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ORIGINAL RESEARCH

Clinical and cost outcomes from different hyaluronic acid treatments in patients with knee osteoarthritis: evidence from a US health plan claims database

Vinod Dasa[1], Mitch DeKoven[2], Kainan Sun[2], Allan Scott[3], Sooyeol Lim[4*]

[1]Louisiana State University, New Orleans, LA, USA; [2]IMS Health, Fairfax, VA, USA; [3]Bioventus LLC, Durham, NC, USA; [4]Seikagaku Corporation, Tokyo, Japan

Abstract

Background: Intra-articular injection of hyaluronic acid (HA) for knee osteoarthritis (OA) effectively reduces pain and delays total knee replacement (TKR) surgery; however, little is known about relative differences in clinical and cost outcomes among different HA products.

Objective: To compare disease-specific costs and risk of TKR among patients receiving different HA treatments in a commercially insured cohort of patients with knee OA in the USA.

Method: Retrospective analyses using IMS Health's PharMetrics Plus Health Plan Claims Database were conducted by identifying knee OA patients with claims indicating initiation of HA treatment at an 'index date' during the selection period (2007–2010). Patients were required to be continuously enrolled in the database for 12 months preindex to 36 months postindex. A generalized linear model (GLM) with a gamma distribution and log-link function was used to model aggregate patient-based changes in disease-specific costs. A Cox proportional hazards model (PHM) was used to model the risk of TKR. Both multivariate models included covariates such as age, gender, comorbidities, and preindex healthcare costs.

Results: 50,389 patients with HA treatment for knee OA were identified. 18,217 (36.2%) patients were treated with HA products indicated for five injections per treatment course (Supartz and Hyalgan). The remainder were treated with HA products indicated for fewer than five injections per treatment course, with 20,518 patients (40.7%) receiving Synvisc; 6,263 (12.4%), Euflexxa; and 5,391 (10.7%), Orthovisc. Synvisc- and Orthovisc-injected patients had greater disease-specific costs compared to Supartz/Hyalgan (9.0%, $p<0.0001$ and 6.8%, $p=0.0050$, respectively). Hazard ratios (HRs) showed a significantly higher risk of TKR for patients receiving Synvisc compared to Supartz/Hyalgan (HR=1.069, $p=0.0009$). Patients treated with Supartz/Hyalgan, Euflexxa, and Orthovisc had longer delays to TKR than those treated with Synvisc.

Conclusion: Analysis of administrative claims data provides real-world evidence that meaningful differences exist among some HA products in disease-specific cost and time to knee replacement surgery.

Keywords: intra-articular, hyaluronic acid, viscosupplementation, knee replacement, health economics, outcomes research.

Abbreviations: AD-HA, avian derived hyaluronic acid; AAOS, American Academy of Orthopedic Surgeons; ACR, American College of Rheumatology; AMSSM, American Medical Society for Sport Medicine; Bio-HA, biological fermentation hyaluronic acid; BMI, body mass index; GLM, generalized linear model; HA, hyaluronic acid; HMW, high molecular weight; HR, hazard ratio; IAHA, intra-articular hyaluronic acid; LMW, low molecular weight; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OR, odds ratio; PHM, proportional hazards model; TKR, total knee replacement

Citation

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Introduction

Osteoarthritis (OA) is a common chronic illness in older adults characterized by deterioration of joint cartilage, accompanied by joint inflammation, pain, and loss of physical function. OA ranks as the fifth leading cause of disability among US adults [1]. Because age is a major risk factor for OA [2], the prevalence of OA is expected to increase as the US population ages. In

addition to age, previous joint injury and obesity are considered major risk factors for knee OA; previous joint injury is a common cause of knee OA among young adults [3], whereas high body mass index (BMI) is associated with increased risk of knee OA, particularly among old adults [4]. Indeed, research shows that the annual estimated number of people in the USA with OA was approximately 30.8 million for 2008–2011 [5]. Knee OA is one of the most common forms of arthritis, with an estimated 644,000 total knee replacement (TKR) surgeries performed in 2011, 97% of which were due to osteoarthritis [6].

