, US$547.80, and US$678.00, respectively. The ICER of the celecoxib strategy compared with the naproxen strategy was US$21,226 per QALY gained. The ICER of the hyaluronan strategy versus the celecoxib strategy was US$42,000 per QALY gained. The ICER of the hyaluronan strategy decreased to about US$25,000 per QALY gained if the weekly treatment cost of hyaluronan was decreased to US$31.

Conclusion. Celecoxib treatment results in a reasonable cost-effectiveness ratio for patients with OA of the knee. Hyaluronan treatment, however, may not be an economically attractive choice under the current healthcare scenario in Taiwan. (J Rheumatol 2004;31:1797–803)

Key Indexing Terms:
COST-BENEFIT ANALYSIS OSTEOARTHRITIS
NAPROXEN CELECOXIB HYALURONAN

Osteoarthritis (OA) is a common disease characterized by progressive deterioration and loss of articular cartilage, subchondral sclerosis, and osteophyte formation. In the Framingham Osteoarthritis Study, one-third of the patients aged > 60 years had radiographic evidence of OA of the knee[1]. The prevalence rate of symptomatic OA in Taiwan is 5.8%, and one-third of cases of OA involved the knee[2].

Current nonoperative treatment of OA is usually focused on reduction of pain, for which nonsteroidal antiinflammatory drugs (NSAID) are frequently used (e.g., naproxen). NSAID exhibit both analgesic and antiinflammatory effects but can also cause frequent and serious adverse effects in the elderly[3,4]. It is estimated that the annual rate of gastrointestinal (GI) complications resulting in hospitalization and death among patients with OA is 0.73% and 0.11%, respectively[5]. Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, has been shown to be effective in treating OA and to reduce GI tract toxic effects compared with other nonselective NSAID[6-8]. However, the safety advantage of celecoxib comes at the expense of higher drug costs.

Hyaluronan (HA) is a natural constituent of joint fluid and all connective tissue. Recent studies using intraarticular injections of HA for OA of the knee have shown a beneficial effect on knee pain and function without serious adverse effects[9-13]. Questions remain about whether the effectiveness of celecoxib and HA injections justifies their higher costs.

The goal of our study was to consider how factors such as costs, improvement rates, side effects, and quality of life might affect drug choices for the treatment of OA of the knee in Taiwan. We therefore developed a decision model to estimate the cost-effectiveness of alternative treatment strategies for OA of the knee. The purpose of this study was to determine the relative merits of each strategy in terms of societal costs and of quality-adjusted life.

From the Department of Emergency Medicine, Department of Orthopedics, and the College of Public Health, National Taiwan University; National Taiwan University Hospital; and National Taiwan University College of Medicine, Taipei, Taiwan.

Supported by the Bureau of National Health Insurance, Taiwan (grant number DOH89-NH-058).

Z-S. Yen, MD, MPH, Department of Emergency Medicine; M-S. Lai, MD, PhD, College of Public Health, National Taiwan University; C-T. Wang, MD, Department of Orthopedics; L-S. Chen, BA, Department of Administration, National Taiwan University Hospital; S-C. Chen, MD; W-J. Chen, MD, PhD, Department of Emergency Medicine; S-M. Hou, MD, PhD, Department of Orthopedics.

Address reprint requests to Dr. S-M. Hou, Department of Orthopedics, National Taiwan University Hospital, No.7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: zuishen@ha.mc.ntu.edu.tw

Submitted July 11, 2003; revision accepted March 15, 2004.

MATERIALS AND METHODS

Study design

This study was conducted utilizing common principles of cost-effectiveness analysis[14]. Three treatment strategies for the management of OA were compared: (1) 250 mg naproxen 3 times daily for 26 weeks, (2) 100 mg celecoxib twice daily for 26 weeks, and (3) 25 mg HA (Artz®, Seikagaku Corp., Tokyo, Japan) by intraarticular injection once per week for 5 weeks followed by conventional treatment for 21 weeks. A base-case scenario and sensitivity analyses were simulated in the study.

