Journal of Back and Musculoskeletal Rehabilitation 29 (2016) 881–886
DOI 10.3233/BMR-160714
IOS Press

Single versus multiple dose hyaluronic acid: Comparison of the results

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Abstract.
OBJECTIVE: The purpose of this study was to compare the effectiveness of three injections of standard linear HA versus single injection of lightly cross-linking HA in patients with knee OA.
METHODS: Forty subjects were randomized into two groups. The first group received single dose intraarticular injection of 4 ml lightly cross-linking sodium hyaluronate (Monovisc), and the second group received three consecutive intraarticular injections of 2.5 ml standard linear sodium hyaluronate (Adant) with one week intervals. Visual analog scale (VAS)-pain and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores were measured.
RESULTS: In both groups, VAS-pain and WOMAC scores (except WOMAC-stiffness) were improved statistically lasting up to the 6^{th} month with respect to before injection values ($p < 0.001$). There were no statistical differences in VAS-pain and WOMAC scores after injections ($p > 0.05$) in both groups. But in the 6^{th} month visit, VAS-resting values were found to be statistically improved in standard linear HA group compared to lightly cross-linking HA group ($p < 0.05$).
CONCLUSION: Although three-dose administration was significantly superior to single-dose at the sixth month, current knowledge is not sufficient to decide whether single-dose or multiple-dose HA injection should be chosen. There is a clear need for verification of our results with long-term studies on larger patient groups.

Keywords: Hyaluronan, intraarticular injection, knee osteoarthritis

1. Introduction

Osteoarthritis (OA) is the most common joint disease in the world. It is also the most common cause of disabilities, especially in the elderly population [1]. Knee joint is symptomatically the most affected joint by osteoarthritis. There are various types of treatment used for the knee OA.

Hyaluronan (HA) is a major component of both synovial fluid and joint cartilage and it is responsible for the elastoviscosity of synovial fluid [2]. In osteoarthritis, both the concentration and molecular weight of HA are reduced, leading to a loss in viscoelasticity of the synovial fluid [3,4]. The purpose of injecting intraarticular HA is to replace HA so that the natural viscosity of synovial fluid is maintained. Intraarticular HA treatment is a safe procedure. Adverse effects are extremely rare and temporary [5]. Some advantages of the procedure are: being a local treatment, having very few side effects and no known drug interactions.

There are numerous heterogenous studies about HA. Among the nine meta-analyses released to date, two reported a general beneficial effect of hyaluronic acid injections [6,7], five concluded a small benefit [8–12], and two found no proof to support hyaluronic acid injection therapy for knee osteoarthritis [13,14]. HA injections were recommended by Osteoarthritis Research Society International (OARSI), The European

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ISSN 1053-8127/16/$35.00

League Against Rheumatism (EULAR), and American College of Rheumatology (ACR) for hip and knee OA [15–18].

According to the traditional approach, viscosupplementation with HA can be achieved by three consecutive intra-articular injections in patients with knee OA. However, single-dose HA injections are recommended recently. There is no consensus concerning the repetition number of HA injections.

The purpose of this study was to compare the effectiveness of three injections of standard linear HA versus single injection of lightly cross-linking HA in patients with knee OA.

2. Methods

In this prospective randomised study, 40 patients (age range, 45–70 years), who were diagnosed with knee OA according to the American College of Rheumatology (ACR) criteria [19] and were classified with radiological stage II or III according to the Kellgren and Lawrence classification [20] were included.

Exclusion criteria were Age $>$ 70, $<$ 45 years; Kellgren-Lawrence score $>$ 3; systemic disorders such as hematological diseases (coagulopathy), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants or antiaggregants, patients with Hb values $<$ 11 g/dl and platelet values $<$ 150,000/mm, history of total knee replacement, any knee injection within 3 months, inflammatory or postinfectious knee arthritis, allergy or intolerance to study medication, body mass index (BMI) greater than 40 kg/m2.

Subjects were divided into two groups by using QuickCalcs randomization software (Fig. 1). Group 1 received single dose intraarticular injection of 4 ml (15–25 mg/1 ml) lightly cross-linking sodium hyaluronate (polysaccharide, molecular weight 1000–2900 kDa, Monovisc®, Anika Therapeutics, Inc.), whereas Group 2 received three consecutive intraarticular injections of 2.5 ml (25 mg/2.5 ml) linear sodium hyaluronate (disaccharide, molecular weight 900–1000 kDa, Adant®, Meiji Seika Kaisha, Inc.) with one week intervals.

2.1. Injection technique

The knee joint injections were performed by an experienced physician under sterile conditions by inserting a 21-gauge needle into the patellofemoral joint space by superolateral approach while the patients were in a supine position (Fig. 2).

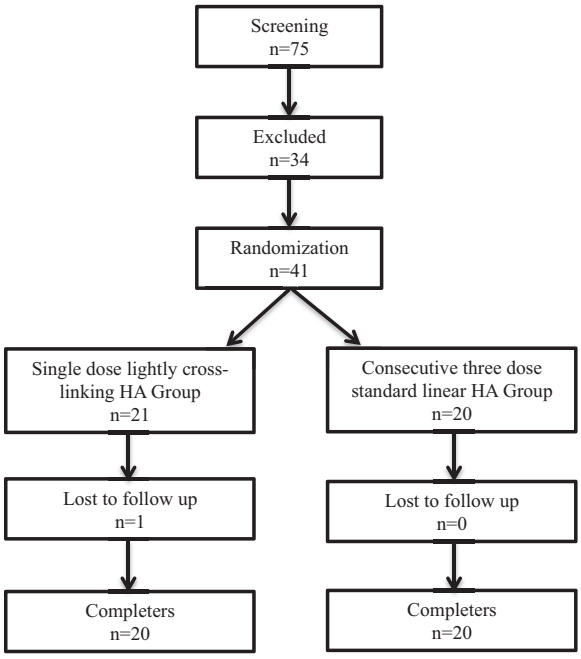

Fig. 1. Flow chart of the study.

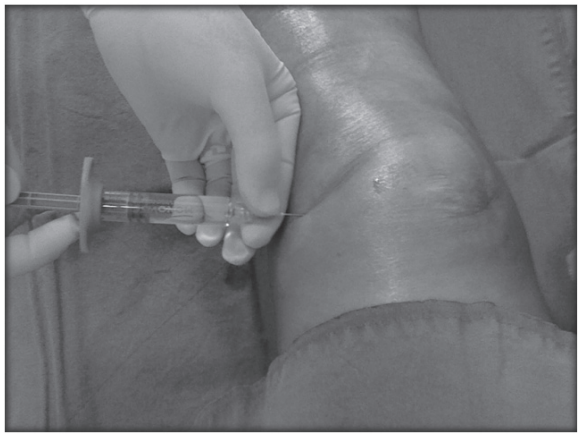

Fig. 2. Intraarticular injection technique with superolateral approach.

2.2. Evaluation

In order to obtain a blind study design, all evaluations were performed by the author who was blind to patients and groups. In both groups, pain levels and functional status of subjects during activity and at rest were measured using a 100 mm visual analog scale (VAS) and Western Ontario and McMaster University Osteoarthritis Index (WOMAC 5-point Likert 3.0)[21] before, right after, 1, 3, and 6 months after the injections.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics, version 21.0). Study data are given as mean, standard deviation, median, frequency and ratio by using descriptive statistical methods. Parameters with normal distribution in both groups were evaluated using Repeated Measures ANOVA. In the evaluation of difference of initial values between the groups, factor of group was included to the model and analysis of repeated measures ANOVA was used. Parameters without normal distribution in both groups were evaluated using Friedman test. Wilcoxon test was used in evaluating the change from initial values of parameters without normal distribution. Mann Whitney U test was used to compare the difference of both values between two groups. A P value < 0.05 was considered statistically significant.

3. Results

The groups were comparable in terms of age, sex, body mass index (BMI), occupation and education level (Table 1). The difference in VAS and WOMAC scores were statistically non-significant at the beginning between two groups ($p > 0.05$).