Viscosupplementation, in which hyaluronic acid (HA) is injected into the knee joint for the symptomatic relief of pain, has been available for treatment of knee OA in the USA since 1997. Various mechanisms of action have been suggested to explain the clinical effects of intra-articular injection of HA (IAHA) [7]: IAHA provides extra lubrication and cushioning within affected knee joints [8] and has been shown to induce direct anti-inflammatory, chondroprotective [9–11], and analgesic effects [12]. Hyaluronic acid injections are recognized as safe and effective for the alleviation of joint pain and improvement of joint function in patients with knee OA [13], with positive clinical evidence demonstrated in clinical trials [14,15]. However, after the American Academy of Orthopedic Surgeons (AAOS) revised its treatment guidelines in 2013 to issue a recommendation against the use of IAHA [16], there has been a debate over the clinical impact of these injections. Evidence from meta-analyses has been mixed. For example, one meta-analysis showed that effects of viscosupplementation were only marginally different from placebo injections [17], whereas another meta-analysis showed that viscosupplementation was more effective than any oral medication for knee OA pain [18,19]. Treatment guidelines issued by different professional medical societies do not point in a single direction either. AAOS recommends against the use of IAHA, but in 2014, the American College of Rheumatology (ACR) made conditional recommendation for the use of IAHA to treat pain in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics in its position statement on viscosupplementation [20,21]; Osteoarthritis Research Society International (OARSI) rates the benefit of IAHA as uncertain [22], whereas American Medical Society for Sport Medicine (AMSSM) recommends the use of IAHA for the appropriate patients with knee OA [23].

Given such conflicting views on the clinical value of IAHA, recent research attention has turned to the real-world evidence that has been accumulating to suggest that IAHA injections result in clinical effectiveness culminating in a delay to total knee replacement [24,25]. One study that utilized US health plan administrative claims retrospectively looked at the data of knee OA patients who ultimately underwent TKR. It showed that the HA cohort had a median 1.0-year longer time to TKR surgery than the non-HA cohort [26]; another retrospective study with a different US health claims database has demonstrated a delay of median 1.6-year difference between the HA cohort and the non-HA cohort [27]. Populations in both studies were relatively similar in age and gender distribution; more than 70% of patients were aged 55 or older and more than 50% of patients were females. In both studies, age distributions between HA and non-HA cohorts were similar, with HA cohorts having had a slightly greater proportion of females than non-HA cohorts. When a Cox proportional hazards model (PHM) was fit to adjust for age and gender, the TKR-delaying effect of repeated HA treatments still remained. As for the duration of knee OA, neither study provided clear information other than the time between the first diagnosis of OA and TKR, so it is uncertain whether HA and non-HA cohorts were clearly identical in disease duration at study entry. However, both studies used the first diagnosis of knee OA as the index date, implying that included patients were unlikely to be at an advanced stage of OA at study entry, and both studies also required the presence of TKR within the study window as an inclusion criterion, implying that included patients were unlikely to be at an early stage of OA at study entry due to chronic nature of knee OA. Thus, it is likely that data for both HA and non-HA cohorts were included and tracked from a relatively moderate stage of disease and thus HA and non-HA cohorts were largely comparable with each other to support valid inference with time-to-TKR analysis.

In light of these findings, additional research on the differences in clinical and cost outcomes among different HA products may be of interest to key decision makers. In the USA, various IAHA injection products, with different molecular properties, production processes, and number of injections per treatment course, are currently FDA approved for use. While a cost-effectiveness analysis of a high molecular weight, bioengineered HA with data obtained from a clinical trial [28] concluded that the HA product was less costly and more effective than conventional care with NSAID and analgesics, previous research has not examined cost and clinical effectiveness data across different HA products in the real-world setting. This study compares different US FDA-approved HA viscosupplements using real-world evidence from an administrative claims database.

Methods

Data source

For this retrospective, observational cohort study, integrated medical and pharmacy claims data were extracted from IMS Health's PharMetrics Plus Health Plan Claims Database, which comprises adjudicated claims for more than 150 million unique patients across the USA and has diverse representation of geography, employers, and payers. The PharMetrics Plus database is thought to be representative of the commercially insured US national population in terms of age and gender. However, the population in the database is slightly younger than the entire US population because all members in the database have commercial insurance coverage with limited

Table 1. Characteristics of different FDA-approved HA viscosupplements.

PMA number	P010029	P950027	P030019	P980044**	P940015***
Current J-code	J7323	J7321	J7324	J7321	J7325
Trade name	Euflexxa	Hyalgan	Orthovisc	Supartz†	Synvisc
Number of injections per treatment course	3	3 to 5*	3 or 4	3 to 5*	3
HA source	Bacterial cells	Avian	Bacterial cells	Avian	Avian
HA concentration (mg/mL)	10	10	15	10	8
Volume per injection	2 mL	2 mL	2 mL	2.5 mL	2 mL
Molecular weight (MDa)	2.4–3.6	0.5–0.73	1.0–2.9	0.62–1.17	>6††

*Indicated for five weekly injections, but product labelling indicates that some patients may receive pain relief with only three injections per course, leading some healthcare professionals to administer these products as three to five injections per treatment course.
**PMA supplement approved by FDA in December 2015 for three injections per treatment course in addition to five injections per treatment course.
***PMA supplement approved by FDA in February 2009 for single 6 mL injection per treatment course in addition to three 2 mL injections per treatment course.
†Trademark used in the US market changed to Supartz FX since October 2015.
††Hylan A's molecular weight is 6 MDa. Hylan B's molecular weight is not displayed in package insert.