Study setting and population

Base case. The base case was a hypothetical 60-year-old woman who had symptomatic and radiologically verified OA of the right knee. She was working fulltime. Her knee pain after a 50-ft walk was 50 mm on 100 mm visual analog scale (VAS). Global assessment of her right knee on a scale from 1 (very poor) to 5 (very good) was 2 (poor). She declined surgical intervention. Three treatment strategies (naproxen, celecoxib, and HA) were available and one of the therapeutic options had to be chosen. Based on the related literature, the probability of improvement of her knee OA was 0.31 with naproxen[7,10,15], 0.35 with celecoxib[6,7], and 0.36 with HA[9-13]. The probability of serious GI complications in 26 weeks was 0.0037 with naproxen[3-5,16] and 0.0000075 with celecoxib[6,7]. The probability of local injection pain from HA was 0.021[9-13].

Decision model. We developed a decision model (Figure 1) to simulate possible outcomes of OA of the knee using treatment with naproxen, celecoxib, or HA. We identified the following clinical outcomes: OA with or without improvement, OA with GI complications, and OA with local injection pain from HA treatment. OA with improvement meant that a patient improved clinically (improvement of ≥ 20 mm on the VAS or of ≥ 2 grades on global assessment). Conventional treatments of OA in the outpatient setting may include nonpharmacologic therapies (e.g., patient education and weight loss), calcium supplements, muscle relaxants, topical analgesics, and acetaminophen.

Over-the-counter medication is not covered by Taiwan's compulsory National Health Insurance (NHI) and was not included in the nonpharmacologic therapies. No NSAID, including naproxen, celecoxib, and HA, was considered conventional treatment. Serious GI complications from naproxen or celecoxib were defined as serious adverse events requiring hospitalization. Common serious GI complications are bleeding and perforated ulcers of the upper or lower GI tract. Patients who have GI complications resulting from naproxen are at risk of mortality during their hospitalization. Patients with minor GI complications such as dyspepsia were treated in an outpatient setting. Except during the period when receiving HA injections and hospitalization, patients were followed up at the outpatient department at 2-week intervals. A timeframe of 26 weeks was used in the model.

Probabilities. Estimates of probabilities (Table 1) used in the model were obtained by surveying the literature and consulting experts. For each variable, a base-case estimate was determined if the study was considered authoritative by the authors or most similar to our clinical practice. For example, in Altman's trial[10], 59 of 164 patients who received HA injections improved clinically. So the improvement probability of the HA strategy was 0.36. We estimated the effectiveness of naproxen, celecoxib, and HA by using the percentage improvement without subtracting the placebo effect. To represent the degree of uncertainty, a plausible range of each estimate was also determined using other studies of similar topics that were not considered authoritative. These ranges of estimates were further used in the sensitivity analyses.

Costs. From a societal perspective, cost data (Table 2) were collected, including costs of outpatient treatments, inpatient treatments for serious GI complications, and time lost from work. Cost data for each treatment strategy represented the average reimbursement from the NHI received by National Taiwan University Hospital from July 2001 to February 2002. These costs (in New Taiwan dollars, NT$) were then converted to 2002 US dollars at the rate of NT$34.96 to US$117.

Three hundred OA patients were selected randomly from the database, and their reimbursements from the NHI were averaged to reflect real societal costs. Weekly costs of each treatment included actual costs of medications, physician fees, and administrative fees (e.g., fees to administer outpatient visits). For example, our estimate of the weekly cost of a single HA injection was US$41.84, which includes the cost of HA, physician fees, and administrative fees, and was the average reimbursement to a patient who received one HA injection in the outpatient department (OPD). Loss of productivity, i.e., time lost from work, was calculated using the average Taiwanese industrial wage of US$239.37/week in 2003[17]. The cost associated with each clinical outcome was determined by aggregating the various elements of the strategy. For example, the total cost for a patient with clinical improvement from 5 HA injections was computed as follows: (5 × the