Analyses within the groups showed in both groups, VAS-activity, VAS-rest, WOMAC-pain, WOMAC-physical function and WOMAC-total value means were improved statistically lasting up until the 6^{th} month with respect to before injection values ($p < 0.001$) (Figs 3–5) (Tables 2–3). Comparison of pre- and post-injection values showed statistically significant difference in none of the parameters studied ($p > 0.05$). In both groups changes in WOMAC-stiffness values were statistically non-significant ($p > 0.05$).

When both groups were compared, there were no statistical differences in VAS-activity, VAS-rest, WOMAC-pain, WOMAC-physical function, WOMAC -stiffness and WOMAC-total values after injections ($p > 0.05$). But in 6^{th} month visit, VAS-rest values were found to be statistically improved in standard linear HA group compared to lightly cross-linking HA group ($p < 0.05$).

None of the patients revealed any adverse event.

4. Discussion

There are differences between various HA preparations on market in terms of molecular weight and

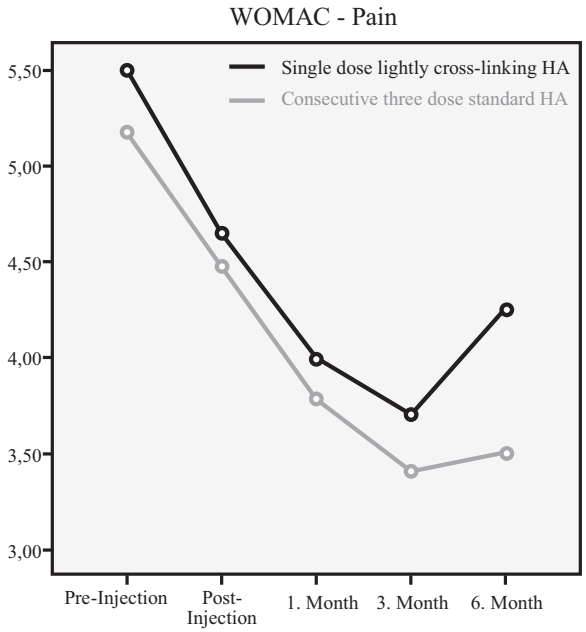

Fig. 3. Comparison of single intraarticular injection of lightly cross-linking HA and three consecutive intraarticular injections of linear HA in terms of WOMAC-pain. WOMAC-pain were improved statistically lasting up until the 6th month with respect to before injection values ($p < 0.001$). There were no statistical differences between the groups ($p > 0.05$).

suggested number of injections. The important clinical question is that which type of HA should be used on what frequency? In this study, the most widely used two different types of HA and two different injection schemes were compared.

HA products are derived from different sources (microbial fermentation vs. extraction from avian tissue). Both HA types used in this study were obtained through microbial fermentation and purification. Standard HA's have usually linear molecular chain. Cross-linking HA have improved viscoelastic properties, increased molecular weight by chemical derivatization, and a longer half-life in the joint compared to non-cross-linked HA [22]. This study shows similar effects of single dose of lightly cross-linking HA and three doses of standard linear HA until six months on pain and functional status of knee OA patients. In our study, both techniques had positive results and they were better than the before-injection period. However, the effect occurs within the first month in both groups. The 6^{th} month control VAS-resting values were found to be statistically improved in standard linear HA group compared to lightly cross-linking HA group.

In a recent study, single 6 ml application of HA and the classical three-weekly 2 ml dose are com-

Table 1
Characteristics of the groups

		Single dose lightly cross-linking HA ($n = 20$)	Consecutive three dose standard linear HA ($n = 20$)	p
Age		57.95 ± 6.97	56.35 ± 5.66	0.431
Sex		16 f/4 m	17 f/3 m	0.67
BMI		30.52 ± 4.94	30.83 ± 3.30	0.82
Occupation	Housewife	13	13	0.55
	Retired	5	4	
	Officer	1	3	
	Employee	1	–	
Education	Primary school	16	15	0.66
	Secondary school	1	0	
	Highschool	2	3	
	University	1	2	

HA-Hyaluronan.

Table 2
VAS-activity pain values before and after injection

	Single dose lightly cross-linking HA	Consecutive three dose standard linear HA	p
Before injection	7.10 ± 1.20	7.10 ± 1.37	1.00
Just after injection	6.40 ± 2.01	5.80 ± 1.82	0.252
1^{st} month after injection	5.60 ± 1.90	4.70 ± 1.86	0.170
3^{rd} mount after injection	4.80 ± 1.50	4.40 ± 2.47	0.699
6^{th} mount after injection	5.20 ± 1.64	4.10 ± 2.10	0.089

VAS-Visual analog scale; HA-Hyaluronan.

Table 3
VAS-rest pain values before and after injection

	Single dose lightly cross-linking HA	Consecutive three dose standard linear HA	p
Before injection	3.10 ± 1.20	3.30 ± 1.62	0.661
Just after injection	3.00 ± 1.65	2.90 ± 1.77	0.670
1^{st} month after injection	3.00 ± 1.65	2.50 ± 2.13	0.166
3^{rd} month after injection	3.06 ± 1.72	2.20 ± 1.43	0.158
6^{th} month after injection	3.10 ± 1.77	2.10 ± 1.51	0.040*

VAS-Visual analog scale; HA-Hyaluronan.

pared and similar results are obtained [23]. There was no statistical difference between the single injection of 6 of sodium hyaluronate and the traditional application with three weekly injections. However, only the classical regime demonstrated statistically significant improvement in relation to the basal values of pain [23]. In the above-mentioned study, similar to our results, the positive effects were started to occur during the first month following injection. The main difference between our study and that study is simultaneous intra-articular corticosteroid injection to all patients. We think that this may prevent clear evaluation of hyaluronic acid injection. We, therefore, used solely hyaluronic acid injections in our study.

The difference on the sixth month between consecutive three dose HA injection and single dose HA injection in terms of resting pain may be related with longer intraarticular exposure in three dose HA administration besides different structures of HA molecules compared. It has been reported that the intra-articular half-life of HA is about 13 hours and it is effective almost seven days [24]. In multiple dose administration, the exposure time of joint surface with HA increases.

There is no concensus on injection volume as well as injection number of HA. There are 2, 2.5, 3, 4 or 6 ml products on the market. In our study, we used 4 ml volume in single dose group and 2.5 ml volume in three dose group as suggested by manufacturer. Higher amounts of injection may cause stretching in the joint capsule and may increase pain, conversely lower amounts may not be effective. The volume of HA, at the same time, may affect proprioceptive sensation of patients [25]. According to our results, single dose of 4 ml and three dose of 2.5 ml (total of 7.5 ml) injections have similar results apart from sixth month rest pain.

Injection technique is one of the important factors determining the response to HA. As a rule of thumb,

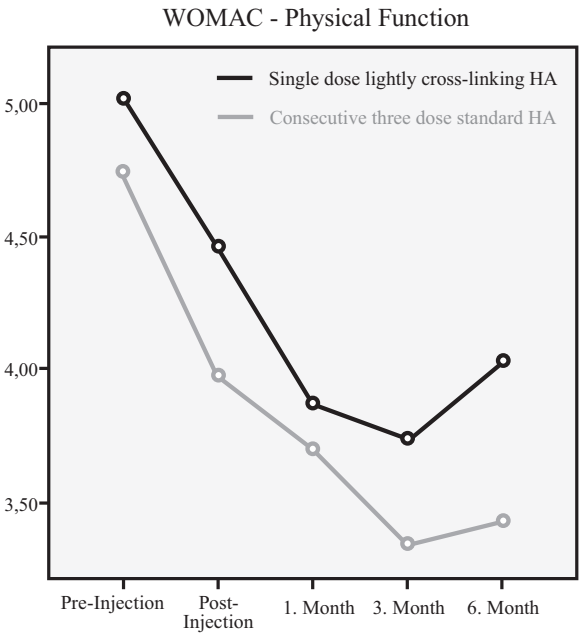

Fig. 4. Comparison of single intraarticular injection of lightly cross-linking HA and three consecutive intraarticular injections of linear HA in terms of WOMAC-physical function. WOMAC-physical function were improved statistically lasting up until the 6th month with respect to before injection values ($p < 0.001$). There were no statistical differences between the groups ($p > 0.05$).