Medicare data. As all data are deidentified to protect patient privacy and are compliant with the Health Insurance Portability and Accountability Act, no informed consent was required.

Study design

Claims data for knee OA patients with outpatient claims were indicating initiation of HA injection during the selection period (July 1, 2007–June 30, 2010). Product J-codes were used to select all common HA agents in the US market during this period (Euflexxa, Hyalgan, Orthovisc, Supartz, Synvisc; Table 1). Because two HA agents (Supartz and Hyalgan) share the same J-code and thus could not be distinguished by J-code, they were categorized as a single group of Supartz/Hyalgan. Likewise, Synvisc-One, which is chemically identical to Synvisc and began to be sold in the USA in 2009 as a single-dose regimen per treatment course, shares the same J-code as Synvisc and was classified together with Synvisc. Thus, four patient cohorts were created (Euflexxa, Orthovisc, Supartz/Hyalgan, Synvisc). The date of the first such claim within the selection window was defined as the 'index date'. This set the stage for a comparative effectiveness study, as different HA products were assumed to be used at the same stage in knee OA treatment pathway and assumed to be relatively similar in disease severity at patient selection. Patients had to meet the following inclusion criteria to be eligible: ≥18 years of age in the year of their index date, at least one clinical knee OA diagnosis during the 12-month preindex period, and continuous enrolment from 12 months preindex to 36 months postindex date. Although lengthier pre- and post-index periods would have been ideal to establish the duration and severity of OA, the ability to follow patients longitudinally for a longer period of time in the data asset was limited. Exclusion criteria included the following: any HA use in the preindex period; a different kind of HA index medication (from the index date/prescription) in the postindex period; a TKR within 30 days following the index event; two different kinds of HA index medications on the index date; and diagnosis of hip OA, fibromyalgia, rheumatoid arthritis, lupus, or gout during the preindex period. Clinical and health economic outcomes were measured over the 36-month postindex period. Baseline information such as demographic characteristics, health plan type, physician specialty, comorbidities, and medications of interest were obtained during the 12-month preindex baseline period.

Outcome measures

The primary outcome measures were disease-specific costs associated with knee OA and time from the index date to TKR surgery. For calculation of disease-specific costs, disease-specific claims were denoted by those claims with an OA of the knee diagnosis code while disease-specific drugs included NSAIDs, Cox-2 inhibitors, non-narcotic analgesics, opioids, and other anti-inflammatory analgesics. All index medications administered in the postindex period were considered disease-specific whether they had an OA of the knee diagnosis or not.

Statistical analysis

Descriptive statistics were reported for continuous and categorical variables. T-tests were used for continuous variables and chi-square tests were used for categorical variables. All statistical tests were two-tailed tests. For statistical significance, we used the conventional alpha level of 0.05. A generalized linear model (GLM) with a gamma distribution and log-link

function was fit to model aggregate patient-based changes in OA-related costs. Survival analysis was carried out with time-to-TKR data via the Kaplan–Meier method. A Cox PHM was used to model risk of TKR. Both GLM and PHM used a prespecified set of covariates such as age, gender, geographic region, health plan type, comorbidities, preindex corticosteroid use, and preindex healthcare costs to adjust for baseline differences among different HA cohorts. Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Following the application of the inclusion/exclusion criteria, a total of 50,389 patients were included for statistical analysis (Figure 1). Among the 50,389 patients who received HA for treatment of knee OA, 6,263 (12.4%) patients received Euflexxa; 5,391 (10.7%) patients, Orthovisc; 18,217 (36.2%) patients, Supartz/Hyalgan; and 20,518 (40.7%) patients, Synvisc.

Figure 1. Selection of study patients.

