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Severe Acute Localized Reactions Following Intra-Articular Hyaluronic Acid Injections in Knee Osteoarthritis

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Abstract

Objective. Concerns have been raised about severe acute localized reactions (SALR) following intra-articular (IA) hyaluronic acid (HA) injections for knee osteoarthritis (OA). We compared surrogate SALR measures between hylan G-F 20 and non-hylan G-F 20 HA patients and evaluated corresponding SALR risk factors for hylan G-F 20 patients. *Design*. Knee OA patients were identified from the Optum Clinformatics dataset (January 2006 to June 2016), stratified into hylan G-F 20 and non-hylan G-F 20 HA users. Occurrences of surrogate SALR measures including inflammation/infection, intra-articular corticosteroid (CS) injections, arthrocentesis/aspiration, and office visits were evaluated within 3 days of HA use. Risk factors were evaluated using logistic regression. *Results*. The cohort involved 748,428 HA patients (23.2% in the hylan G-F 20 group). Inflammation/infection rate was 0.001% for hylan G-F 20 and 0.002% for non-hylan G-F 20 HA groups. Risk of CS injection (any diagnosis) was greater for hylan G-F 20 patients by 28% ($P < 0.001$). Combined rates of CS injection and arthrocentesis/aspiration (any diagnosis) were comparable for both groups (hylan G-F 20, 2.2%; non-hylan G-F 20 HA, 2.6%). The risk of any visit or studied responses was lower for the hylan G-F 20 cohort by 12% ($P < 0.001$). Clinical characteristics, such as CS injections within 1 week before HA and fluoroscopic imaging, were associated with the outcomes. *Conclusions*. The diagnosis of inflammations or infections within 3 days of the HA injection was extremely rare. The overall risk of surrogate SALR measures was similar for hylan G-F 20 and non-hylan G-F 20 HA patients.

Keywords

hyaluronic acid, hylan, inflammatory reaction, pseudosepsis, safety

Introduction

Intra-articular hyaluronic acid (HA) is an option in the armamentarium of therapies for managing knee osteoarthritis (OA). The safety profile of HA is well established,[1] but some concerns have been raised regarding reactions that follow in a limited number of HA patients.[2-19] These symptoms are generally manifested within several hours to 72 hours after the HA injection, with some occurring 5 to 6 days later.[2-4,6,8,9,12-14,17-19] Patients may present with severe pain, hot and/or swollen joint, effusion, and loss of function.[2-4,8,9,12-15,17,19] Some patients may also have a fever,[3,4,8] but others may have normal body temperatures.[2,13,17,18] Others have claimed that these patients have similar clinical presentation as infectious arthritis and having blood test results that show generally high C-reactive protein and sedimentation levels.[3,17]

In addition to the variation in their clinical presentations, these reactions are described inconsistently in the literature as inflammatory flares,[13] septic arthritis,[2,17] acute pseudoseptic arthritis,[3,8,16,18] pseudosepsis or severe acute inflammatory reaction,[6] acute local reaction,[9,14] inflammatory reaction,[12] aseptic acute arthritis,[4] pseudogout,[20] acute calcium pyrophosphate dihydrate arthritis,[21] and systemic reaction.[15] Goldberg and Coutts[6] clarified pseudosepsis or severe acute inflammatory reaction as being clinically distinct from an inflammatory reaction or "flare," whereby the latter reactions are typically mild and resolve without treatment or with local therapy.[6] Instead, they defined pseudosepsis as having certain characteristics, which include

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severe inflammation of the joint, often with significant polymorphonuclear cellular effusion and significant pain; occurrence after more than 1 injection; ruling out of gout, sepsis, or pseudogout through the absence of infectious agents and uric acid or calcium pyrophosphate crystals in the synovial fluid; and high counts of mononuclear cells in the synovial fluid. The authors also noted that pseudosepsis required clinical intervention, such as arthrocentesis, intra-articular steroid injection, nonsteroidal anti-inflammatory drugs (NSAIDs).