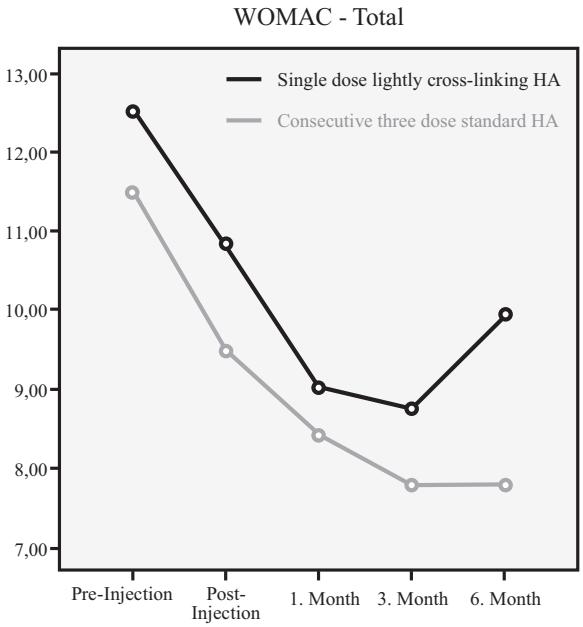

Fig. 5. Comparison of single intraarticular injection of lightly cross-linking HA and three consecutive intraarticular injections of linear HA in terms of WOMAC-total. WOMAC-total were improved statistically lasting up until the 6th month with respect to before injection values ($p < 0.001$). There were no statistical differences between the groups ($p > 0.05$).

resistance should not be felt during intra-articular fluid injection. Sense of resistance during injection suggests that the needle might be inserted into high density regions such as periosteum or tendon [26]. The viscosity of cross-linking HA is higher than standard linear HA which may lead to more resistance than expected in case of inadequate needle size. This may technically complicate adequate location of the needle. This is seen as a technical disadvantage for cross-linking HA. Nevertheless, we experienced no negative condition resulting from injection technique in our study.

More time and increasing number of patient visits are needed for three injections. Three consecutive intra-articular injections of HA may increase the risks of injection-related adverse situations. These risks may include extra articular needle placement, bleeding, infection, pseudoseptic reaction, and anaphylaxis [27]. Additionally, patient comfort can be negatively affected depending on three injections. When deciding for single vs multiple dose treatment, injection-related adverse event risks, difficulty of coming to the hospital, work-day losses, costs and patient preferences should be taken into consideration.

Limitations of this study include small number of sample size and absence of a placebo control group. In this study, we compared two different HA preparations administered by two different injection protocols. That's why we did not include a placebo-control arm. In addition, the lack of statistical calculation of the sample size is the another limitation.

5. Conclusion

Although three-dose administration was significantly superior to single-dose on resting pain at the sixth month, current knowledge is not sufficient to decide whether single-dose or multiple-dose HA injection should be chosen in patients with knee osteoarthritis. Therefore, there is a clear need for verification of our results with long-term studies on larger patient groups.

Conflict of interest

The authors have no conflict of interest to declare.

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Journal of Medical Economics 2014, 1–12

1369-6998
doi:10.3111/13696998.2014.902843

Article 0145.R1/902843

Original article

Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain

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Keywords:
Bioengineered hyaluronic acid – NSAIDs – Analgesics – Knee – Osteoarthritis – Cost-effectiveness

Accepted: 3 March 2014; published online: 21 March 2014
Citation: J Med Econ 2014; 1–12

Abstract

Objective:
To determine the cost-effectiveness of bioengineered hyaluronic acid (BioHA, 1% sodium hyaluronate) intra-articular injections in treating osteoarthritis knee pain in poor responders to conventional care (CC) including non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics.

Methods:
Two decision analytic models compared BioHA treatment with either continuation of patient's baseline CC with no assumption of disease progression (Model 1), or CC including escalating care costs due to disease progression (NSAIDs and analgesics, corticosteroid injections, and surgery; Model 2). Analyses were based on patients who received two courses of 3-weekly intra-articular BioHA (26-week FLEXX Trial + 26-week Extension Study). BioHA group costs included fees for physician assessment and injection regimen, plus half of CC costs. Cost-effectiveness ratios were expressed as averages and incremental costs per QALY. One-way sensitivity analyses used the 95% confidence interval (CI) of QALYs gained in BioHA-treated patients, and ±20% of BioHA treatment and CC costs. Probabilistic sensitivity analyses were performed for Model 2.

Results:
For 214 BioHA patients, the average utility gain was 0.163 QALYs (95% CI = −0.162 to 0.488) over 52 weeks. Model 1 treatment costs were $3469 and $4562 for the BioHA and CC groups, respectively; sensitivity analyses showed BioHA to be the dominant treatment strategy, except when at the lower end of the 95% CI. Model 2 annual treatment costs per QALY gained were $1446 and $516 for the BioHA and CC groups, respectively. Using CC as baseline strategy, the incremental cost-effectiveness ratio (ICER) of BioHA was $38,741/QALY gained, and was sensitive to response rates in either the BioHA or CC groups.

Conclusion:
BioHA is less costly and more effective than CC with NSAIDs and analgesics, and is the dominant treatment strategy. Compared with escalating CC, the $38,741/QALY ICER of BioHA remains within the $50,000 per QALY willingness-to-pay threshold to adopt a new technology.

Introduction

Osteoarthritis (OA), the most common form of arthritis, affects millions of adults worldwide[1,2]. OA is characterized by the breakdown of joint cartilage, resulting in joint swelling and inflammation, with associated pain and loss of movement[3]. The World Health Organization estimates that at least 10% of

adults aged ≥60 years experience OA-related health issues[4]. In addition, OA is the fifth leading cause of disability among US adults[5].

Due to heterogeneity in research methods, OA prevalence rates are difficult to determine[4]. Studies have used radiographic, clinical, or symptomatic definitions to identify OA patients[6]. Based on available data, the lifetime risk of developing symptomatic knee OA has been estimated at ~40% in men and ~47% in women, with obese persons at higher risk[7]. While the current prevalence of OA is unknown, it is clear that rates are increasing. In the US, estimated OA prevalence increased from 21 million in 1990 to 27 million in 2005[1], and by 2030 an estimated 67 million adults are projected to be diagnosed with arthritis[8]. Because OA is associated with older age, an increasing elderly population also signals future significant rises in prevalence[4].

As a leading cause of disability in men and women[9], OA significantly impacts patient health-related quality-of-life (HRQoL), causing fatigue, decreased sleep quality, and impaired mental health, social function, and work productivity. As shown in a 2007 Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report (MMWR), OA-related annual costs to US society in terms of medical care and lost wages exceeded $128 billion in 2003 (equivalent to $197 billion in adjusted 2013 US dollars)[10,11]. Medical expenditures accounted for $80.8 billion in costs, while indirect costs were $47 billion[10]. The CDC MMWR report noted that, nationally, direct costs associated with OA increased by 24% from 1997–2003, and these costs are expected to increase as OA prevalence continues to rise[10]. As the leading cause of joint replacement surgery, $42.3 billion was spent on OA-related surgeries in 2009 alone[6]. Also in 2009, OA was responsible for an estimated 921,000 hospitalizations, with a mean cost per stay of $45,443 [6]. Moreover, a 2011 evaluation of national inpatient hospital costs ranked OA treatment as the second most expensive condition treated in US hospitals[12].

Injection with intra-articular hyaluronic acid (HA), also known as viscosupplementation, is indicated for the symptomatic relief from pain in patients with OA of the knee after the failure of conservative treatment. Results from a 2006 Cochrane Review found viscosupplementation to be an effective treatment for OA of the knee, with beneficial effects on pain, function, and Patient Global Assessment. Hyaluronic acid treatment was associated with a moderate-to-large effect size, depending on preparation used, outcome indicators, and evaluation time points. For example, viscosupplementation provides the largest benefit on weight-bearing pain at 5–13 weeks post-injection[13]. A 2012 update to the American College of Rheumatology (ACR) guidelines on management of OA of the hand, hip, and knee recommends the use of intra-articular HA injections for patients deemed poor responders to conventional therapy. Conventional therapy includes non-pharmacologic therapies (e.g., exercise, weight loss, physical therapy, walking aids, and support devices, etc.) and pharmacologic therapies (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], topical NSAIDs, tramadol, and corticosteroid injections)[14].