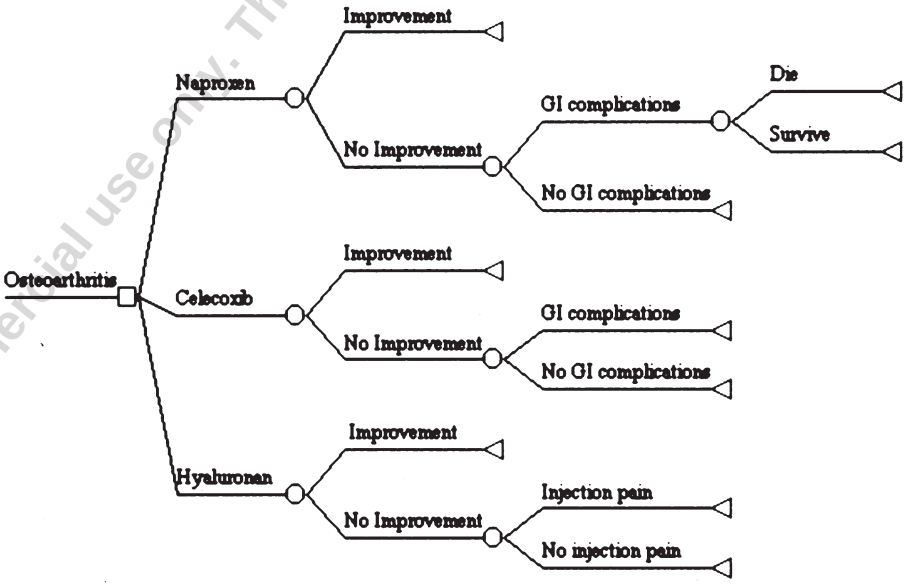

Figure 1. The decision model.

Table 1. Estimates of variables used in the decision model.

Variable	Base-Case Estimate	Plausible Range	References
Probability of improvement			
Naproxen	0.31	0.2~0.6	7, 10, 15
Celecoxib	0.35	0.2~0.6	6, 7
Hyaluronan	0.36	0.2~0.6	9–13
Probability of serious GI complications from naproxen treatment	0.0037	0.001~0.05	3–5, 16
Probability of mortality from serious GI complications	0.0006	0.0001~0.006	4, 5, 16
Probability of serious GI complications from celecoxib treatment	0.0000075	0~0.0001	8
Injection pain from hyaluronan treatment	0.036	0.01~0.10	9–13
Quality-of-life adjustments			
OA with improvement from treatment with naproxen, celecoxib, or hyaluronan	0.95	0.94~0.96	¶
OA without improvement from treatment with naproxen or celecoxib	0.84	0.83~0.85	¶
OA with conventional treatment	0.85	0.84~0.86	¶
OA with hyaluronan injections	0.84	0.83~0.85	¶
OA with injection pain from hyaluronan treatment	0.83	0.82~0.84	¶
Serious GI complications	0.75	0.74~0.76	¶

¶ Based on an assessment by an expert panel. GI: gastrointestinal; OA: osteoarthritis.

Table 2. Estimated OA-related costs. All values are in 2002 US dollars. Ranges for cost estimates represent 30% of the baseline estimate.

Variable	Base-Case Cost, US$	Range, US$	Source
Weekly OPD treatment cost			
Naproxen	10.48	7.34~13.62	Reimbursement¶
Celecoxib	12.52	8.76~16.28	Reimbursement¶
Hyaluronan	41.84	29.29~54.39	Reimbursement¶
Conventional treatment	9.88	6.92~12.84	Reimbursement¶
GI complications	14.54	10.18~18.90	Reimbursement¶
Weekly inpatient treatment cost			
Serious GI complications	423.31	296.32~550.30	Reimbursement¶
Weekly time lost from work	239.37	167.56~311.18	§
Unit cost of medication			
Naproxen 250 mg	0.16	–	Reimbursement¶
Celecoxib 100 mg	0.48	–	Reimbursement¶
Hyaluronan 25 mg	34.58	–	Reimbursement¶
Administrative fee per OPD visit	1.52	–	Reimbursement¶
Physician fee per OPD visit	5.56	–	Reimbursement¶

¶ Average reimbursement of the National Health Insurance to National Taiwan University Hospital from July 2001 to February 2002. § Average industrial wage rate in 2002 in Taiwan. OA: osteoarthritis; OPD: outpatient department; GI: gastrointestinal.

weekly cost of HA) + (21 × the weekly cost of conventional treatment of OA) + [15.5 (number of OPD visits) × 0.5 (0.5 days/OPD visit) × the weekly wage loss/7 (daily wage loss due to an OPD visit)]. Costs were not discounted in our analysis because of the short timeframe (26 weeks).