These reactions, termed herein as severe acute localized reactions (SALR), have been speculated to be possibly related to the crosslink of hylan or an allergic reaction to hyaluronan of avian origin.[5,6] However, this is debatable as similar reactions have been reported following the use of non-crosslinked, non-animal, and/or naturally derived HA.[3,8,10,16,18] With conflicting reports regarding SALR following hylan versus non-hylan products, the objective of the current study was to compare the risk of surrogate SALR measures between patients who used hylan G-F 20 and non-hylan G-F 20 HA and to evaluate the risk factors for surrogate SALR measures for hylan G-F 20 patients.

Methods

Study Population

Knee OA patients were identified from the Optum Clinformatics (Eden Prairie, MN) data from January 2006 until the end of the second quarter of 2016. This U.S. dataset incorporates medical claims from all 50 states for approximately 13 million lives annually, who are covered by UnitedHealth Group, which is a commercial/private payer. The data are compiled from administrative claims through affiliated health plans, Optum employer customer health plans, and Optum payer customer health plans. The patient-level anonymized data is then integrated from physician, facility, and pharmacy claims. Various data elements are captured, such as demographics (age, gender), procedure codes, diagnoses codes, admission and discharge dates, and payments. These data are publicly available for purchase and are exempt from institutional review board approval. At the initiation of the study, 2016 was the most recent data available. The study was designed to evaluate a 10-year period, therefore the dataset started from 2006. Knee OA and non-specific OA with knee pain International Classification of Diseases (ICD) codes were used to identify the study cohort (Supplementary Table S1). A look-back period of 6 months with no previous knee OA diagnosis was used to identify the first diagnosis of knee OA, therefore those without at least 6 months of prior claim history were excluded. Patients younger than 18 years and those who had intra-articular (IA) HA treatment prior to the knee OA diagnosis were also excluded. Patients were also required to have at least 6 months of follow-up following knee OA diagnosis to be included in the study. The patients who underwent at least 1 treatment of HA were selected from the knee OA cohort, based on the Healthcare Common Procedure Coding System (HCPCS) codes for HA (Supplementary Table S1). The HA patients were then stratified into hylan G-F 20 and non-hylan G-F 20 HA cohorts. The hylan G-F 20 cohort included patients who only received hylan G-F 20, while the remaining patients who received either multiple types of HAs or only 1 type of non-hylan G-F 20 HA during the study period were grouped into the non-hylan G-F 20 HA cohort. Patient data used for this study were de-identified. The use of such data is considered exempt from the institutional review board oversight according to Health Insurance Portability and Accountability Act.

Surrogate SALR Measures

The occurrence of surrogate SALR measures or clinical encounters was evaluated for the HA patients within 3 days of each HA use. Surrogate measures included office visit, emergency room (ER) visit, urgent care visit, intra-articular corticosteroid (CS) injection, arthrocentesis/aspiration, and diagnosis of any inflammatory response/infection (Supplementary Table S1). ER visit was included, along with other facility visits, due to previous reports of patients who encountered reactions following HA and presented at the ER.[12,17] CS injections[3,6,9,12-15] and arthrocentesis/aspiration[6,9,12,14] are used in the management of HA patients with reactions, thus these were included as outcomes. These were evaluated when considering occurrences that have a corresponding knee OA diagnosis (knee OA–related), as well as for any occurrence (i.e., any diagnosis, which may not include a knee OA diagnosis) as a sensitivity analysis. The requirement of a knee OA diagnosis was to restrict the conditions and visits to those likely related to the knee. However, since claims data were used for this analysis, any occurrence of the specified conditions or visits was also included in the event of miscoding or lack of knee OA diagnosis coding even though the condition or visit was due to the knee.

Statistical Analysis

To compare the risk of the surrogate SALR measures between the hylan G-F 20 and non-hylan G-F 20 HA groups, a logistic regression model was used, adjusting for various patient demographics, comorbidities, and other potential confounding clinical factors (SAS, SAS Institute Inc., Cary, NC). A P value of less than or equal to 0.05 was used to determine statistical significance. The patient factors included age, race, census region, and gender, while comorbidities were assessed using the composite Charlson score. Potential confounding clinical factors included (1) use of CS injection during the HA injection, (2) prior use of CS (within 1 week or 12 months before HA), (3) prior use of