Sodium hyaluronate 1% (EUFLEXXA*) is a highly purified, BioHA produced from *Streptococcus zooepidemicus* using a fermentation, recovery, and purification process, which creates high molecular weight HA without chemical cross-linking. In a 3-month registration randomized controlled trial (RCT) that evaluated OA patients with moderate-to-severe pain who failed to respond or responded poorly to conventional therapy, BioHA was shown to have comparable efficacy to hylan G-F 20, an avian-derived, cross-linked, HA-based preparation (CL-HA)[15]. The 26-week FLEXX Trial assessed the safety and efficacy of BioHA in a randomized, placebo-controlled study of 588 patients who were non-responders or poor responders to prior conventional therapy. Results showed a decrease in 100 mm visual analog scale (VAS) scores of 25.7 mm and 18.5 mm for the BioHA and intra-articular saline groups, respectively, with a least-squares means difference of −6.6 mm ($p = 0.002$). This corresponded to a 53% median reduction in pain score from baseline for the BioHA group, compared with a 38% reduction for the intra-articular saline group ($p = 0.002$)[16]. The FLEXX Trial also found that the effect of BioHA injections was durable in that the reduction in pain was sustained for up to 26 weeks[16]. These results led to the additional 26-week open-label FLEXX Trial Extension Study which evaluated the safety of a repeated series of 3-weekly BioHA injections, and demonstrated that repeat injections of BioHA were safe, well tolerated, and not associated with an increase in adverse events (AEs) such as synovial effusions[17].

Additionally, a recent study of FLEXX Trial patients examined the effects of BioHA on HRQoL. This analysis found that patients treated with BioHA had significant improvements in physical functioning, bodily pain, general health perceptions, and the physical component summary score, as measured by the 36-item Short-Form Health Survey[18].

Cost-effectiveness analysis is a tool for comparing the costs and outcomes of specific treatment programs[19]. Often, outcomes are presented in terms of a measurement of patient preference or utility, the quality-adjusted life year (QALY) being the most common[20]. The calculation of QALYs is based on utility values, which are quantifications of the desirability of health states[19]. Cost-effectiveness analysis then takes costs from real-world data and uses them to rank the programs being

*Euflexxa is a registered trademark of Ferring B.V., Parsippany, NJ, USA.

compared, frequently in terms of an incremental cost-effectiveness ratio, which divides the difference in cost by the difference in outcome[19]. Although real-world cost parameters are variable, cost-effectiveness analysis must use fixed data points and estimates. However, cost-effectiveness analysis typically includes sensitivity analysis as well, in which the values used are adjusted to account for uncertainties or imprecision in the base case[19].

Only a few studies have been published in North America and Europe on the cost-effectiveness of CL-HA (Synvisc*) in OA of the knee[21–23]. In 2001, Waddell *et al.*[23] simulated viscosupplementation treatment in a managed care setting. The authors found that, over a 3-year period, the addition of CL-HA to the standard treatment pathway yielded savings of $4706 per OA patient treated, or ~$1569 per year in 1998 US dollars. A 2002 study by Torrance *et al.*[21], based on a 1997 RCT of CL-HA, compared appropriate care (defined as following ACR guidelines) plus CL-HA, vs appropriate care without CL-HA. This study showed an incremental cost-effectiveness ratio (ICER) of $10,000 (in 1999 Canadian dollars) per QALY gained for CL-HA plus appropriate care. In a 2003 study, Kahan *et al.*[22] compared CL-HA to conventional care and found that CL-HA was more effective with no additional cost. Similarly, a French observational study ($n = 296$) found that costs associated with HA injections were offset by reductions in medical and non-medical costs[24]. Results from a few studies conducted outside of North America and Europe have also mostly found intra-articular HA treatment to be cost-effective with associated increased short-term costs and increased QALYs[25,26]. Results from a study in Thailand ($n = 146$) found that intra-articular HA injections increased short-term treatment costs, but were associated with the delay or cancellation of surgical treatment and a consequent savings of 63.3%[25]. One Taiwan-based study by Yen *et al.*[26] modeled a comparison of naproxen, celecoxib, and intra-articular HA treatment. Results from this study show that intra-articular HA had an ICER of $42,000 per QALY, and was, thus, not a cost-effective therapy for the Taiwanese healthcare system.

The objective of the present study is to assess the use of BioHA in adult patients with moderate-to-severe knee pain due to OA, who either failed to respond or responded poorly to conventional therapy, using data from the FLEXX Trial and Extension Study as the basis for treatment data in 2 cost-effectiveness analyses. The first analysis (Model 1) was developed to determine, from the payers' perspective, if BioHA treatment makes economic as well as clinical sense. Model 1 evaluated costs associated with the continuation of therapies that patients were using prior to study enrollment, and compared those to the cost of BioHA treatment in the same patient population. In this model, the patient population was derived from the FLEXX Trial and Extension Study with the conventional care arm modeled from baseline data. A threshold of $50,000 per QALY was applied to investigate whether BioHA could be adopted as a cost-effective technology[27]. To further test the cost-effectiveness of BioHA treatment for OA, a secondary analysis (Model 2) was run using BioHA response data from the FLEXX trial. In this analysis, the modeled conventional care program was based on the response rate from the conventional care arm of an RCT of CL-HA, in which appropriate care was based on ACR guidelines, but did not include intra-articular injections[28].

*Synvisc is a registered trademark of Genzyme Corporation, Ridgefield, NJ, USA.

Patients and methods

Study design

The Model 1 study used a decision analytic model to compare BioHA treatment with continuation of patients' existing conventional OA care (Figure 1a). This model assumed patients would have been maintained on their pre-study conventional treatment had they not enrolled in the FLEXX Trial and Extension Study. This approach allowed for a model that estimated the incremental outcome if patients remained on their conventional, baseline treatment vs if they received BioHA.

Model 1 assumed that the conventional care group continued to receive conventional treatment and did not achieve any additional QALY improvements over the course of the study (corresponding with a FLEXX trial inclusion criteria stipulating that patients did not respond, or responded poorly to usual care treatment), while the

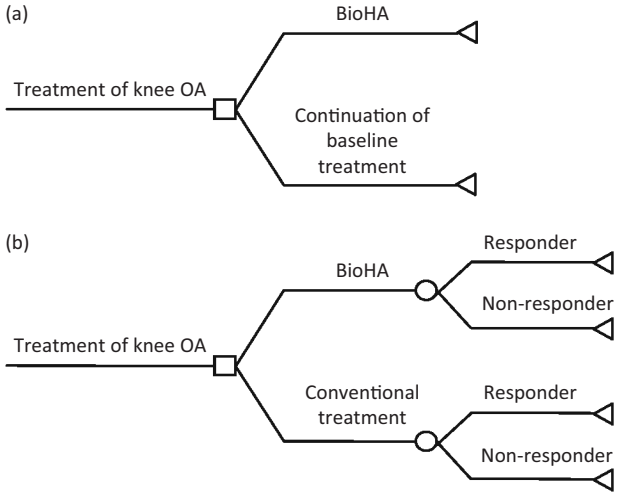

Figure 1. (a) Model 1: Cost-effectiveness model of BioHA vs continuation of baseline treatment. (b) Model 2: Cost-effectiveness model of BioHA vs conventional care, responders and non-responders. BioHA, bioengineered hyaluronic acid; OA, osteoarthritis.

BioHA group achieved average QALY changes as observed in the FLEXX Trial. This allowed for a strict comparison using the same patient population that either maintained their conventional, baseline treatment, or added BioHA treatment to the treatment regimen.

The Model 2 study also used a decision analytic model to compare the costs and utilities in patients with OA of the knee treated with BioHA vs conventional therapy (Figure 1b). In this model, the conventional therapy group was based on the appropriate care group from a study by Raynauld *et al.*[28], which allowed for a comparison between treatment with BioHA and typical conventional treatment, up to and including total knee replacement (TKR). For Model 2, treatment outcome was patient response based on the Raynauld study criterion, defined as achieving a $\geq$20% improvement from baseline on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score[28].