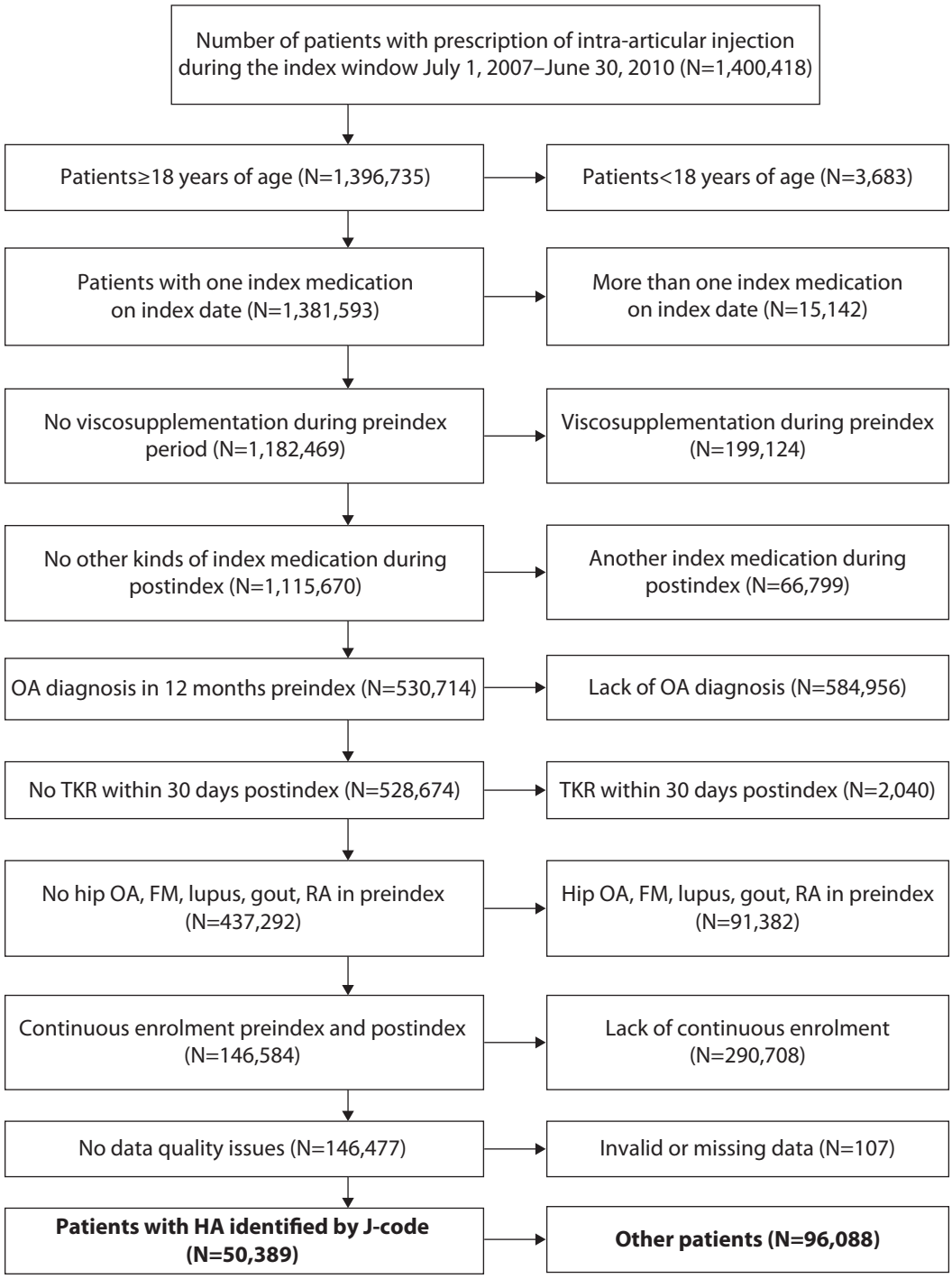


Table 2. Patient demographics and characteristics at baseline.

	Euflexxa only		Synvisc only		Supartz/Hyalgan		Orthovisc only		*p* value		
									Supartz/ Hyalgan compared with Euflexxa	Supartz/ Hyalgan compared with Synvisc	Supartz/ Hyalgancompared with Orthovisc
Total patients	6,263		20,518		18,217		5,391				
Age (years) (n, %)											
18–44	658	10.5%	1,725	8.4%	1,645	9.0%	569	10.6%	0.0001*	0.1353	<0.0001*
45–54	1,842	29.4%	5,991	29.2%	5,264	28.9%	1,636	30.3%			
55–64	2,542	40.6%	8,417	41.0%	7,373	40.5%	2,135	39.6%			
65+	1,221	19.5%	4,385	21.4%	3,935	21.6%	1,051	19.5%			
Mean	57.0		57.7		57.7		56.8		<0.0001*	0.4798	<0.0001*
SD	10.6		10.4		10.6		10.5				
Median	57		57		57		57		0.0002*	0.8306	<0.0001*
First quartile	51		51		51		51				
Third quartile	62		63		63		62				
Gender (n, %)											
Male	2,463	39.3%	8,450	41.2%	7,314	40.1%	2,194	40.7%	0.2512	0.0387*	0.4710
Female	3,800	60.7%	12,068	58.8%	10,903	59.9%	3,197	59.3%			
Plan type (n, %)											
Consumer-directed healthcare product	17	0.3%	47	0.2%	52	0.3%	7	0.1%	<0.0001*	<0.0001*	<0.0001*
Health Maintenance Organization (HMO)	1,169	18.7%	2,950	14.4%	2,509	13.8%	543	10.1%			
Indemnity plan	473	7.6%	1,443	7.0%	1,374	7.5%	338	6.3%			
Point of service (POS)	331	5.3%	1,111	5.4%	754	4.1%	267	5.0%			
Preferred Provider Organization (PPO)	4,182	66.8%	14,728	71.8%	13,372	73.4%	4,197	77.9%			
Unknown	91	1.5%	239	1.2%	156	0.9%	39	0.7%			
Payer type (n, %)											
Commercial plan	3,830	61.2%	11,470	55.9%	10,425	57.2%	3,041	56.4%	<0.0001*	0.0002*	<0.0001*
Medicaid	23	0.4%	81	0.4%	37	0.2%	6	0.1%			
Medicare risk	107	1.7%	476	2.3%	348	1.9%	79	1.5%			
Medicare cost	107	1.7%	435	2.1%	383	2.1%	44	0.8%			