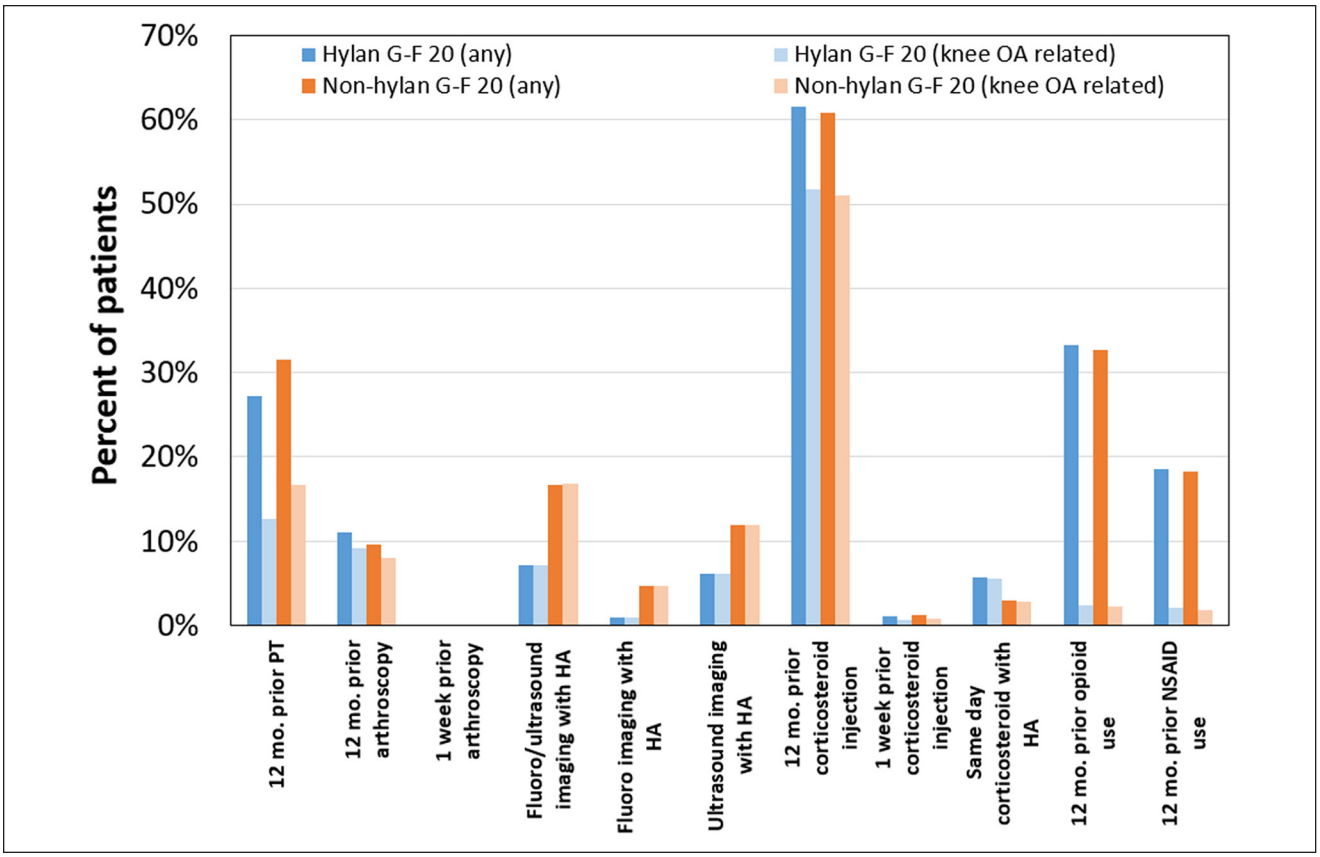

Figure 1. Prior use of health care resources and therapies before HA use. HA = hyaluronic acid; mo. = months; NSAID = nonsteroidal anti-inflammatory drug; fluoro = fluoroscopic; PT = physical therapy.

knee arthroscopy (within 1 week or 12 months before HA), (4) use of fluoroscopic/ultrasound imaging during HA injection, (5) physician HA experience/volume in terms of total number of any HA injections, (6) hylan G-F 20 physician experience/volume in terms of total number of hylan G-F 20 injections, (7) use of NSAIDs (in 12 months before HA), (8) use of opioids (in 12 months before HA), (9) use of physical therapy (PT) (in 12 months before HA), and (10) year. Same time and prior use of CS injection with HA was considered as a potential confounder, as it has been reported that clinicians may inject CS followed by HA 1 week apart to avoid the risk of pseudoseptic arthritis.[22] Moreover, reactions have also been reported following CS injections.[17] The prior use of NSAIDs and opioids (Supplementary Table S1) required a prescription fill within 7 days following a knee OA–related office visit to be considered as a knee OA–related pharmacy claim.