Data source for outcome probabilities

BioHA treatment response rates for both Model 1 and Model 2 were based on the FLEXX Trial and Extension Study[16,17]. The FLEXX Trial was a randomized, double-blind, US multi-center, placebo (saline)-controlled study, which investigated the efficacy and safety of BioHA for the treatment of mild-to-moderate OA knee pain in patients who did not respond adequately to conventional therapies[16]. Inclusion criteria included OA of the knee, a moderate-to-severe pain score on the 100 mm VAS immediately following a 50-foot walk test, bilateral standing anterior–posterior radiograph demonstrating Kellgren-Lawrence grade 2 or 3 OA of the target knee, ability and willingness to use only acetaminophen as the study rescue medication, and unassisted walking 50 feet on level ground and going up and down stairs. Patients received a course of 3-weekly injections of either BioHA or saline. The primary efficacy outcome measure was the least-squares mean difference between BioHA and saline in patients' changes in knee pain from baseline to week 26 on a 100 mm VAS following a 50-foot walk test. In addition, changes in WOMAC subscales of pain, stiffness, and physical function were also assessed at baseline and follow-up. In this trial, intra-articular BioHA therapy resulted in significant OA knee pain relief with a mean reduction from baseline of 53% for intra-articular BioHA vs 38% for intra-articular saline ($p = 0.002$)[16]. Patients treated with BioHA also experienced significant improvements in joint function, treatment satisfaction, and general HRQoL[16].

In the 26-week, open-label FLEXX Trial Extension Study, patients who completed the FLEXX Trial and elected to participate continued to be masked to their treatment assignment, and received either an initial course of BioHA injections (if they received saline in the FLEXX Trial; $n = 214$) or a second course of BioHA injections ($n = 219$)[17]. Extension Study results show that a repeated BioHA injection series was safe and well tolerated. No patients reported joint effusion over the course of the 52-week FLEXX Trial and Extension Study. The outcomes of BioHA treatment were assessed for the 214 patients in the intent-to-treat population who received BioHA in both the FLEXX Trial and the FLEXX Trial Extension Study[17].

The response rate for conventional treatment in Model 2 was adopted from the appropriate care arm of a prospective, randomized, open-label, 1-year multicenter trial conducted in Canada, comparing appropriate care with CL-HA to appropriate care without CL-HA[28]. Patient inclusion criteria included age $\geq$40 years, radiologically verified OA, VAS pain score >175 mm of 500 mm on the WOMAC scale despite treatment with acetaminophen or NSAIDs, and ambulatory status[28]. Appropriate care included analgesics; NSAIDs; corticosteroid injections; supportive measures such as education and counseling, weight loss, joint rest, application of heat or ice, and use of devices, physical therapy, and arthroscopy; and total joint replacement[28].

Derivation of utility scores

Utility represents the value, or weight, that patients place on their health status outcomes. In this study, QALYs were assessed by combining the weights calculated for health states achieved with an intervention, alongside the time spent in those health states. In essence, any QALY gains observed were the product of 2 variables: the increase in HRQoL afforded by the intervention and any additional lifespan gained by an individual due to treatment. Combining the QALYs gained with the respective incremental costs of healthcare resources, consumption resulted in cost-per-QALY estimates.

Since health utility was not directly measured in the FLEXX Trial or Extension Study, a method developed by Grootendorst *et al.*[29] was employed to derive health-state utilities. This approach used a widely used measure of health-state utilities, the Health Utilities Index Mark 3 (HUI-3), which was predicted using WOMAC pain, stiffness, and function subscales, demographic variables, and duration of OA as inputs in a multiple regression model. In the FLEXX Trial and Extension Study, WOMAC was measured at baseline and at weeks 1, 2, 3, 6, 12, 18, 26, 27, 28, 41, and 52. For patients with missing WOMAC data, the last observation carried forward method was used to impute missing values.

Model 1 assumed that all patients who continued on the conventional, baseline treatment would be non-responders with no additional gain in QALY. Therefore, Model 2 is more conservative because it was assumed that

there will still be some responders in the conventional treatment arm; the response rate for Model 2 was adapted from published literature[28].

OA treatment costs

The estimated cost of a course of 3-weekly BioHA injections was $342 in 2012. BioHA-treated patients received a total of 2 treatment courses over the 52-week study period. Since patients had to visit the physician's office for BioHA injections (as per the clinical study protocol and preparation labeling), fees for a physician visit and 2 courses of 3 injectable drug administrations were added to the cost of BioHA treatment. To calculate these costs, the median 2012 fee for all carriers and localities of the Centers for Medicare & Medicaid Services Physician Fee Schedule rates for office visits ($42.55) and injectable drug administration ($69.78) was applied[30].

Several studies have reported on the direct health economic impact of OA in community-based settings[23,31,32]. In this study, Model 1 adopted conventional cost figures reported by Waddell *et al.*[23] because this research grouped OA costs specifically by treatment types that closely resembled modalities used in the current study (i.e., conventional treatment with NSAIDs or analgesics). Waddell *et al.*[23] compiled treatment costs from a large claims database with 2 million members, and included costs directly related to OA of the knee. Also included was the cost of OA treatment-related side effects such as gastrointestinal bleeding from NSAID use. The authors reported total annual costs for the group that received conventional treatment at $2622 in 1998 US dollars[23]. This was equivalent to $4562 in 2012 dollars after adjustment using the Medical Care Consumer Price Index (CPI).

In Model 2, the costs of conventional OA treatment were taken from a 2013 study by Losina *et al.*[33] that examined the cost-effectiveness of disease-modifying OA drugs. This study included 4 levels of conventional care: NSAIDs, acetaminophen, physical therapy, and assistive devices. For this analysis, the cost estimate for the first level of conventional care was used, amounting to an annual cost of $483 per patient in 2010 dollars. After adjustment to 2012 dollars using CPI data, the average annual treatment cost for an OA patient receiving conventional care was $516.

In both Models 1 and 2, 50% of the costs associated with conventional OA treatment were added to the costs of BioHA. The justification for this came from 2 previous studies. In the first study (1996), Lussier *et al.*[34] reported that approximately one-half of patients who used an HA-based preparation were able to reduce their NSAID use. In the second study (2011), Berger *et al.*[35] examined healthcare utilization costs prior to TKR and found that mean healthcare costs increased by 50% between the eighth calendar quarter and the quarter immediately preceding surgery. These costs were largely attributable to prescription NSAIDs, opioids, and injectable corticosteroids, as well as physician office visits and emergency department visits. Therefore, the BioHA arm was assumed to incur half the costs of NSAID/analgesic treatment, while the conventional care group was assumed to incur the full costs of conventional treatment. However, because Models 1 and 2 used different sources for conventional costs, the amounts added to the BioHA costs varied between models. Costs and other parameters used in the base case decision analysis model are summarized in Table 1.

Incremental cost-effectiveness ratio

Treatment with BioHA was compared with conventional care by calculating the ICER (the ratio of incremental costs over incremental changes in utility during the 52-week study period for the 2 treatments under comparison). The Model 1 analysis computed the incremental cost per QALY of the FLEXX BioHA-treated group compared with the conventional care group, assumed to be maintained on their existing pre-study therapy. The Model 2 analysis computed the incremental cost per QALY of the FLEXX BioHA-treated group compared with the conventional care group (using response rates and costs from Raynauld *et al.*[28] and Losina *et al.*[33], respectively).

Sensitivity analysis

For both models, one-way sensitivity analyses were performed to test the robustness of study results by varying baseline costs and utilities by ±20%. Input variables in the sensitivity analyses were BioHA costs and annual healthcare costs for conventional treatment with NSAIDs and analgesics. For Model 1, the sensitivity analysis also tested variance in QALYs gained for the BioHA arm (95% confidence interval [CI]). For Model 2, response rates for both BioHA and conventional care were varied by ±20% from the base case scenario. Also in Model 2, for probabilistic sensitivity analysis, a Monte Carlo Simulation was performed using 10,000 joint distribution samples of the three parameters (costs, utility, and response rates). The ICER distributions resulting from these simulations were reported, and acceptability curves were charted for the 2 treatments under various willingness-to-pay assumptions. All decision model and sensitivity analyses were carried out using TreeAge Pro Interactive, decision analysis Software (TreeAge Software, Inc., Williamstown, MA). In addition to base case values, low and high parameter values for the sensitivity analyses of both Models 1 and 2 are shown in Table 1.