Quality of life. Estimates of quality-of-life adjustments for various clinical outcomes in the model for patients in Taiwan were unknown prior to this study, but were required to perform a decision analysis that includes patient preferences. Since no existing data were available on the health utilities relating to the issue of OA, a panel of experts was used. This panel, composed of 2 orthopedic physicians, 2 emergency physicians, and one internist with extensive experience in the treatment of knee OA, agreed to participate in a standard-gamble procedure. They assessed their own utilities for each health status by using the standard reference gamble technique[18] (Table 1). The quality-adjusted life-year (QALY) associated with each clinical outcome during the 26 weeks (timeframe) was determined by aggregating the various time periods of health status multiplied by their quality-of-life adjustments (utilities).

Assumptions in the model. We used various assumptions in this model. First, only patients with serious GI complications were admitted. Patients with minor GI complications were treated as outpatients. Second, if patients failed to improve after receiving therapies, they could not change to other treatment strategies. For example, if patients received naproxen

treatment but failed to improve, they could not change to celecoxib or HA therapies. If patients suffered from serious GI complications, they were assigned to the "OA without improvement" group and received conventional therapies for OA and outpatient treatments for GI complications after discharge. We also assumed that there were no mortality events, except death from GI complications. When performing the sensitivity analyses, changes in the weekly costs of the 3 treatment strategies were assumed to affect only the costs of naproxen, celecoxib, or HA, while the costs of physician fees, administrative fees, and other medications remained constant.

Measurements and outcome variables

The outcome measurements for this analysis were aggregate costs, QALY, and incremental cost per QALY. These outcome variables were calculated for all 3 treatment strategies. The expected total costs and the effectiveness of the QALY were calculated according to our decision model simulation.

Data analysis

Cost-effectiveness was tabulated. Because of variations in published data, costs, and varying responses to treatments, we also performed sensitivity analyses on most variables used in the decision model to see how changing these estimates over a wide range affected selection of the optimal strategy. A computer program (Data 3.5 of TreeAge) was used for all calculations.

RESULTS

Base-case analysis. According to the simulation results, on average, when a 60-year-old woman with OA of the right knee was treated with naproxen, the expected total cost was US$498.98 and the expected effectiveness was 0.4357 QALY. On the other hand, if treated with celecoxib or HA, the expected total cost increased to US$547.80 or US$678.00, respectively. Values for the expected effectiveness of the celecoxib and HA strategies were 0.4380 and 0.4411 QALY, respectively (Table 3). The incremental cost-effectiveness ratio (ICER) of the celecoxib strategy compared with naproxen was US$21,226 per QALY gained. The ICER of the HA strategy versus celecoxib was US$42,000 per QALY gained.

Sensitivity analysis. One-way sensitivity analyses identified several influential variables (Figures 2 and 3). Although the probability of serious GI complications from naproxen treatment was estimated from a large epidemiology study[5], we increased this probability by 10 times that of the base-case estimate to evaluate the effect of changing this probability on the ICER of the celecoxib strategy as compared with the naproxen strategy (Figure 2). The ICER of the celecoxib strategy decreased to about US$3170 per QALY gained if the probability of serious GI complications from naproxen treatment were increased to 0.037. If the probability of serious GI complications from naproxen treatment were increased to > 0.0464, the celecoxib strategy would offer patients a better quality of life, save societal resources, and become a dominant strategy compared with naproxen.

Not surprisingly, the improvement probability of HA treatment had a potentially notable impact on the cost-effectiveness of the HA strategy as compared with the celecoxib strategy (Figure 3). When the improvement probability of HA treatment was increased to 0.60, the ICER of the HA strategy decreased to about US$8900 per QALY gained. However, as the improvement probability of HA treatment was decreased to between 0.36 and 0.297, the ICER of the HA strategy increased far beyond the US$42,000 per QALY gained, the base-case result. If the improvement probability of HA treatment was decreased to < 0.297, the HA strategy would offer patients a worse quality of life, but would still cost more compared with celecoxib. Therefore, HA treatment would be dominated by celecoxib.

