ORIGINAL ARTICLE

Hylan G-F 20 Has Better Pain Relief and Cost-effectiveness than Sodium Hyaluronate in Treating Early Osteoarthritic Knees in Taiwan

*Chi-Wen Chou,[1] Ko-Huang Lue,[2] Hong-Shen Lee,[3] Renn-Chia Lin,[1] Ko-Hsiu Lu[1,2]**

Background/Purpose: Intra-articular injection of hyaluronan (hyaluronic acid; HA) products is available to treat early osteoarthritis (OA) of the knee in Taiwan. We tested whether HA products with different molecular weights have significantly different effects on clinical efficacy and cost-effectiveness.

Methods: Thirty-seven patients with mild to moderate OA of both knees underwent five weekly intra-articular injections of sodium hyaluronate (Artz®) in one knee and three weekly intra-articular injections of chemically cross-linked Hylan G-F 20 (Synvisc®) in the other. Visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne's index, and Hospital for Special Surgery (HSS) knee scores were compared initially and at the last injection, and at 8, 12, 16, 20, and 26 weeks after the first injection.

Results: VAS, WOMAC, WOMAC-A1 (pain when walking on a flat surface) scores before week 16, HSS scores before week 12, and Lequesne's index scores except at week 26 all showed that HA significantly improved the scores time-dependently. In VAS scores, Synvisc® showed better improvement before week 20, while this effect appeared at week 12 for the WOMAC-A1 scores. The incremental cost-effectiveness ratio of the Taiwan National Health Insurance Program, of the patient, and both of these was lower for Synvisc®, which also reduced the number of additional hospital visits for injections by two.

Conclusion: Synvisc® possesses better symptom-modifying ability and cost–utility in treating early OA of the knee in Taiwan. [*J Formos Med Assoc* 2009;108(8):663–672]

Key Words: cost-effectiveness, hyaluronic acid, hylan G-F 20, osteoarthritis

Osteoarthritis (OA) is the most common form of chronic joint disorder worldwide. In OA of the knee, pathogenic changes result in cartilage erosion, meniscal degenerative tears, subchondral bone remodeling, osteophyte formation, and synovial inflammation.[1] According to the recommendations of the American College of Rheumatology (ACR) for knee OA, the primary goals for contemporary management include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy.[2] If noninvasive or nonoperative treatment is not indicated, is ineffective, or is not tolerated, intra-articular injection with steroids or hyaluronan (hyaluronic acid; HA) is considered.[2,3]

[1]Department of Orthopedics, Chung Shan Medical University Hospital, and Schools of [2]Medicine and [3]Public Health, Chung Shan Medical University, Taichung, Taiwan.

Received: September 22, 2008
Revised: December 30, 2008
Accepted: February 9, 2009

***Correspondence to:** Professor Ko-Hsiu Lu, Department of Orthopedics, Chung Shan Medical University Hospital, No. 110, Section 1, Chien-Kuo North Road, Taichung 402, Taiwan.
E-mail: cshy307@csh.org.tw

Injecting exogenous HA into the knee joint can enhance chondrocyte HA and proteoglycan synthesis, reduce the production and activity of pro-inflammatory mediators, urokinase-type plasminogen activator (u-PA), plasminogen activator inhibitor-1 (PAI-1), and matrix metalloproteinases (MMPs), and alter the behavior of immune cells.[4–7] Exogenous HA is also known to inhibit nitric oxide production,[8] delay degradation of cartilage by inhibiting glycosaminoglycan release from cartilage tissue,[9] and have anti-inflammatory effects.[10] This efficacy might be related to the rheological properties and different molecular weight (MW), which enhance penetration through the extracellular matrix or promote binding to specific cell receptors, such as cluster determinants (CDs).[11,12]

Currently, sodium hyaluronate (MW = 600–1200 kDa; Artz®; Seikagaku Corp., Tokyo, Japan) and chemically-cross-linked Hylan G-F 20 (MW = 6000 kDa; Synvisc®; Genzyme Biosurgery, Ridgefield, NJ, USA) are available in Asia, the European Union, and the United States. The MW of Artz® is much lower than that of HA in normal healthy synovial fluid.[11] Synvisc® has been developed to yield solutions with greatly enhanced elastoviscous properties like those in the knee joints of healthy young adults (18–27 years of age), and to prolong its intra-articular residence time to improve the efficacy of viscosupplementation therapy of OA.

The true outcomes in clinical viscosupplementation with HA are difficult to determine, because most investigators have used nebulous inclusion criteria, inadequate study designs, short-term follow-up times, and limited outcome-based analyses, and have ignored safety and cost-effectiveness.[13–18] In OA, there is a hypercoagulable and prothrombotic state with hypofibrinolysis, and indirect evidence of increased fibrin generation,[19] while HA with a high MW provides greater inhibition of proteolysis and fibrinolysis.[20,21] We have also found that Synvisc® can downregulate the expression of u-PA and PAI-1 and their downstream enzymes MMP-2 and MMP-9 more effectively than Artz® can.[5] These effects seem to contribute, at least in part, to the apparent irreversibility of the OA disease process.

In Taiwan, treatment of mild-to-moderate OA of the knee with either Artz® or Synvisc® is covered by the National Health Insurance Program. Therefore, we tested the hypothesis that Synvisc® has greater clinical efficacy than Artz®, and also whether Synvisc® is more cost-effective than Artz®.