Table 1. Models 1 and 2: Input parameters for the base case and ranges of the parameters for sensitivity analysis.

Parameters	Base case	Plausible range	
		Low	High
Two courses of BioHA	$684	$547	$821
Cost of 1 physician visit (HCPCS code, 99201)	$42.55	NA	NA
Cost of 1 knee injection (HCPCS code, 20610)	$69.78	NA	NA
Model 1			
Annual healthcare costs for conventional treatment of OA with NSAIDs and analgesics	$4562	$3650	$5474
QALYs gained per year			
BioHA	0.163	−0.162	0.488
Model 2			
Annual healthcare costs for conventional treatment of OA with NSAIDs and analgesics	$516	$413	$619
Response rate of BioHA	56%	45%	67%
Response rate of appropriate care	40%	32%	48%
QALYs gained per year			
Responder	0.23	0.184	0.276
Non-responder	0.08	0.064	0.096

BioHA, bioengineered hyaluronic acid; HCPCS, Health Care Financing Administrators Common Procedure Coding System; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; QALYs, quality-adjusted life years.

Table 2. FLEXX Trial baseline demographics[16].

	IA-SA ($n = 295$)	IA-BioHA ($n = 291$)
Men, *n* (%)	109 (37)	107 (37)
Women, *n* (%)	186 (63)	184 (63)
Age, years, mean (SD)	60.8 (10.0)	62.5 (11.0)
BMI, kg/m^2 (mean)	33.0 (7.0)	32.4 (7.0)
Kellgren-Lawrence grade, *n* (%)		
2	115 (39)	119 (41)
3	180 (61)	172 (59)
Prior year target knee treatment, *n* (%)	203 (69)	199 (68)
Physical therapy	23 (8)	16 (6)
Arthrocentesis	8 (3)	16 (6)
Steroid injection	52 (18)	55 (19)
Other injection	8 (3)	10 (3)
NSAID	176 (60)	172 (59)
Mean baseline pain (100 mm VAS 50 foot walk), mean (SD)	54.7 (22.0)	55.6 (22.0)

Reprinted with permission from Altman *et al.*[16].
IA-SA, intra-articular buffered saline; IA-BioHA, intra-articular 1% sodium hyaluronate; SD, standard deviation; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analog scale.

Results

Patient baseline characteristics

At baseline, mean patient age in the FLEXX Trial and Extension Study was 61.7 years, and mean body mass index (BMI) was 32.8 kg/m^2 [17]. Other baseline demographic information, including Kellgren-Lawrence grade and prior OA treatment, are shown in Table 2[16,17].

The Raynauld *et al.*[28] study was used as the conventional treatment arm in Model 2. In that study, mean patient age was 63 years, mean BMI was 32.5 kg/m^2, and mean WOMAC pain was 11.7 on a scale of 0–20. The mean duration of OA symptoms in the study knee was 9.45 years, with the majority of patients (60%) showing radiological Grade 3 or 4 in the year prior to enrollment in the study. At baseline, 69% of patients rated their global assessment of OA in the study knee as either "poor" or "very poor".

Model 1

QALYs gained over 52 weeks

At the end of the FLEXX Extension Study (week 52), the estimated average QALYs gained were 0.163 (95% CI = −0.162 to 0.488) for the 214 patients who received 2 courses of 3-weekly BioHA injections. The HUI-3 scores for the BioHA-treated patients during the 52-week follow-up are plotted in Figure 2. For the conventional care group, patients were maintained on their original OA care and did not gain any QALYs.

Base case cost-utility analysis scenario

Total treatment costs over 1 year were $3469 for the BioHA group and $4562 for conventional care with NSAIDs. Because BioHA treatment was less costly and more effective than conventional care, BioHA was the dominant strategy, and no ICER was calculated (Table 3).

Sensitivity analysis

Results from one-way sensitivity analyses showed that BioHA remained the dominant strategy (both less expensive and more effective) when BioHA and conventional care treatment costs were set at ±20% (Table 4). BioHA also remained dominant when QALYs gained were set at the high end of the 95% CI. The only scenario in which

BioHA was not dominant was when the QALYs gained with intra-articular BioHA were assumed to be at the lowest end (−0.162).

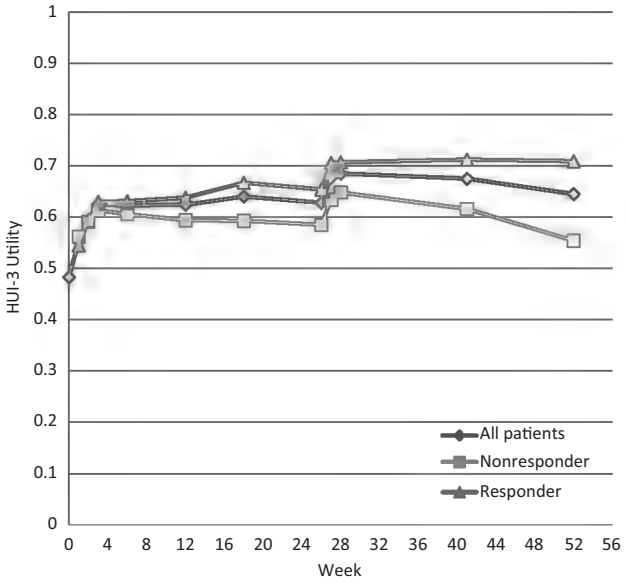

Figure 2. HUI-3 scores for all patients, responders, and non-responders with BioHA treatment. HUI-3, Health Utilities Index Mark 3.

Model 2

Response rates

Patients who received two courses of intra-articular BioHA in the FLEXX Trial and Extension Study achieved a response rate of 56% by the end of the 52-week period. The response rate for conventional treatment was 40%, as reported by Raynauld *et al.*[28].

QALYs gained over 52 weeks

Among patients achieving a response after two courses of intra-articular BioHA, an average of 0.23 QALYs were gained over the 1-year period. Among non-responders, there was an average of 0.08 QALYs gained over the same time period. These utility values were applied to a cost-effectiveness model for responders and non-responders in both the BioHA and conventional care arms (Figure 2).

Base case CEA scenario

Total treatment costs over 1 year were $1446 for the BioHA group and $516 for patients receiving conventional treatment. Quality-adjusted life year gained was 0.16 for BioHA and 0.14 for conventional treatment. The average cost-effectiveness ratio was $8816 per QALY for BioHA treatment and $3686 per QALY for conventional treatment. The ICER of BioHA, with

Table 3. Model 1: Cost effectiveness of intra-articular BioHA vs conventional care.

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	Cost-effectiveness	Incremental cost-effectiveness
Conventional care	$4562.00		0.000 QALY			Dominated
BioHA	$3468.78	−$1093.22	0.163 QALY	0.163 QALY	$21,281/QALY	

BioHA, bioengineered hyaluronic acid; QALY, quality-adjusted life year.

Table 4. Model 1: Results of one-way sensitivity analysis.

Parameters	Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	Cost effectiveness	ICER
Costs of BioHA							
Low	Conventional care	$4562.00		0.0000 QALY			Dominated
	BioHA	$3331.78	−$1230.22	0.1630 QALY	0.1630 QALY	$20,440/QALY	
High	Conventional care	$4562.00		0.0000 QALY			Dominated
	BioHA	$3605.78	−$956.22	0.1630 QALY	0.1630 QALY	$22,121/QALY	
Costs of conventional treatment							
Low	Conventional care	$3,012.78		0.0000 QALY			Dominated
	BioHA	$3,650.00	−$637.22	0.1630 QALY	0.1630 QALY	$18,483/QALY	
High	Conventional care	$5474.00		0.0000 QALY			Dominated
	BioHA	$3924.78	−$1549.22	0.1630 QALY	0.1630 QALY	$24,078/QALY	
QALYs gained per year in BioHA							
Low	Conventional care	$4562.00		0.0000 QALY		NA	$6748/QALY
	BioHA	$3468.78	$1093.22	−0.1620 QALY	0.1620 QALY	NA	
High	Conventional care	$4562.00		0.0000 QALY		NA	Dominated
	BioHA	$3468.78	−$1093.22	0.4880 QALY	0.4880 QALY	$7108/QALY	

BioHA, bioengineered hyaluronic acid (via intra-articular administration); ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 5. Model 2: Base case scenario results.