(*Continued*)

Table 2. Patient demographics and characteristics at baseline (Continued).

Self-insured	2,135	34.1%	7,943	38.7%	6,934	38.1%	2,200	40.8%			
Unknown	61	1.0%	113	0.6%	90	0.5%	21	0.4%			
Physician specialty (n, %)											
Orthopedic surgery	3,084	49.2%	9,660	47.1%	8,430	46.3%	2,957	54.9%	<0.0001*	<0.0001*	<0.0001*
GP/FP/IM	395	6.3%	1,528	7.4%	1,678	9.2%	251	4.7%			
Orthopedics	382	6.1%	1,339	6.5%	1,089	6.0%	173	3.2%			
Physical medicine and rehabilitation	180	2.9%	611	3.0%	653	3.6%	76	1.4%			
Rheumatology	183	2.9%	393	1.9%	284	1.6%	108	2.0%			
Other	2,039	32.6%	6,987	34.1%	6,083	33.4%	1,826	33.9%			
Charlson Comorbidity Score (n, %)											
0	3,854	61.5%	12,502	60.9%	11,104	61.0%	3,301	61.2%	0.5022	0.9211	0.8228
1	1,259	20.1%	4,066	19.8%	3,585	19.7%	1,067	19.8%			
2	685	10.9%	2,323	11.3%	2,086	11.5%	609	11.3%			
3	255	4.1%	884	4.3%	805	4.4%	243	4.5%			
4+	210	3.4%	743	3.6%	637	3.5%	171	3.2%			
Medications of interest (n, %)											
Corticosteroids	3,685	58.8%	12,591	61.4%	11,267	61.8%	3,318	61.5%	<0.0001*	0.3291	0.6887
NSAIDS	2,386	38.1%	7,864	38.3%	6,920	38.0%	2,221	41.2%	0.8768	0.4907	<0.0001*
Cox-2 inhibitors	461	7.4%	1,792	8.7%	1,611	8.8%	517	9.6%	0.0003*	0.7037	0.0926
Analgesics non-narcotic	76	1.2%	348	1.7%	333	1.8%	102	1.9%	0.0011*	0.3242	0.7586
Opioids	2,933	46.8%	10,131	49.4%	9,010	49.5%	2,727	50.6%	0.0003*	0.8702	0.1467
Anti-inflammatory analgesics (non-NSAID)	15	0.2%	56	0.3%	45	0.2%	23	0.4%	0.9173	0.6177	0.0306*
H2 blocker	150	2.4%	567	2.8%	491	2.7%	134	2.5%	0.1992	0.6813	0.3996
PPI	1,304	20.8%	4,280	20.9%	3,872	21.3%	1,108	20.6%	0.4679	0.3410	0.2670
Preindex healthcare costs (US $)	10,732.4		11,117.9		10,747.3		11,356.2		0.9552	0.0438*	0.0264*

*Statistically significant at alpha level of 0.05.

The four different HA cohort groups were similar in baseline characteristics (Table 2), with only relatively minor differences among them. The Euflexxa cohort had a greater proportion of patients insured through commercial health plans (61.2%) compared to the other cohorts (55.9–57.2%). In terms of physician specialty, the Orthovisc cohort had a greater proportion of patients who saw orthopedic surgeons (54.9%) compared to the other cohorts (46.3–49.2%). The four groups were similar in terms of comorbidities of interest at baseline, but for medications of interest, the Euflexxa cohort had a lower proportion of patients receiving corticosteroids (58.8%) compared to the other three cohorts (61.4–61.8%). With regards to healthcare costs, the Synvisc and Orthovisc cohorts had slightly greater preindex healthcare costs ($11,118 and $11,356) compared to the Euflexxa and Supartz/Hyalgan cohorts ($10,732 and $10,747).