The weekly treatment costs of HA and conventional treatment had significant effects on the ICER of the HA strategy as compared with the celecoxib strategy. The ICER of the HA strategy decreased to about US$25,000 per QALY gained if the weekly treatment cost of HA was decreased to US$31 (Figure 3). If the weekly cost of conventional treatment was decreased to US$7, the ICER of the HA strategy decreased to about US$22,400 per QALY gained.

The cost of time lost from work did not have a significant influence on the ICER. The results of base-case analysis were insensitive to costs of outpatient and inpatient treatment of GI complications.

DISCUSSION

Considering the limited resources available for healthcare, it is important to consider the impact of incorporating new technologies that affect patient outcomes and healthcare expenditures. Using results from available studies and cost data, we developed a decision-making model to simulate possible clinical outcomes. Our results suggest that naproxen and celecoxib treatments result in reasonable cost-effectiveness ratios. However, the ICER of the HA strategy was 3.3 times the 2002 Taiwan gross domestic product per capita (US$12,588)[19] and was also more than the suggested

Table 3. Base-case results. Costs are in 2002 US dollars.

Strategy	Expected Cost, US$	Incremental Cost, US$	Effectiveness, QALY	Incremental Effectiveness, QALY	Cost/QALY, $/QALY	Incremental costs/QALY, $/QALY
Naproxen	498.98	—	0.4357	—	1145	—
Celecoxib	547.80	48.82	0.4380	0.0023	1251	21,226
Hyaluronan	678.00	130.20	0.4411	0.0031	1537	42,000

QALY: quality-adjusted life-year; dashes, not applicable.

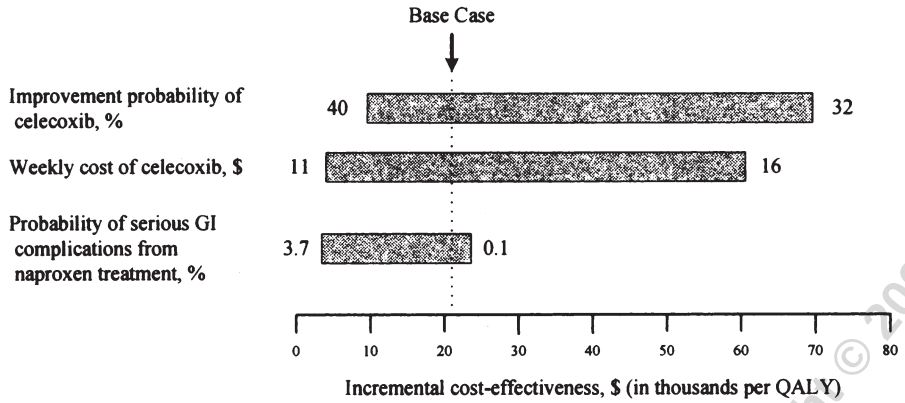

Figure 2. One-way sensitivity analyses of the incremental cost-effectiveness of celecoxib treatment compared with naproxen treatment. Bars indicate the variability of the incremental cost-effectiveness ratio (x-axis) caused by changes in the value of the indicated variable, with all other variables being held constant. Labels on the horizontal bars indicate a certain range of each one-way sensitivity analysis. The range levels in this figure only indicate partial results of our one-way sensitivity analyses. Costs are in 2002 US dollars. QALY: quality-adjusted life-year.