Methods

Patients

Under the Taiwan National Health Insurance Program, treatment of mild-to-moderate knee OA with HA, such as five weekly intra-articular injections of Artz® from 1999, or three weekly intra-articular injections of Synvisc® from 2005 was indicated for patients who did not have adequate pain relief despite conservative treatment with oral analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), exercise and physical therapy, and whose knees were not affected sufficiently to warrant total joint replacement. From October 2005 to June 2006, patients with symptomatic, mild-to-moderate OA of both knees, who met the inclusion criteria, were included in this study. The inclusion criteria were ambulatory patients aged ≥ 55 years with primary OA of both knees, who fulfilled the ACR criteria[22] and corresponded to stage I–III in the Ahlback classification system.[23] In each case, the diagnosis was confirmed with weight-bearing anteroposterior, lateral and Merchant's X-rays of both knees. We also enrolled patients who feared the deleterious effects of long-term use of oral analgesics and NSAIDs. The exclusion criteria were: treatment with steroids or HA preparations within the past 6 months; significant effusions in the knee; previous intra-articular fractures of the knee; inflammatory joint disease as defined by ACR criteria; joint infection; chicken or egg allergy, or poor skin conditions over the joint area, which may cause the administration of injections to be problematic. This study was conducted in accordance with the principles

embodied in the Declaration of Helsinki and all the patients gave informed consent.

Study design

Based on Student's *t* tests with a probability level of 5%, assuming a standard deviation of 30 mm, a significance level of $p = 0.05$, and a power of 0.80, the sample size calculations indicated that 32 patients (64 knees) would be sufficient to detect a difference of 15 mm in visual analog scale (VAS) scores. Therefore, 41 patients were enrolled to allow for dropouts. Patients with OA of both knees underwent five weekly intra-articular injections of sodium hyaluronate (Artz®; Seikagaku Corp.) in one knee and three weekly intra-articular injections of Hylan G-F 20 (Synvisc®; Genzyme Biosurgery) in the other. All injections were performed by the same clinician. The outcome variables were recorded prior to participation, at 5 weeks for Artz® or 3 weeks for Synvisc® (the final injection), and at 8, 12, 16, 20 and 26 weeks after the first injection. No concomitant analgesics, NSAIDs or steroids were administered (Figure 1).

Outcome measurement

We documented the outcome variables using global 100 mm VAS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne's index, and Hospital for Special Surgery (HSS) knee score criteria, initially and at each follow-up. The VAS pain score was evaluated for relief of knee pain. The WOMAC score was patient-administered and assessed the three dimensions of pain, stiffness and physical function of the knee, using a battery of 24 questions, and a total score was provided. WOMAC-A1 was the score of walking on a flat surface. Lequesne's index provided scores for pain, maximal walking distance and the activities of daily living, and the maximum score was 26. The HSS score was composed of seven classifications: pain, function, range of motion, muscle strength, flexion deformity, instability and subtractions, with a total of 100 points. We measured and compared the differences of the degree of improvement between Artz®- and Synvisc®-treated groups.

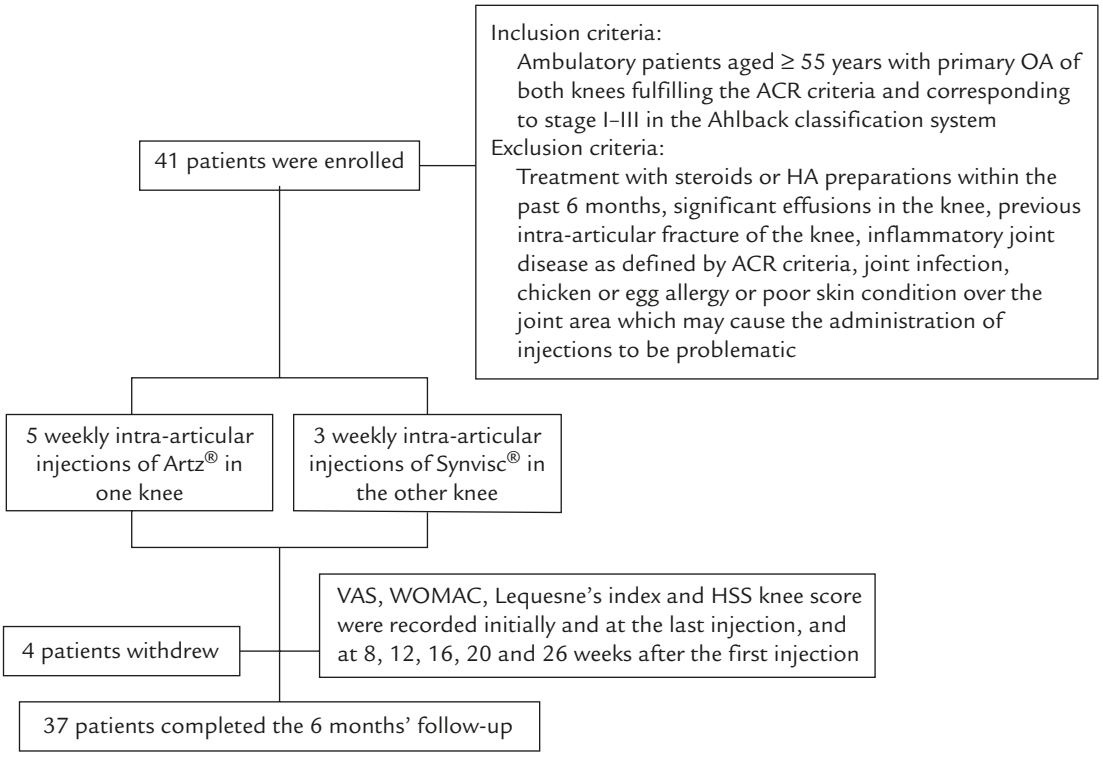

Figure 1. Study profile. OA = osteoarthritis; ACR = American College of Rheumatology; HA = hyaluronic acid; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; HSS = Hospital for Special Surgery.