Procedures of interest

The majority of patients in all four cohorts received a single course of HA treatment over the 3-year time period, ranging from 69.7% in the Synvisc cohort to 74.4% in the Supartz/Hyalgan cohort (Table 3). The number of injections patients received for the index course of HA treatment were 2.4 injections for the Synvisc cohort, 2.6 injections for the Euflexxa cohort, 2.8 injections for the Orthovisc cohort, and 3.7 injections for the Supartz/Hyalgan cohort. More than 50% of the patients in the Supartz/Hyalgan cohort received fewer than five injections for the index course, and 26.3% of the patients in the Supartz/Hyalgan cohort received 3 injections for the index course. The amount allowed for the index injections was greatest for the Synvisc cohort ($446) and smallest for the Supartz/Hyalgan cohort ($224). The paid amount of the index injections for the Synvisc cohort ($366) was nearly twice the paid amount of the index injections for the Supartz/Hyalgan cohort ($181).

Disease-specific healthcare costs

Comparison of the unadjusted disease-specific costs showed that the Euflexxa cohort incurred the lowest costs (mean=$13,160, median=$4,808) over the postindex period,

Table 3. Measures of procedural outcomes.

	Euflexxa only N=6,263		Synvisc only N=20,518		Supartz/Hyalgan N=18,217		Orthovisc only N=5,391	
	N	%	N	%	N	%	N	%
Injection courses								
1	4,501	71.9%	14,303	69.7%	13,561	74.4%	3,895	72.3%
2	1,037	16.6%	3,773	18.4%	2,999	16.5%	900	16.7%
3	399	6.4%	1,451	7.1%	1,012	5.6%	317	5.9%
4	210	3.4%	592	2.9%	404	2.2%	148	2.7%
5	80	1.3%	257	1.3%	189	1.0%	91	1.7%
6+	36	0.6%	142	0.7%	52	0.3%	40	0.7%
Injections in index course								
1	1,210	19.3%	6,431	31.3%	2,616	14.4%	679	12.6%
2	477	7.6%	1,517	7.4%	909	5.0%	389	7.2%
3	4,311	68.8%	11,834	57.7%	4,793	26.3%	3,968	73.6%
4	105	1.7%	329	1.6%	1,191	6.5%	194	3.6%
5+	160	2.6%	407	2.0%	8,708	47.8%	161	3.0%
Average number of injections in index course	2.6		2.4		3.7		2.8	
Patients experiencing TKR (n, %) within 3-year postindex period	1,553.0	24.8%	5,484.0	26.7%	4,566.0	25.1%	1,355.0	25.1%
Disease-specific cost (US $)	13,160		14,959		13,947		14,224	
Charge amount of index injections (US $)	346.2		575.7		296.8		512.1	
Allowed amount of index injections (US $)	246.5		446.4		223.8		337.1	
Paid amount of index injections (US $)	203.0		365.6		181.2		273.5	

whereas the Synvisc cohort incurred the highest costs (mean=$14,959, median=$6,388), the Supartz/Hyalgan cohort incurred mean cost of $13,947 (median=$5,720), and the Orthovisc cohort incurred mean cost of $14,224 (median=$6,188), respectively. Adjusting for confounders via a GLM showed that the Synvisc cohort (9.0%, $p<0.0001$) and the Orthovisc cohort (6.8%, $p=0.0050$) incurred greater patient-based changes in disease-specific costs than the Supartz/Hyalgan cohort with statistically significant difference (Table 4). After covariate adjustment, the patient-based change in disease-specific costs of the Euflexxa group was actually slightly greater than the Supartz/Hyalgan cohort but with no statistically significant difference (2.2%, $p=0.3304$). This implies that switching Synvisc and Orthovisc users with average disease-specific costs of $14,959 and $14,224, respectively to Supartz/Hyalgan could save $1,235 and $906 per patient over 3 years, but switching Euflexxa users to Supartz/Hyalgan would lead to little change in average disease-specific costs.

Time to TKR

The Synvisc cohort had a higher proportion of patients who received TKR (26.7%) than the other three cohorts (Table 3), which had similar rates of patients who received TKR (24.8–25.1%). The logistic regression model of incidence rates of TKR showed the Synvisc cohort had statistically significantly greater odds ratio (OR) of having a TKR than the Supartz/Hyalgan cohort (OR=1.077, $p=0.0017$), but there were no statistically significant differences in the ORs of having a TKR among the Euflexxa, Orthovisc, and Supartz/Hyalgan cohorts (Table 5).

Kaplan–Meier survival curves representing proportions of subjects who had not experienced TKR across the 3-year time span were generated for the different HA cohorts (Figure 2). Survival curves for the Euflexxa, Orthovisc, and Supartz/Hyalgan cohorts were similar and close together. The results of a log-rank test of survival curves suggest that Synvisc patients tended to reach TKR earlier than patients receiving other HA injections; there was a statistically significant difference between survival times of the Synvisc cohort and the Supartz/Hyalgan cohort ($p=0.0001$) but no statistically significant differences among the survival times of the Euflexxa, Orthovisc, and Supartz/Hyalgan cohorts (Table 6). Likewise, the results of a Cox PHM for time-to-TKR (Table 7) adjusting for background covariates confirmed that the Synvisc cohort had statistically significantly greater hazard ratio (HR) of having a TKR than the Supartz/Hyalgan cohort (HR=1.069, $p=0.0009$), but there were no statistically significant differences in the HRs of having a TKR among the Euflexxa, Orthovisc, and Supartz/Hyalgan cohorts.