Strategy	Cost	Incremental cost	Effectiveness (QALY)	Incremental effectiveness (QALY)	Average cost effectiveness	ICER
Conventional treatment	$516.00		0.1400		$3686/QALY	
Intra-articular BioHA	$1445.80	$929.80	0.1640	0.0240	$8816/QALY	$38,741/QALY

BioHA, bioengineered hyaluronic acid; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

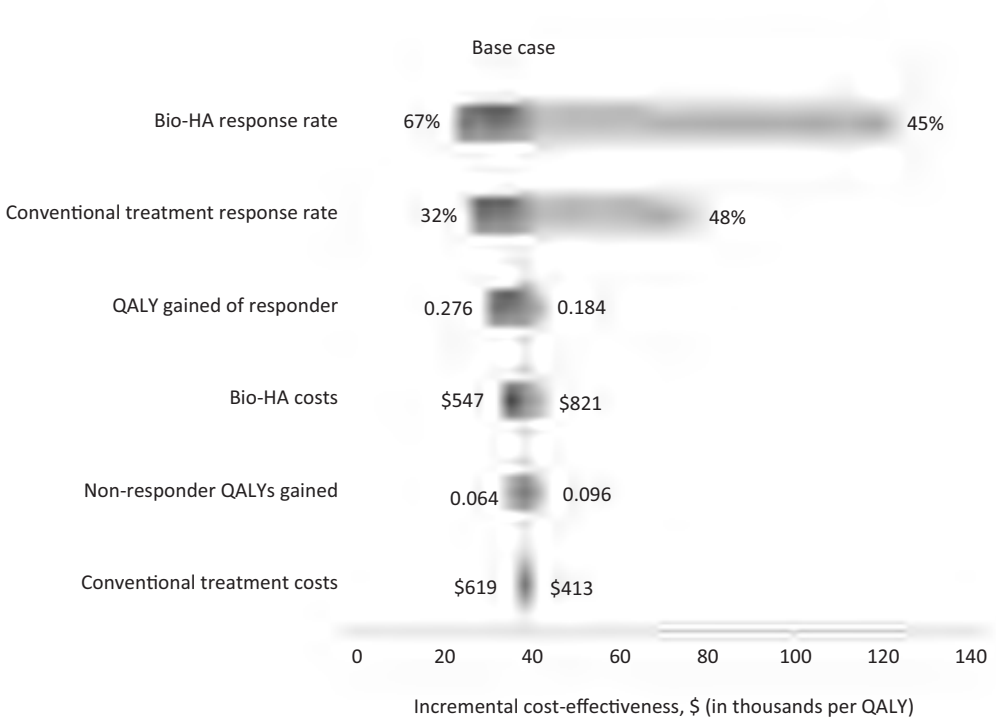

Figure 3. Model 2: Results of one-way sensitivity analysis. BioHA, bioengineered hyaluronic acid; QALY, quality-adjusted life year.

conventional treatment as the baseline strategy, was $38,741 per QALY gained (Table 5).

Sensitivity analyses

Results from one-way sensitivity analyses showed that the ICER calculated for BioHA was most sensitive to response rates in both the BioHA and the conventional treatment groups. When the BioHA response rate was at the lowest end (45%), the BioHA ICER was nearly $124,000 per QALY. Similarly, if the response rate for conventional care was set high (48%), the BioHA ICER was $77,500 per QALY. The average QALYs gained per responder also affected the BioHA ICER. When the QALY gained per responder was low (0.184), the BioHA ICER was $55,876 per QALY. However, when the QALY gained was high (0.276), the ICER was $29,649 per QALY (Figure 3).

In a probabilistic sensitivity analysis with Monte Carlo Simulation, when the willingness-to-pay level was set at $50,000 per QALY, BioHA was shown to be a cost-effective strategy for OA treatment in ~70% of simulations (Figure 4). This simulation was run under various willingness-to-pay assumptions, and corresponding acceptability curves were derived for the 2 treatments (Figure 5). If the willingness-to-pay threshold was increased to $100,000 per QALY, then the acceptability of BioHA reached 91%, while that of the conventional treatment declined to 9% (Figure 5).

Discussion

In 2004, the US Food and Drug Administration approved BioHA for the treatment of OA knee pain in patients who do not receive adequate relief from simple pain medication (e.g., acetaminophen) or from exercise and physical therapy. In this cost-effectiveness analysis (Model 1), when outcomes for a BioHA-treated group were compared with patients continuing on conventional care with NSAIDs or other conventional OA treatments (Model 1), BioHA was the dominant strategy. The approach used in Model 1 allowed for a direct comparison of the

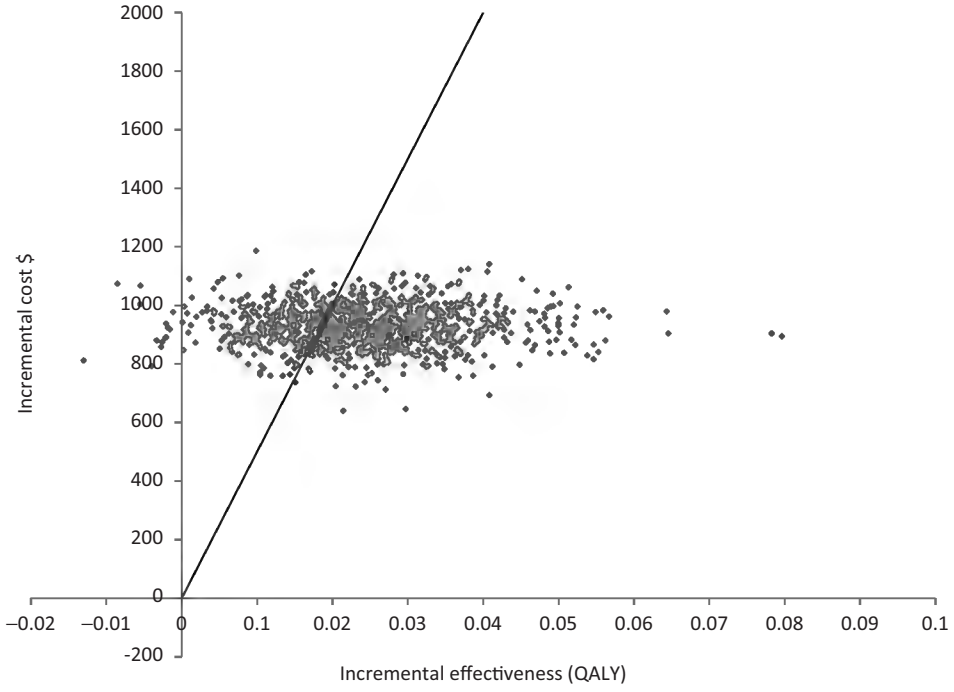

Figure 4. Model 2: Cost-effectiveness plane of joint distribution of incremental cost and effectiveness for BioHA. The diagonal line represents a willingness-to-pay threshold of $50,000/QALYs. BioHA, bioengineered hyaluronic acid; QALYs, quality-adjusted life years.