Results

Patient Characteristics

The study cohort involved a total of 748,428 HA patients, of whom 23.2% (n = 173,297) were in the hylan G-F 20 group. At least 1 knee OA–related CS injection was used in approximately 60% of both the hylan G-F 20 and non-hylan G-F 20 HA groups in the 12 months prior to their HA injection (**Fig. 1**). When limited to 1 week before the HA injection, about 1% of the HA patients had at least 1 CS injection. On the other hand, 5.7% of hylan G-F 20 patients had a CS injection at the same visit as the HA injection compared with 3.0% of non-hylan G-F 20 HA patients. Ultrasound and fluoroscopic imaging with the HA injection appeared to be used more frequently in the non-hylan G-F 20 HA group (16.7% vs. 7.2%). About one-third of the HA patients had used opioids and about 18% had used NSAIDs within a year before the HA injection.

Incidences and Hazard Ratios of Surrogate SALR Outcomes

An office visit within 3 days following the HA injection was the most common clinical encounter that was examined in the present study (**Fig. 2**). When limited to office visits with a knee OA diagnosis, the frequency was lower for hylan G-F 20 patients (2.9%) than non-hylan G-F 20 HA patients (4.2%), with the corresponding adjusted risk also

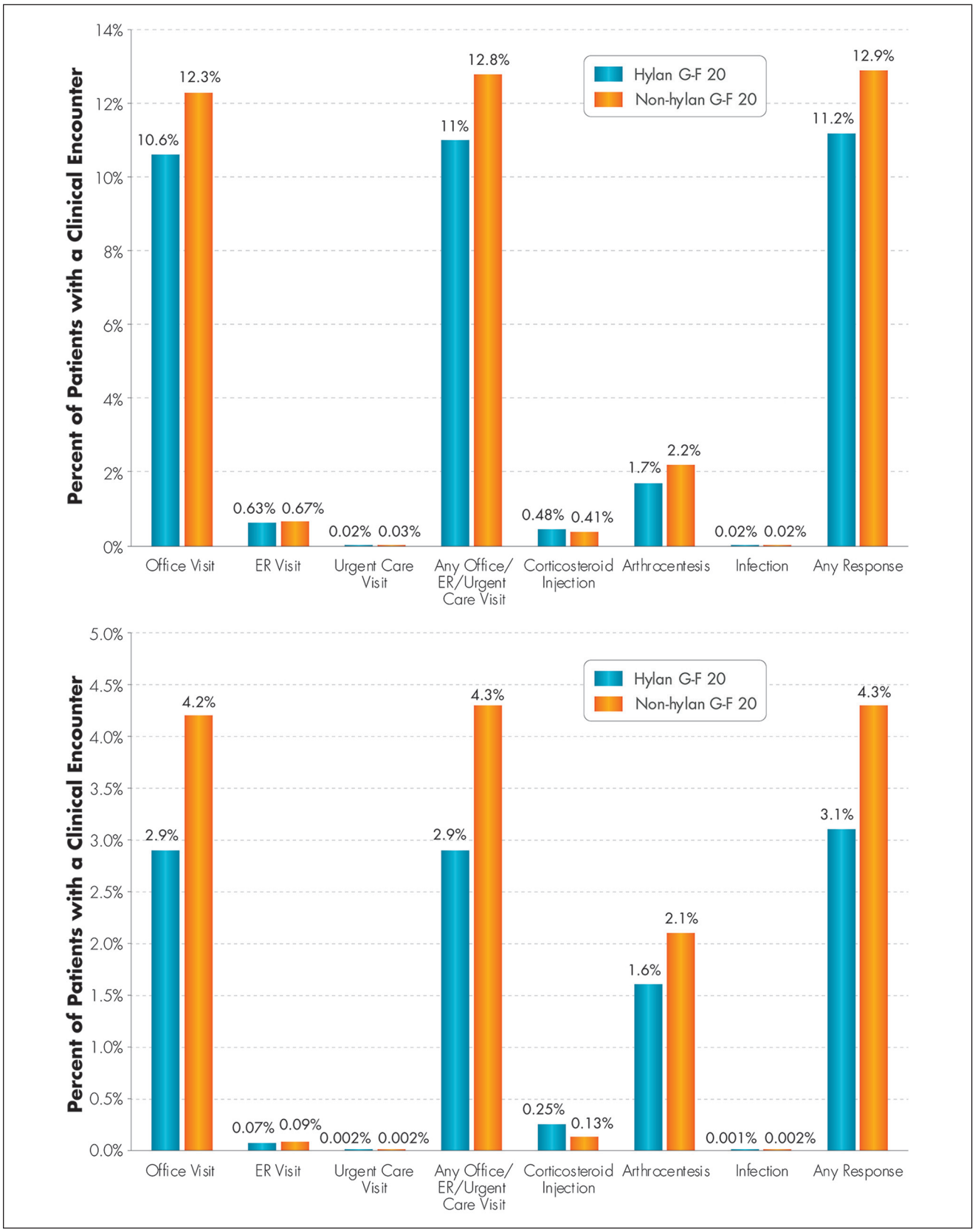