Table 4. Generalized linear model: patient-based changes in disease-specific costs.

				Exponential of Wald 95% confidence limits		*p* value
Parameters	**Parameter estimate**	**Standard error**	**Exponential of parameter est.**	**Lower limit**	**Upper limit**	
Euflexxa compared with Supartz/ Hyalgan	0.021	0.022	1.022	0.979	1.067	0.3304
Synvisc compared with Supartz/ Hyalgan	0.086	0.015	1.090	1.058	1.123	<0.0001*
Orthovisc compared with Supartz/ Hyalgan	0.065	0.023	1.068	1.020	1.117	0.0050*

*Statistically significant at alpha level of 0.05.

Table 5. Logistic regression model for odds of having a TKR.

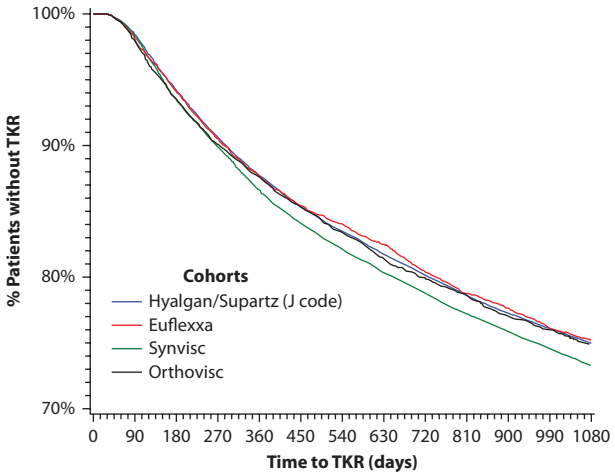
				95% confidence limits		
Parameters	**Parameter estimate**	**Standard error**	**Odds ratio**	**Lower limit**	**Upper limit**	***p* value**
Euflexxa compared with Supartz/ Hyalgan	0.000	0.035	1.000	0.935	1.071	0.9942
Synvisc compared with Supartz/ Hyalgan	0.075	0.024	1.077	1.028	1.129	0.0017*
Orthovisc compared with Supartz/ Hyalgan	0.018	0.037	1.018	0.948	1.094	0.6199

*Statistically significant at alpha level of 0.05.

Discussion

Real-world evidence suggests that individual HA products have clinically detectable differences in clinical and cost outcomes.

Figure 2. Kaplan–Meier survival curves of time to TKR data for different HA cohorts.



The survival curve of the Synvisc cohort was statistically different from that of the Supartz/Hyalgan cohort (p=0.0001, log-rank test).

Table 6. Log-rank tests of time to TKR among different HA cohorts.

Log-rank test		
Index therapy	**Chi-square**	***p* value**
Euflexxa compared with Supartz/Hyalgan	1.013	0.3142
Synvisc compared with Supartz/Hyalgan	14.914	0.0001*
Orthovisc compared with Supartz/Hyalgan	2.274	0.1315

*Statistically significant at alpha level of 0.05.

With regards to healthcare costs, in spite of the popular perception among payers that the HA products indicated for five injections per course are uneconomical, the Supartz/Hyalgan cohort demonstrated better cost outcomes than the Synvisc and Orthovisc cohorts and similar cost outcomes of the Euflexxa cohort. This confirms the finding from an earlier study which showed that though patients in the Supartz/Hyalgan received more injections per course than patients in the Synvisc cohort, the costs to the health plan were less for the Supartz/Hyalgan cohort than for the Synvisc cohort [29].

For the comparative effectiveness outcome of TKR delay, all HA cohorts were rather similar in their ability to delay TKR, except the Synvisc cohort which had a statistically significantly greater risk of having a TKR than the other cohorts. The statistical significance for the difference in time to TKR between the Synvisc cohort and the Supartz/Hyalgan cohort still persisted after adjustment of background covariates. This real-world finding sheds interesting light on another debate surrounding the use of IAHA regarding whether certain intrinsic properties of particular HA products such as molecular weights or production process can influence clinical outcomes [30]. Regarding molecular weight, one study suggested potential benefit of high molecular weight (HMW) HA through the CD44 receptor binding with greater affinity [31], but another study suggested better anti-inflammatory effects of HMW HA but better chondroprotective effects of low molecular weight (LMW) HA [32]. Another study concluded that low and high molecular weight HAs were similar in efficacy and safety [33]. The current study does not show any clear relationship between molecular weight of HA and its ability to delay TKR. Regarding production process, one study showed a HA product produced by biological fermentation (Bio-HA) has a significantly smaller incidence of injection site adverse reactions than a HA product derived from avian sources (AD-HA) [34]. However, in the current study, Supartz/Hyalgan, both of which are avian-derived hyaluronic acid (AD-HA) products, delayed TKR as effectively as other Bio-HA products, and delayed TKR longer than another AD-HA product (Synvisc). The current dataset and analyses do not provide a clear reason for this difference, but the unique chemical composition of Synvisc, which is an admixture

Table 7. Cox proportional hazards model of the risk of having TKR.