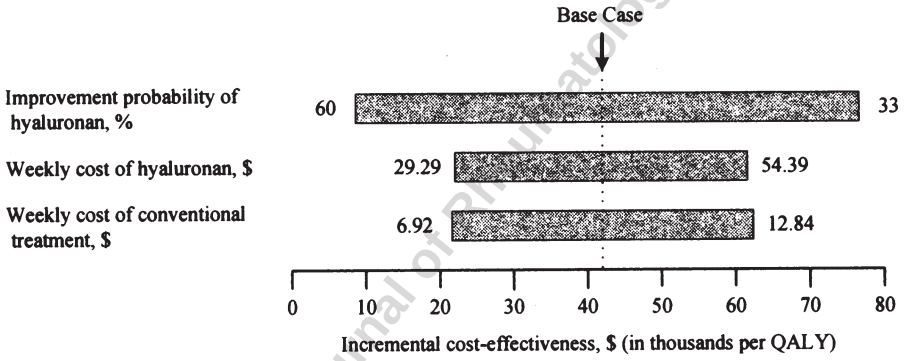

Figure 3. One-way sensitivity analyses of the incremental cost-effectiveness of hyaluronan treatment compared with celecoxib treatment. Bars indicate the variability of the incremental cost-effectiveness ratio (x-axis) caused by changes in the value of the indicated variable, with all other variables being held constant. Labels on the horizontal bars indicate a certain range of each one-way sensitivity analysis. The range levels in this figure only indicate partial results of our one-way sensitivity analyses. Costs are in 2002 US dollars. QALY: quality-adjusted life-year.

cost-effectiveness threshold, US$32,000 per QALY (CDN$1.57:US$1), for Canada and the United States[20,21]. Taiwan has fewer health resources than Canada and the US; therefore, adopting HA treatment for treatment of OA of the knee may not be cost-effective in Taiwan.

The probability for improvement with HA treatment has varied. In most randomized clinical trials, the improvement probabilities were about 0.36[9–12]. In a recent open-label study, however, the improvement probability was 69%[13], and the ICER of HA treatment was US$6369 per QALY gained compared with appropriate care[22]. We performed an analysis using their improvement probability of 69% and naproxen treatment as appropriate care. We found no large difference from Torrance, *et al*'s analysis[22], as the ICER of HA strategy would be US$8321 per QALY gained. However, based on our clinical experience with HA treatment, the high improvement probability did not seem applicable to our patients, and therefore we decided not to adopt it for our analysis.

Studies have shown similar efficacies of COX-2 inhibitors and naproxen for the treatment of OA[7,23,24]. In our analysis, celecoxib was found to be a more cost-effective or even cost-saving strategy if the probability of serious GI complications from traditional NSAID treatments was increased. In elderly patients and patients at high risk of GI complications, the probability of serious GI complications could be > 0.0037. In those cases, the ICER of celecoxib treatment was < US$21,226 per QALY gained, and celecoxib treatment became even more attractive. In terms of cost-effectiveness, the results of our analyses led us to

recommend COX-2 inhibitors for elderly patients and patients at high risk of GI bleeding.

New medical treatments, such as HA, are often more effective, but also more costly than traditional ones. Some health interventions such as use of a tissue plasminogen activator for acute ischemic stroke[25] or norfloxacin for acute uncomplicated pyelonephritis[26] may appear very costly at first, but have been proven to be cost-saving strategies in terms of cost-effectiveness. Nevertheless, our results suggest that the incremental effectiveness of HA treatment might not justify its higher costs. If the weekly cost of HA treatment could be considerably decreased, then HA would become more attractive. In our analyses, HA treatment would become a cost-saving strategy only if its weekly cost fell below US$15.32.

We used an average weekly-cost approach instead of simply adding up the components to estimate the weekly costs, because the average weekly-cost approach produced values closer to actual costs. Simply adding up components may underestimate the true costs. For example, for patients treated with celecoxib, in addition to the cost of celecoxib, the physician fee, and the administrative fee, there were costs for medications other than celecoxib. Those medications may include some that are relatively costly with uncertain effects on OA, such as calcium supplements, antacids, etc. The weekly cost of celecoxib ($12.52) was larger than the total amount ($10.26) from simply adding up the cost of celecoxib ($0.48 × 2 × 7 = $6.72), the physician fee ($5.56/2 = $2.78, with followup at 2-week intervals), and the administration fee ($1.52/2 = $0.76, with followup at 2-week intervals). The cost of "extra" medications may be seen as a kind of "externality" associated with the treatment strategy. This phenomenon was most obvious for naproxen treatment and least obvious for HA treatment among the 3 compared strategies. We did not investigate this phenomenon closely because it was beyond the main purpose of our study.

There were several limitations of our analysis. First, our results might not be applicable to patients in areas where medical financial structures and clinical practice patterns differ markedly from those in Taiwan. Further studies are needed to test the external validity of our analysis. Second, our analysis was not done concurrently with any clinical trial. The efficacy and cost data were collected from different patient populations. We did our best to summarize results from good-quality clinical trials and epidemiological studies. And we also performed sensitivity analyses to evaluate the stability of our conclusions. We think our results are still applicable to patients in Taiwan.