Figure 2. Clinical encounters (top: for any diagnosis; bottom: with knee OA diagnosis) within 3 days post-HA injection (note: *y*-axis scales are different for the graphs). OA = osteoarthritis; HA = hyaluronic acid; ER = emergency room.

Table 1. Relative Risk of Clinical Encounters within 3 Days Post-HA Injection between Hylan G-F 20 and Non-Hylan G-F 20 HA (Reference) Cohorts.

	HR[a] (Lower to Upper 95% Confidence Interval HR)	*P*
Office visits		
Any visit	0.92 (0.90-0.93)	<0.001
Knee OA–related visit	0.84 (0.81-0.87)	<0.001
ER visits		
Any visit	0.99 (0.92-1.06)	0.689
Knee OA–related visit	0.94 (0.77-1.15)	0.560
Urgent care visits		
Any visit	0.87 (0.62-1.23)	0.435
Knee OA–related visit	1.16 (0.35-3.87)	0.807
Any office or ER or urgent care visits		
Any visit	0.93 (0.91-0.94)	<0.001
Knee OA–related visit	0.85 (0.82-0.88)	<0.001
Corticosteroid injection		
Any visit	1.28 (1.18-1.39)	<0.001
Knee OA–related visit	2.16 (1.91-2.44)	<0.001
Arthrocentesis/aspiration		
Any visit	0.98 (0.94-1.02)	0.322
Knee OA–related visit	0.97 (0.93-1.01)	0.201
Inflammation or infection[b]		
Any visit	n/a	n/a
Knee OA–related visit	n/a	n/a
Any visits or response		
Any visit	0.94 (0.92-0.95)	<0.001
Knee OA–related visit	0.88 (0.85-0.91)	<0.001

ER = emergency room; HA = hyaluronic acid; HR = hazard ratio; OA = osteoarthritis; n/a = not applicable.
[a]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.
[b]Incidence was too low.