Utility measurement

The quality-adjusted life year (QALY) was used as the unit of outcome in the cost-effectiveness analysis. A QALY is a composite index that includes effects in terms of both quality of life (utility) and the duration of time in such a health state. We analyzed the cost–utility between Artz® and Synvisc® injections by calculating the QALY from the baseline to 26 weeks (0.5 years) to evaluate the cost-effectiveness. Utility was derived from the transformed VAS $\left(\frac{100-\text{VAS scores}}{100}\right)$ for general health, where a weight of 1 corresponded to 0 of the VAS score (best state of health), and a weight of 0 to a state of 100 of the VAS score (worst state of health). For the utility of Artz® or Synvisc®, there were seven therapeutic values (known points) on the curve. We assumed it was a graph of function expressed by a polynomial of degree six determined by seven given points, including the baseline point. The function $f(x)$ we obtained was an approximate equation of the curve, where x was time (baseline to 0.5 years), and $f(x)$ was the utility. Accordingly, each patient had two curves for the utility for Artz® and Synvisc®: $f_{An}(x)=a_{An}x^6+b_{An}x^5+c_{An}x^4+d_{An}x^3+e_{An}x^2+f_{An}x+g_{An}$ and $f_{Sn}(x)=a_{Sn}x^6+b_{Sn}x^5+c_{Sn}x^4+d_{Sn}x^3+e_{Sn}x^2+f_{Sn}x+g_{Sn}$ (A = Artz®; S = Synvisc®; $n=1$–37). We substituted the value of each point for $f(x)$ and x, thus giving seven simultaneous equations and obtained values for a, b, c, d, e, f and g of each curve by solving the set of simultaneous equations. The area between the curve of utility and the equation of the baseline [$f_{An}(0)=g_{An}$ and $f_{Sn}(0)=g_{Sn}$] could be calculated by the integration of $f_{An}(x)$ and $f_{Sn}(x)$ with respect to x, to define the quality of life per period from the baseline to 0.5 years. There were 37 paired quality of life values per period for Artz® and Synvisc® obtained and Δ(QALYs) was expressed by the results:[24] $\Delta(\text{QALY})_{An}=\int_{0.0}^{0.5}\left(f_{An}(x)-f_{An}(0)\right)dx$ and $\Delta(\text{QALYs})_{Sn}=\int_{0.0}^{0.5}\left(f_{Sn}(x)-f_{Sn}(0)\right)dx$. We then calculated the incremental cost-effectiveness ratio (ICER) by dividing Δ(QALYs) into the total cost (in Taiwan dollars, NT$).[25] ICER (cost–utility) = $\frac{\text{total cost}(\text{NT\$})}{\Delta(\text{QALYs})}$.

Statistical analysis

Two-way repeated-measures analysis of variance (ANOVA) was applied to assess the differences before and after HA treatment. Wilcoxon rank sum test was used to analyze the differences in radiographic stages between Artz®- and Synvisc®-treated knees prior to treatment. Statistical calculations of the baseline of all scores and the degree of improvement between Artz®- and Synvisc®-treated groups were performed by Student's t test. The Mann–Whitney U test was used for the analysis of data concerning Δ(QALYs) and ICER between the Artz®- and Synvisc®-treated groups. Statistical significance was set at $p<0.05$.

Results

A total of 41 patients met the criteria for inclusion in the study and received the whole treatment course. Thirty-seven patients (mean age, 71.3 ± 7.5 years), including six men (mean age, 74.5 ± 7.4 years) and 31 women (mean age, 70.7 ± 7.5 years), finally completed the 6 months' follow-up, while four patients (9.8%) were withdrawn from the study for poor compliance with follow-up. No systemic adverse effects were recorded. A few local adverse effects occurred, which consisted of local pain or swelling of the injection site, which were relieved after resting. Prior to treatment, neither radiological staging nor VAS, WOMAC, WOMAC-A1, Lequesne's index or HSS scores showed a significant difference ($p>0.05$) between the Artz®- and Synvisc®-treated groups (Table).