				95% CI of hazard ratio		
Parameters	**Coefficient**	**Standard error**	**Hazard ratio**	**Lower limit**	**Upper limit**	***p* value**
Euflexxa compared with Supartz/Hyalgan	0.004	0.030	1.004	0.948	1.064	0.8806
Synvisc compared with Supartz/Hyalgan	0.067	0.020	1.069	1.027	1.112	0.0009*
Orthovisc compared with Supartz/Hyalgan	0.021	0.031	1.021	0.961	1.085	0.5071

*Statistically significant at alpha level of 0.05.

of two distinctive chemically modified HAs (hylan A and hylan B) that are different from compositions of other HA products [35], may play a part. Our findings also suggest that one may need to go beyond simple categorizations of HAs by molecular weight or production sources to account for differences in real-world clinical outcomes among HA products.

By linking the clinical outcome of delay to a major surgery and the cost outcome, the current study shows that, among the HA products considered, Euflexxa, Orthovisc, and Supartz/Hyalgan may potentially offer more value than Synvisc for payers in the US healthcare system because those HA products are more effective in delaying TKR and less costly than Synvisc. Moreover, Euflexxa and Supartz/Hyalgan may be able to achieve better cost minimization than Orthovisc given similar clinical outcomes on time to TKR. This can be valuable information to healthcare payers that need to cope with the huge economic burden that the debilitating nature and high prevalence of OA imposes on the US healthcare system. In 2009, OA resulted in approximately 921,000 hospitalizations with a mean cost per stay of $45,443, and OA-related surgeries cost the US healthcare system $42.3 billion [36]. A recent meta-analysis showed evidence that US-approved HA viscosupplements are safe and efficacious through 26 weeks in patients with knee OA and had better efficacy than non–US approved HA viscosupplements [37]. The results of this study take one further step by yielding information on the clinical and cost differences amongst various HA products that may be of interest to payers who need to shape formulary and reimbursement policies in the presence of different intra-articular HA injection products in the US healthcare market.

Limitations

As the claims data for this study is representative of the US commercially insured population, results may not be generalizable to other non–commercially insured populations such as fee-for-service Medicare, who differ with regards to demographics such as age, resource utilization, and prescription usage patterns from the commercially insured patients in our study.

This retrospective study has limitations similar to other retrospective design studies that make use of claims data, such as coding errors or omissions. Because HA products were identified via J-codes, the products that share the same J-code (Supartz and Hyalgan, Synvisc, and Synvisc-One which is identical to Synvisc in chemical composition) were analyzed together as single groups. Because the index event was defined as the initiation of HA injection treatment, a non-HA cohort was not defined in this study due to the lack of a clearly identifiable index event equivalent to the initiation of HA treatment and its stage in knee OA treatment pathway. In addition, certain systemic factors that could affect care, such as utilization management policies or plan limits on medication use, are not available in this dataset.

Because knee OA progresses slowly and it may take a long time between OA diagnosis and TKR, a long follow-up period would be ideal. However, the follow-up period in this study had to be limited to 3 years post index date due to a lack of longer follow-up data at the time of study design. In addition, direct indicators of OA disease severity including Kellgren–Lawrence scores, complete medical records of past disease duration, or patient-reported outcomes such as pain and function questionnaire scores were not available in the claims database. In their place, other demographic or clinical characteristics at baseline available within the database were used in multivariate analyses to adjust for potential differences in disease state among patients in different cohorts.

Conclusion

Analysis of the retrospective cohort data in a US health plan claims database provides real-world evidence that some intra-articular HA products may offer more value in delaying TKR than other HA products. The current finding also suggests that explanation of real-world clinical outcomes for IAHA may require considerations that go beyond simple categorization of HA by molecular weight or production process. Additional research is needed to find out more about which aspects of intrinsic HA product properties and external factors may influence clinical outcomes associated with IAHA in the real-world clinical practice.

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Correspondence: Sooyeol Lim, Seikagaku Corporation, Marunouchi Center Building, 6-1, Marunouchi 1-chome Chiyoda-ku, Tokyo 100-0005, Japan. sooyeol.lim@seikagaku.co.jp

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