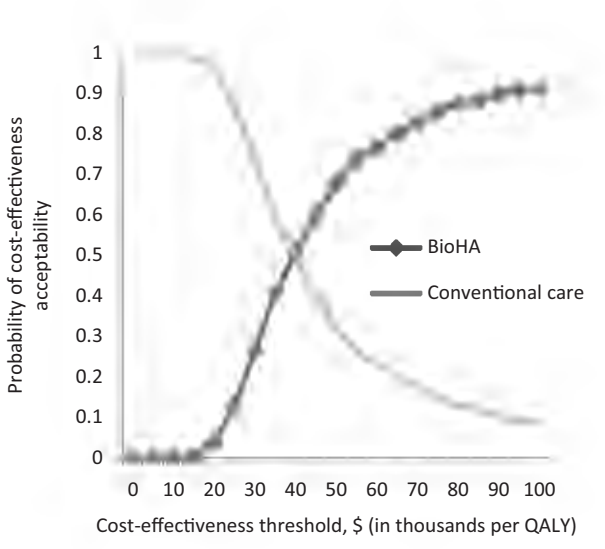

Figure 5. Model 2: Cost-effectiveness acceptability curve for BioHA vs conventional care under various willingness-to-pay thresholds. BioHA, bioengineered hyaluronic acid; QALY, quality-adjusted life year.

treatment of non-responding conventional care patients to the addition of BioHA vs ongoing conventional treatment. Sensitivity analyses varying the QALYs gained from BioHA treatment and costs of BioHA and conventional care demonstrated the robustness of these study results. BioHA dominance was eliminated only when the QALYs gained from BioHA were of negative value, an unlikely scenario.

Similarly, when a secondary analysis was run using response rates and cost estimates from alternate sources (Model 2), results still showed BioHA to be more cost-effective than conventional care. Model 2 provides a useful adjunct to the primary study in that it used different inputs for the conventional care group. In Model 2, conventional care was less costly and included all ACR-recommended treatments (except viscosupplementation), including non-pharmacologic, pharmacologic, and surgical approaches[28]. For example, by study end, 70% of patients randomized to the appropriate care group in Model 2 (using data from Raynauld *et al.*[28]) had received corticosteroid injections to the study knee. In contrast, the FLEXX Trial required all patients to stop corticosteroid injections 3 months before study start, and corticosteroids were not permitted for the study duration. Therefore, the conventional treatment response rate used in Model 2 was likely inflated compared with Model 1. Nonetheless, when compared against a more cost-conservative and aggressively treated conventional care group in Model 2, BioHA still met the $50,000 per QALY cost-effectiveness threshold. These secondary results were maintained under the majority of sensitivity analysis scenarios.

It is noteworthy that the conservative cost estimates used in both of the models in this study may have biased the outcomes against BioHA. Although there are several economic studies reporting the treatment costs of conventional care for OA, most are at least 10 years old, making

the cost figures obsolete[21,23,31–33,36]. In addition, there is a wide range of reported costs in the published literature, with those reported by Waddell *et al.*[23] (applied to Model 1) among the highest estimates in 2012 US dollars ($4562), and the lowest (reported by Losina *et al.*[33], applied to Model 2) at $516.

The use of conventional OA treatment costs from the study by Waddell *et al.*[23] as the input for Model 1 was based in part on the specificity of the costing data reported by these researchers, and in part because these selected costs were conservative estimates. For instance, Mapel *et al.*[37] reported average annual outpatient costs of $4684 in 2001 for OA patients, while Gabriel *et al.*[38] estimated average direct medical charges for OA patients at $2654 in 1997 (adjusted to $4694 for 2012)[11]. If higher costs for conventional treatment with NSAIDs and analgesics were used in Model 1, it is likely that treatment with BioHA would show even more substantial dominance.

Model 2 used data from Losina *et al.*[33] as the basis for conventional OA treatment costs; this represented ~11% of the costs reported by Waddell *et al.*[23] With this approach, the BioHA arm was further handicapped by adding 50% of the costs of conventional care to total BioHA costs. Thus, this study's ICER of $38,741 for BioHA is the most conservative cost estimate of all published research.

It is also worth noting that cost computations for the BioHA group did not include all cost consequences associated with NSAID and analgesic treatments, e.g., the potential for improved patient HRQoL due to the elimination of NSAID treatment side effects. Also, not considered in Model 1 were any downstream consequences from conventional OA therapies. For example, previous studies show that improved outcomes due to viscosupplementation may delay the need for TKR in OA patients (typically reserved as a "last resort" for patients experiencing severe symptoms, functional limitations, and quality-of-life reductions)[3,39]. An analysis by Waddell and Bricker[39] suggests that an average cost of $1420 per knee treated with viscosupplementation could delay TKR by a median of 2.1 years. In addition to quality-of-life improvements, delaying initial TKR may reduce the need for eventual revision TKR by reducing the amount of time the patient has the new joint. Again, if these factors were considered in Model 1, the total costs associated with BioHA would likely be even lower than those observed. Furthermore, Model 2 of this study used conventional care response rates based on Raynauld *et al.*[28]; in this case, TKR was included in conventional care inputs and is considered in the cost-effectiveness findings.

The costs of potential AEs due to BioHA treatment were not included in these analytic models because these AEs are generally localized (e.g., pain and swelling of the injected joint) and infrequent, and normally resolve spontaneously or with conventional treatment of symptoms[40]. Moreover, recent guidelines and reviews by Osteoarthritis Research Society International point out that HA treatments do not have appreciable safety issues, except for transient pain at the injection site[2]. Arnold *et al.*[41] reasoned that, in light of systemic side effects of therapies for OA of the knee (e.g., hepatoxicity with acetaminophen, gastrointestinal bleeding with NSAIDs, etc.), patients may prefer local therapy for their joint disease. As such, viscosupplementation therapy with HA in the managed care setting may improve patient outcomes and the efficient use of healthcare resources.

Study limitations

There are several limitations to this study. First, it is important to note that, for both models, the reported cost-effectiveness ratios were dependent on the method used to convert WOMAC scores to HUI-3 values to determine QALYs[29]. Second, the FLEXX Trial and Extension Study, the clinical trial used as the source for the efficacy assumptions of both models, did not collect downstream healthcare resource utilization data, requiring the use of published literature to identify the costs of conventional treatments. Because the FLEXX trial did not include a conventional treatment comparison arm, Model 1 used data from pre-study conventional treatment. This provided a strict comparison of the same patient group before or after the introduction of BioHA treatment. The analysis favors BioHA under the assumption that the condition of the conventional care group did not either improve or deteriorate over time. However, Model 2 addresses this limitation. A 40% conventional treatment response rate was obtained from a 1-year, multicenter trial conducted by Raynauld *et al.*[28] comparing appropriate care plus CL-HA against appropriate care without CL-HA. In this trial, conventional care included the full range of OA treatments, including NSAIDs and analgesics, corticosteroid injections, and surgical options such as TKR. Thus, Model 2 provides a more "real-world" treatment comparison.

Conclusions

Results from this cost-effectiveness analysis demonstrate that BioHA injection in patients with OA of the knee with inadequate response to conventional therapies is a viable option in terms of both efficacy and cost. When compared with conventional care with NSAIDs and analgesics, BioHA was a dominant treatment strategy. When compared with conventional care with NSAIDs, analgesics, corticosteroids, and surgical options, BioHA was still the cost-effective strategy.

Transparency

Declaration of funding

Financial support for this study and for assistance with medical editing was provided by Ferring Pharmaceuticals Inc.

Declaration of financial/other relationships

Hind T. Hatoum, PhD, is a paid consultant for Ferring Pharmaceuticals Inc., the marketer of one of the study drugs. Funding for the study was provided by Ferring Pharmaceuticals Inc. through a contract with Hind T. Hatoum & Company. Anke L. Fierlinger, MD, is a paid employee of Ferring Pharmaceuticals Inc. Swu-Jane Lin, PhD, is a paid consultant for Hind T. Hatoum & Company. Roy D. Altman, MD, is a paid consultant for Ferring Pharmaceuticals Inc., Abbott Theralogix, LLC, Ortho-McNeil-Janssen Pharmaceuticals, Inc., Rotta Pharmaceuticals Inc., Toltec Pharmaceuticals, LLC, Iroko Pharmaceuticals, LLC, and Novartis Pharmaceuticals Corporation, and also receives clinical trial funding from Ferring Pharmaceuticals Inc. and Novartis Pharmaceuticals Corporation. JME Peer Reviewers on this manuscript have no relevant financial relationships to disclose.

Acknowledgments

The authors of this study acknowledge the medical writing and editorial assistance of Alanna Kennedy, PhD, at Educational Alliances in Clinical Medicine (Manhasset, NY) for preparation of this manuscript and Ferring Pharmaceuticals Inc. for providing funding for editorial assistance.

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