HA improved clinical symptoms and physical functions

In two-way repeated-measures ANOVA, none of the outcome variables had significant interactions between the drugs and time points (drug × time

Table. Patients' radiographic evaluation and baseline disease characteristics prior to treatment

	Artz®	Synvisc®	*p*
Ahlback classification			
I	14	11	0.705†
II	16	23	
III	7	3	
VAS*	68.8 ± 9.7	65.7 ± 8.5	0.148‡
WOMAC*	54.7 ± 14.4	52.7 ± 14.8	0.437‡
WOMAC-A1*	2.7 ± 0.9	2.5 ± 0.8	0.235‡
Lequesne's index*	15.1 ± 3.6	14.7 ± 3.4	0.596‡
HSS*	70.8 ± 10.8	72.0 ± 9.2	0.595‡

**Results shown as mean ± standard deviation (n = 37); †differences in radiographic stages between Artz®- and Synvisc®-treated groups (Wilcoxon rank sum test); ‡differences at baseline between Artz®- and Synvisc®-treated groups (Student's t test). VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC-A1 = WOMAC—pain when walking on a flat surface; HSS = Hospital for Special Surgery.*

effects: $p > 0.05$) (Figure 2). VAS, WOMAC and Lequesne's index scores all showed that HA significantly decreased the scores in a time-dependent manner (time effects: $p < 0.05$), except for Lequesne's index scores at week 26. Before week 16, WOMAC-A1 scores also showed significant decreases in a time-dependent manner (time effects: $p < 0.05$). HSS scores only showed significant improvements before week 12 (time effects: $p < 0.05$) and then this effect reached a plateau. Both VAS and WOMAC-A1 scores showed that Synvisc® had stronger effects than Artz® (drug effects: $p < 0.05$), whereas WOMAC, Lequesne's index and HSS scores did not show significant differences (drug effects: $p = 0.095$, $p = 0.103$ and $p = 0.316$, respectively).

Synvisc® had greater pain-relieving effects and QALY gains

Since Synvisc® had stronger effects than Artz® on VAS and WOMAC-A1 scores, we further compared the degree of improvement in the individual HA-treated knees, and documented these to find the source of differences between Artz® and Synvisc® (Figure 3). For VAS scores, Synvisc® showed better improvement before week 20 ($p < 0.05$), while this effect only appeared at week 12 for the WOMAC-A1 scores ($p < 0.05$). Thereafter, two curves for the utility of Artz® and Synvisc® were derived from the transformed VAS, and significant differences in Δ(QALYs) between Artz®- and Synvisc®-treated groups were observed ($p = 0.018$; Figures 4A and 4B).

Synvisc® had better ICER and patient satisfaction

The payment under the Taiwan National Health Insurance Program for one Artz® injection was NT$1415; for one Synvisc® injection, it was NT$1915, including an intra-articular injection fee of NT$100 and a clinician fee of NT$213. The cost of one treatment course of five Artz® injections was higher than the cost of one treatment course of three Synvisc® injections (NT$7075 *vs.* NT$5745). The direct medical cost for the Taiwan National Health Insurance Program per QALY gained (ICER) was NT$7075/0.04101 = NT$297,355 [95% confidence interval (CI): 1,268,650 to 1,863,359) for five Artz® injections and NT$5745/0.05977 = NT$241,456 (95% CI: 1,030,162 to 1,513,074) for three Synvisc® injections using the transformed VAS. In addition, the administration fee for each outpatient clinic visit was NT$460, so the patient needed to pay NT$2300 for five weekly visits for Artz® injections and NT$1380 for three weekly visits for Synvisc® injections. If the patient received three Synvisc® injections for one OA knee rather than five Artz® injections, they could save NT$920 in total, and reduced the number of visits for the injections by two. The direct medical