Longterm side effects of naproxen, celecoxib, and HA were not included in our analysis. Current limited data suggest that celecoxib is associated with fewer incidents of longterm GI, renal, and cardiovascular toxicity than traditional NSAID[27,28]. These features could make celecoxib more favorable. We admit that our model did not cover all possible outcomes and all possible real-world treatment strategies. In the process, we had to balance between the complexity and feasibility of the model. Therefore, we did not include unlikely outcomes such as mortality events from celecoxib or HA treatments. Ideally, the source of quality-of-life measurements is obtained from community preferences. In our study, experts' opinions were used instead due to a lack of valid culture-specific and disease-specific generic measurements in Taiwan. Future studies should involve large-scale, multicenter prospective, randomized, controlled analyses to assess the validity of the costs and benefits estimated here.

With the advent of increasingly costly treatments with greater effectiveness and fewer side effects, it is necessary to perform cost-effectiveness analyses to justify their use, especially when medical resources are limited. The results of our analysis suggest that celecoxib treatment produces reasonable cost-effectiveness ratios for patients with OA of the knee. HA treatment, however, may not be an economically attractive choice under the current healthcare scenario in Taiwan.

REFERENCES

1. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee arthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914-8.
2. Chou CT, Pei L, Chang DM, Lee CF, Schumacher HR, Liang MH. Prevalence of rheumatic diseases in Taiwan: a population study of urban, suburban, rural differences. J Rheumatol 1994;21:302-6.
3. Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:1075-8.
4. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. Gastroenterology 1989;96:647-55.
5. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol 1999;26:18-24.
6. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum 1998;41:1591-602.
7. Bensen WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc 1999;74:1095-105.
8. Singh G, Ramey DR, Triadafilopoulos G. Early experience with selective COX-2 inhibitors: safety profile in over 340,000 patient years of use [abstract]. Arthritis Rheum 1999;42 Suppl:S296.
9. Brandt KD, Block JA, Michalski JP, et al. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. Clin Orthop Rel Res 2000;385:130-43.
10. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. The Hyalgan Study Group. J Rheumatol 1998;25:2203-12.
11. Adams ME, Lussier AJ, Peyron JG. A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. Drug Saf 2000;23:115-30.

12. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled multicentre trial. Ann Rheum Dis 1996;55:424-31.
13. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002;10:506-17.
14. Ferraz MB, Maetzel A, Bombardier C. A summary of economic evaluations published in the field of rheumatology and related disciplines. Arthritis Rheum 1997;40:1587-93.
15. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;36:1196-206.
16. MacDonald TM. Epidemiology and pharmacoeconomic implications of non-steroidal anti-inflammatory drug-associated gastrointestinal toxicity. Rheumatology 2000;39:13-20.
17. Statistics Taiwan. Average industrial aggregate and foreign currency exchange rate. Taipei: Statistics Taiwan; 2003.
18. Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ 1986;5:1-30.
19. Statistics Taiwan. Gross domestic product per capita. Taipei: Statistics Taiwan; 2003.
20. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473-81.
21. Laupacis A. Inclusion of drugs in provincial drug benefit programs: who is making these decisions, and are they the right ones? CMAJ 2002;166:44-7.
22. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis Cartilage 2002;10:518-27.
23. Myllykangas-Luosujarvi R, Lu HS, Chen SL, et al. Comparison of low-dose rofecoxib versus 1000 mg naproxen in patients with osteoarthritis. Results of two randomized treatment trials of six weeks duration. Scand J Rheumatol 2002;31:337-44.
24. Kivitz AJ, Moskowitz RW, Woods E, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. J Int Med Res 2001;29:467-79.
25. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. Neurology 1998;50:883-90.
26. Yen ZS, Davis MA, Chen SC, Chen WJ. A cost-effectiveness analysis of treatment strategies for acute uncomplicated pyelonephritis in women. Acad Emerg Med 2003;10:309-14.
27. Tive L. Celecoxib clinical profile. Rheumatology 2000;39:21-8.
28. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247-55.