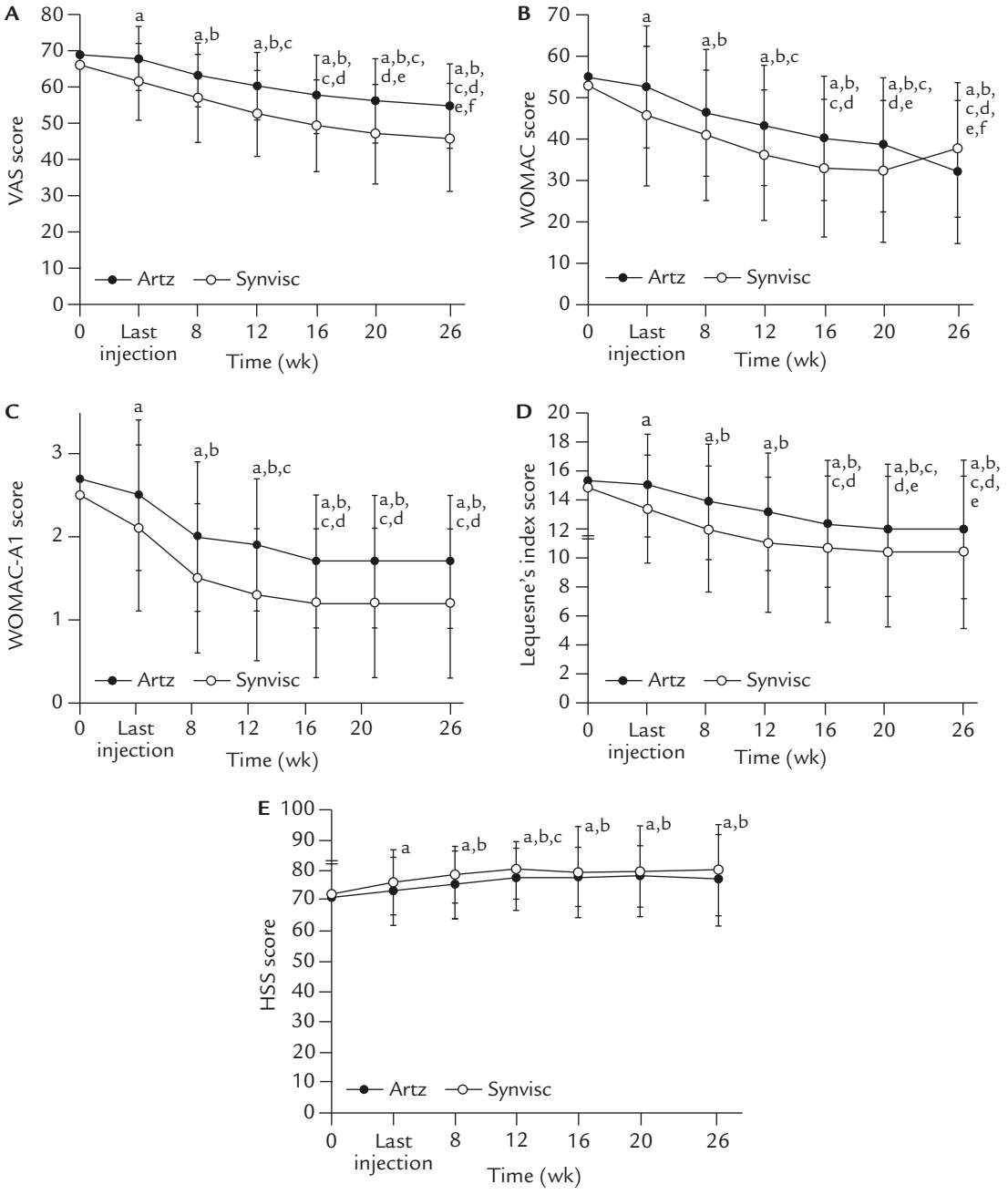

Figure 2. (A) VAS (drug × time effects: $F = 2.055$, $p = 0.057$; drug effects: $F = 9.582$, $p = 0.003$; time effects: $F = 84.247$, $p < 0.000$); (B) WOMAC (drug × time effects: $F = 1.621$, $p = 0.140$; drug effects: $F = 2.866$, $p = 0.095$; time effects: $F = 131.620$, $p < 0.000$); (C) WOMAC-A1 (drug × time effects: $F = 1.047$, $p = 0.394$; drug effects: $F = 5.331$, $p = 0.024$; time effects: $F = 84.985$, $p < 0.000$); (D) Lequesne's index (drug × time effects: $F = 1.823$, $p = 0.093$; drug effects: $F = 2.724$, $p = 0.103$; time effects: $F = 56.020$, $p < 0.000$); and (E) HSS (drug × time effects: $F = 0.388$, $p = 0.887$; drug effects: $F = 1.022$, $p = 0.316$; time effects: $F = 15.248$, $p < 0.000$) measured at baseline, the last injection (5 weeks for Artz® or 3 weeks for Synvisc®), and 8, 12, 16, 20 and 26 weeks after the first injection in both HA-treated knees. Two-way repeated-measures ANOVA was used. Values are mean ± standard deviation ($n = 37$). [a]Significantly different, $p < 0.05$, when compared with baseline. [b]Significantly different, $p < 0.05$, when compared with the last injection. [c]Significantly different, $p < 0.05$, when compared with 8 weeks. [d]Significantly different, $p < 0.05$, when compared with 12 weeks. [e]Significantly different, $p < 0.05$, when compared with 16 weeks. [f]Significantly different, $p < 0.05$, when compared with 20 weeks. VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC-A1 = WOMAC — pain when walking on a flat surface; HSS = Hospital for Special Surgery; HA = hyaluronic acid; ANOVA = analysis of variance.

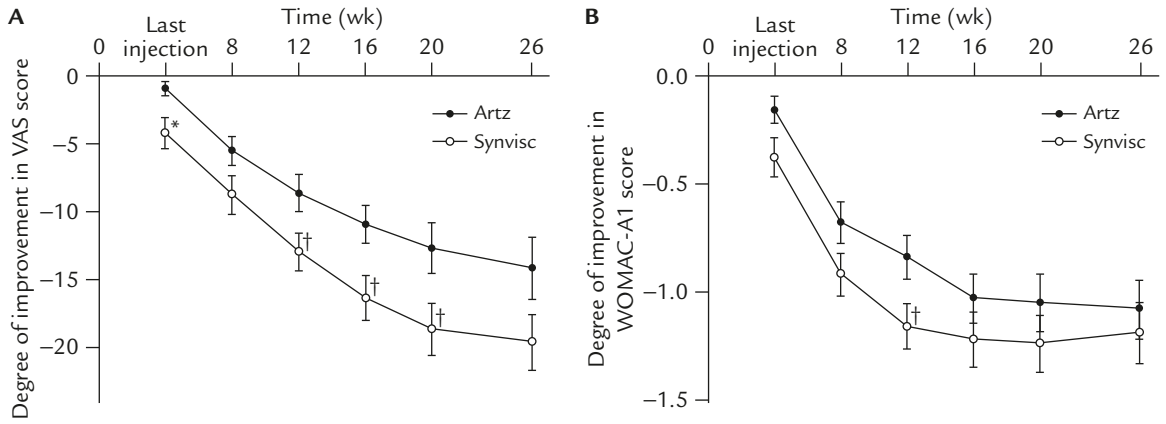

Figure 3. Change in scores in (A) VAS and (B) WOMAC-A1 of both HA-treated knees at the last injection (5 weeks for Artz® or 3 weeks for Synvisc®), and 8, 12, 16, 20 and 26 weeks after the first injection. Student's *t* test was used. Values are mean ± standard deviation ($n = 37$). *$p < 0.01$; †$p < 0.05$. VAS = visual analog scale; WOMAC-A1 = WOMAC — pain when walking on a flat surface; HA = hyaluronic acid.

cost for the patient per QALY gained (ICER) was NT$2300/0.04101 = NT$96,667 (95% CI: 412,423 to 605,757) for five Artz® injections, and NT$1380/0.05977 = NT$58,000 (95% CI: 247,454 to 363,434) for three Synvisc® injections using the transformed VAS. Without incorporating direct non-medical and indirect costs, the total medical cost for the patient and the Taiwan National Health Insurance Program per QALY gained (ICER) was NT$9375/0.04101 = NT$394,021 (95% CI: 1,681,074 to 2,469,116) for five Artz® injections, and NT$7125/0.05977 = NT$299,456 (95% CI: 1,277,616 to 1,876,529) for three Synvisc® injections using the transformed VAS. There were also significant differences between the Artz®- and Synvisc®-treated groups for ICER for the patient ($p < 0.001$), Taiwan National Health Insurance Program ($p = 0.002$), and both of these ($p = 0.001$; Figures 4C–E). At 26 weeks of follow-up, 31 patients (83.8%) agreed to receive the same treatment with Artz® injections for their knee OA for the next course, and 26 of them (83.9%) opted for three weekly Synvisc® injections.

Discussion

Two well-known characteristics of OA are a consequence of a reduction in molecular size and concentration of HA in synovial fluid.[26,27] In addition to the rheological properties, HA with cross-linked forms can affect its depolymerization and degradation, and then prolong the MW-dependent binding ability to specific cell receptors, notably CD44, which allows HA to modulate cell function directly and promote downregulation of the expression of u-PA, PAI-1, MMP-2 and MMP-9.[5,12,28] This might explain some of the possible mechanisms for the different clinical efficacy. Although Artz® has a short intra-articular residence time (with a half-life < 1 day), a little Synvisc® remains in the synovial fluid 7 days after intra-articular injection, and significant quantities are present in the synovial tissue and on the cartilage surface.[7] This is the reason why we did not include OA knees with significant effusions, which needed to be aspirated before subsequent injections.

Several cases of pseudoseptic arthritis have been reported after intra-articular HA injections, especially Synvisc® injection,[29,30] whereas no systemic and few local adverse effects were observed in the present study. In 6 months of VAS and WOMAC scores, in 5 months of Lequesne's index scores, in 4 months of WOMAC-A1 scores, and in 3 months of HSS scores, Artz® and Synvisc® improved clinical symptoms and physical functions. It is therefore reasonable that 31 patients (83.8%) agreed to receive the same treatment with HA injections for the next course. As previously reported, HA with higher MW has a greater

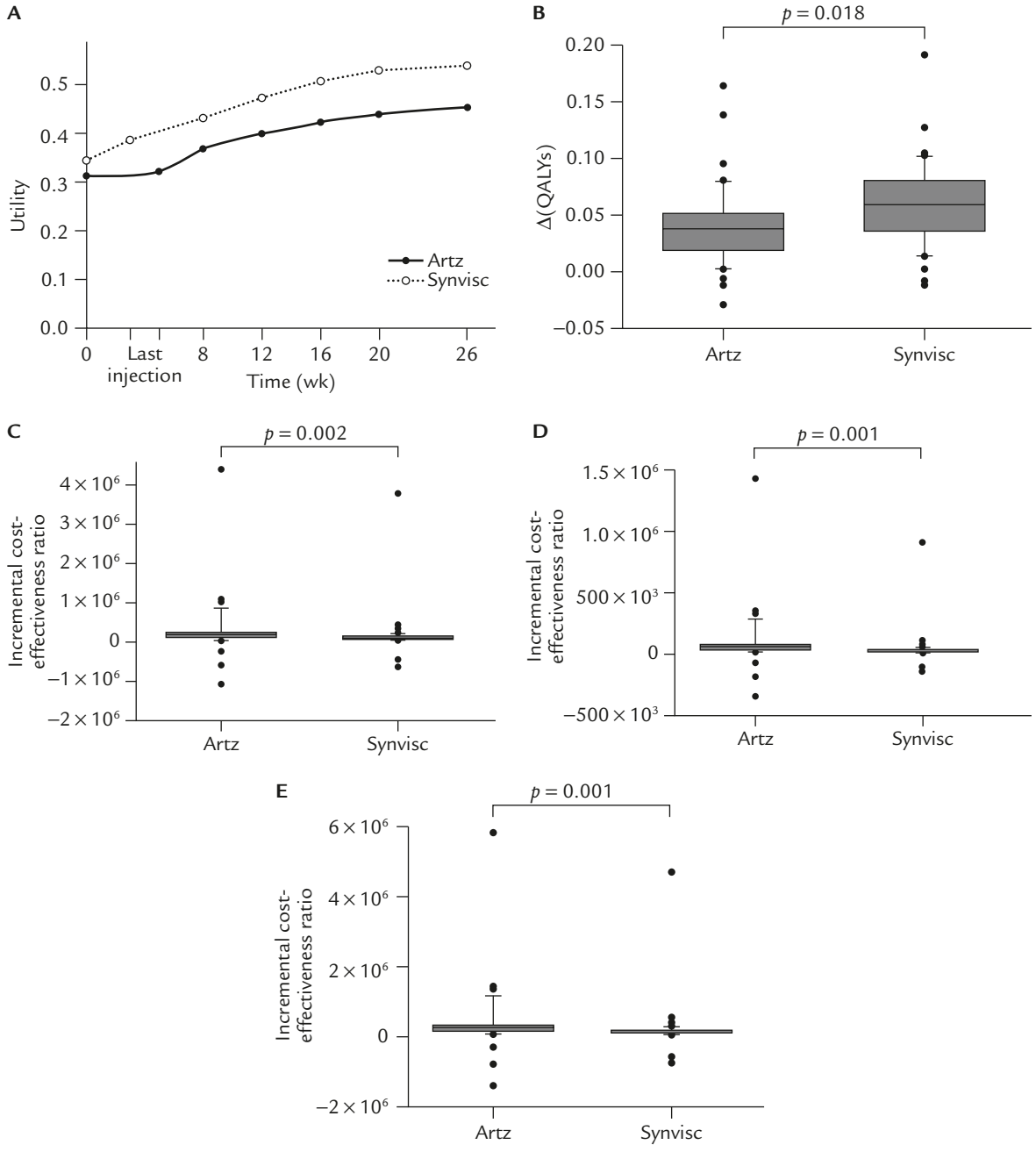

Figure 4. (A) Utilities derived from the transformed VAS of both HA-treated knees at baseline, the last injection, and 8, 12, 16, 20 and 26 weeks after the first injection. (B) Quality of life per period Δ(QALYs) (0–26 weeks) between Artz®- and Synvisc®-treated knees. (C) Direct medical cost for the Taiwan National Health Insurance Program per QALY gained (ICER) for five Artz® injections and three Synvisc® injections. (D) Direct medical cost for the patient per QALY gained (ICER) for five Artz® injections and three Synvisc® injections. (E) Total medical cost for the Taiwan National Health Insurance Program and the patient per QALY gained (ICER) for five Artz® injections and three Synvisc® injections. The Mann–Whitney *U* test was used ($n = 37$). VAS = visual analog scale; HA = hyaluronic acid; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.

effect on the performance of viscosupplementation.[31,32] In the present study, Synvisc® had better pain-relieving effects, as shown by the VAS scores at 5 months and of the WOMAC-A1 scores at 12 weeks. Moreover, by injecting Synvisc® instead of Artz® to treat knee OA, patients saved at least NT$920 and did not need two additional hospital visits. This meant savings in both direct costs and transportation, and they only needed three injections instead of five. Notably, 83.9% of the

31 patients who were satisfied with HA treatment chose Synvisc® for the next course. In addition, clinicians did not spend time treating the patients and the Taiwan National Health Insurance Program did not spend time processing the payment for the two additional hospital visits.

In the present study, the quality of life per period, Δ(QALYs), for Synvisc® was significantly greater than that for Artz®. Therefore, the direct medical costs for the Taiwan National Health Insurance Program and the patient per QALY gained (ICER) of three Synvisc® injections were lower than those of five Artz® injections, as were the total costs for the Taiwan National Health Insurance Program and the patient. Thus, we suggest that our results are applicable to patients in Taiwan with early OA of the knee, especially in terms of cost-effectiveness. Indeed, the data are still valuable for reference in other countries.

Our study had some limitations. First, there may be subtle differences in the degree of improvement with the same treatment between different stages of knee OA. The knees in this study were not assigned randomly into two groups, and we divided each pair of knees and compared both of them. Synvisc® was introduced in Taiwan in 2005; therefore, there has been little therapeutic experience in treating knee OA with intra-articular injections of Synvisc®. As a result of ethical considerations, the decision to choose five weekly injections of Artz® or three weekly injections of Synvisc® for the more painful knee depended on the patients themselves. The majority of the patients might have chosen the five weekly Artz® injections for the more painful knee because Artz® was the most popular option in Taiwan. Nevertheless, no significant differences were found between these two treated groups before treatment with regard to radiological staging and all VAS, WOMAC, WOMAC-A1, Lequesne's index and HSS scores. Therefore, their baselines should have been similar, although the scores in Artz®-treated knees seemed to be worse than those in Synvisc®-treated knees.

Second, there is a strong placebo effect from joint injections, which may cause an approximately 30% reduction in pain relief during the first few weeks.[33] Although we did not have a placebo group, the placebo effects should be the same for both treated knees and most should have been seen in the early periods. Therefore, we believe that the late findings (4–6 months after the first injection) of this study should reflect reliable results for the comparison. Third, we should comment carefully on a comparison of treatment efficacy with short-term follow-up and a small sample size. Under the Taiwan National Health Insurance Program, a patient can receive two courses of HA treatment for one OA knee in 1 year, and we therefore designed the 6-month follow-up study on this basis. However, this result should be validated in a larger cohort.

In conclusion, our study clearly demonstrated that both types of viscosupplementation produced subjective symptom-modifying effects and an improvement in physical function during a 26-week follow-up period. Synvisc® provided better pain relief and reduced the number of hospital visits for injections by two, as well as reduced the cost per patient by at least NT$920. Synvisc® also has better ICER than Artz® for the Taiwan National Health Insurance Program, the patient, and both combined. Consequently, injecting HA to treat knees with early OA is a safe and efficacious management for selected patients in Taiwan. However, further studies are required to better define the population responsiveness to HA injections, which may decrease the burden on healthcare systems, and optimize cost-effectiveness as part of a conservative strategy for OA management.

References

1. Hedbom E, Hauselmann HJ. Molecular aspects of pathogenesis in osteoarthritis: the role of inflammation. *Cell Mol Life Sci* 2002;59:45–53.
2. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000;43:1905–15.
3. Divine JG, Zazulak BT, Hewett TE. Viscosupplementation for knee osteoarthritis: a systematic review. *Clin Orthop Relat Res* 2007;455:113–22.

4. Bagga H, Burkhardt D, Sambrook P, et al. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol* 2006;33:946–50.
5. Hsieh YS, Yang SF, Lue KH, et al. Effects of different molecular weight hyaluronan products on the expression of urokinase plasminogen activator and inhibitor and gelatinases during the early stage of osteoarthritis. *J Orthop Res* 2008;26:475–84.
6. Takahashi K, Goomer RS, Harwood F, et al. The effects of hyaluronan on matrix metalloproteinase-3 (MMP-3), interleukin-1beta (IL-1beta), and tissue inhibitor of metalloproteinase-1 (TIMP-1) gene expression during the development of osteoarthritis. *Osteoarthr Cartil* 1999;7:182–90.
7. Weiss C, Band P. Musculoskeletal applications of hyaluronan and hylan. Potential uses in the foot and ankle. *Clin Podiatr Med Surg* 1995;12:497–517.
8. Takahashi K, Hashimoto S, Kubo T, et al. Hyaluronan suppressed nitric oxide production in the meniscus and synovium of rabbit osteoarthritis model. *J Orthop Res* 2001; 19:500–3.
9. Kikuchi T, Denda S, Yamaguchi T. Effect of sodium hyaluronate (SL-1010) on glycosaminoglycan synthesis and release in rabbit articular cartilage. *Jpn Pharmacol Ther* 1993;127:157.
10. Tobetto K, Yasui T, Ando T, et al. Inhibitory effects of hyaluronan on [14C]arachidonic acid release from labeled human synovial fibroblasts. *Jpn J Pharmacol* 1992;60: 79–84.
11. Balazs EA. The physical properties of synovial fluid and the special role of hyaluronic acid. In: Helfet AJ, ed. *Disorders of the Knee*, 2nd edition. Philadelphia: JB Lippincott, 1982:61–74.
12. Gomis A, Pawlak M, Balazs EA, et al. Effects of different molecular weight elastoviscous hyaluronan solutions on articular nociceptive afferents. *Arthritis Rheum* 2004;50: 314–26.
13. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2005;2:CD005321.
14. Juni P, Reichenbach S, Trelle S, et al. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. *Arthritis Rheum* 2007;56:3610–9.
15. Lo GH, LaValley M, McAlindon T, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003;290:3115–21.
16. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. *Arthritis Rheum* 2007;57: 1410–8.
17. Strand V, Conaghan PG, Lohmander LS, et al. An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee. *Osteoarthr Cartil* 2006;14:859–66.
18. Wang CT, Lin J, Chang CJ, et al. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004;86-A:538–45.
19. Cheras PA, Whitaker AN, Blackwell EA, et al. Hypercoagulability and hypofibrinolysis in primary osteoarthritis. *Clin Orthop Relat Res* 1997;334:57–67.
20. Murphy G, Knauper V, Atkinson S, et al. Matrix metalloproteinases in arthritic disease. *Arthritis Res* 2002;4(Suppl 3): S39–49.
21. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol* 2001;17: 463–516.
22. Altman RD. Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl* 1991;27:10–2.
23. Galli M, De Santis V, Tafuro L. Reliability of the Ahlback classification of knee osteoarthritis. *Osteoarthr Cartil* 2003; 11:580–4.
24. Zijlstra TR, Braakman-Jansen LM, Taal E, et al. Cost-effectiveness of spa treatment for fibromyalgia: general health improvement is not for free. *Rheumatology (Oxford)* 2007;46:1454–9.
25. Cheng AK, Rubin HR, Powe NR, et al. Cost–utility analysis of the cochlear implant in children. *JAMA* 2000;284:850–6.
26. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthr Cartil* 1995;3:213–25.
27. Balazs EA, Watson D, Duff IF, et al. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. *Arthritis Rheum* 1967; 10:357–76.
28. Miyake K, Underhill CB, Lesley J, et al. Hyaluronate can function as a cell adhesion molecule and CD44 participates in hyaluronate recognition. *J Exp Med* 1990;172:69–75.
29. Brown DJ, Wood EV, Hannah HM, et al. Prospective comparison of sodium hyaluronate and hylan G-F 20 in a clinical practice: comment on the concise communication by Martens. *Arthritis Rheum* 2004;50:1697–8.
30. Pagnano M, Westrich G. Successful nonoperative management of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. *Osteoarthritis Cartilage* 2005;13:751–61.
31. Jackson DW, Simon TM. Intra-articular distribution and residence time of Hylan A and B: a study in the goat knee. *Osteoarthr Cartil* 2006;14:1248–57.
32. Wang CT, Lin YT, Chiang BL, et al. High molecular weight hyaluronic acid down-regulates the gene expression of osteoarthritis-associated cytokines and enzymes in fibroblast-like synoviocytes from patients with early osteoarthritis. *Osteoarthr Cartil* 2006;14:1237–47.
33. Kirwan J. Is there a place for intra-articular hyaluronate in osteoarthritis of the knee? *Knee* 2001;8:93–101.