being lower by 16% (adjusted hazard ratio [AHR] = 0.84 [95% confidence interval (CI) 0.81-0.87]; $P < 0.001$) (**Table 1**). ER visits were infrequent (<0.1% for knee OA–related and <0.7% for any diagnosis) for both groups, with no significant difference in adjusted risk between groups ($P = 0.560$ for knee OA–related and $P = 0.689$ for any). Inflammations or infections were extremely rare within 3 days of HA injections, with knee OA–related ones at 0.001% for hylan G-F 20 and 0.002% for non-hylan G-F 20 HA groups. Even when expanded to include those with any diagnosis, the occurrence rate was 0.02% for both groups. These frequencies were too low to allow adjusted comparisons between groups via logistic regression. The rate of knee OA–related arthrocentesis/aspiration appeared greater for non-hylan G-F 20 HA patients (2.1% vs. 1.6%) but was not found to be significantly different in terms of adjusted risk (AHR = 0.97 [95% CI 0.93-1.01]; $P = 0.201$). On the other hand, the rate of CS injection (any diagnosis) appeared greater for hylan G-F 20 patients (0.48% vs. 0.41%), with a significantly higher risk by 28% (AHR = 1.28 [95% CI 1.18-1.39]; $P < 0.001$). However, the combined rates of CS injection and arthrocentesis/aspiration were comparable between hylan G-F 20 (1.9% [knee OA–related]; 2.2% [any]) and non-hylan G-F 20 HA: 2.2% (knee OA–related); 2.6% [any]) groups. The collective occurrence of any visit or studied responses was found to be lower for the hylan G-F 20 cohort (3.1% vs. 4.3%), with a significantly reduced risk by 12% (AHR = 0.88 [95% CI 0.85-0.91]; $P < 0.001$).

Risk Factors of Surrogate SALR Outcomes

For the hylan G-F 20 cohort, significant risk factors for knee OA–related office visits included age ($P < 0.001$), use of arthroscopy within 1 week before HA ($P < 0.001$), use of CS injection within 1 week and 12 months before HA ($P < 0.001$ for both), race ($P < 0.001$), use of CS injection during HA injection ($P < 0.001$), use of fluoroscopic imaging for HA ($P = 0.002$), and use of ultrasound imaging for HA ($P < 0.001$) (**Table 2**). Specifically, patients who were 55 years and older had significantly lower risk than those younger than 40 years ($P \leq 0.029$). Patients who had arthroscopy or underwent CS injection within 1 week prior to HA had elevated risk of office visits by 299% and 90%, respectively. Conversely, use of CS

Table 2. Risk Factors for Office Visits (with Knee OA Diagnosis) within 3 Days Post-HA Injection for Hylan G-F 20 Cohort.

Factor/Variable	*P*	Level[a]	Reference Level	HR[b] (Lower HR to Upper HR)	*P*
Age (years)	<0.001	40-44	<40	0.95 (0.80-1.11)	0.501
		45-49		0.88 (0.76-1.02)	0.090
		50-54		0.92 (0.80-1.06)	0.253
		55-59		0.83 (0.72-0.95)	0.007
		60-64		0.85 (0.74-0.98)	0.029
		65-69		0.55 (0.47-0.64)	<0.001
		70-74		0.54 (0.46-0.63)	<0.001
		75-79		0.41 (0.34-0.50)	<0.001
		80+		0.38 (0.32-0.46)	<0.001
Charlson Comorbidity Index (CCI)	0.043	CCI 1-2	CCI 0	1.02 (0.95-1.09)	0.621
		CCI 3-4		0.82 (0.71-0.95)	0.009
		CCI 5+		0.91 (0.70-1.18)	0.490
1 week prior arthroscopy	<0.001	Yes	No	3.99 (2.03-7.86)	<0.001
1 week prior CS injection	<0.001	Yes	No	1.90 (1.55-2.32)	<0.001
12 mo. prior arthroscopy	0.512	Yes	No	1.03 (0.95-1.12)	0.512
12 mo. prior CS injection	<0.001	Yes	No	0.85 (0.80-0.91)	<0.001
12 mo. prior NSAID Rx	0.249	Yes	No	1.04 (0.97-1.12)	0.249
12 mo. prior opioid Rx	0.337	Yes	No	1.03 (0.97-1.10)	0.337
12 mo. prior PT	<0.001	Yes	No	2.22 (2.09-2.35)	<0.001
Provider HA volume	<0.001	001-024	150+	0.80 (0.65-0.99)	0.041
		025-049		0.86 (0.71-1.04)	0.124
		050-074		0.74 (0.62-0.90)	0.002
		075-099		0.67 (0.55-0.81)	<0.001
		100-124		0.74 (0.64-0.85)	<0.001
		125-149		0.55 (0.47-0.65)	<0.001
Provider Synvisc volume	<0.001	001-019	100+	0.41 (0.33-0.50)	<0.001
		020-039		0.42 (0.35-0.51)	<0.001
		040-059		0.44 (0.37-0.52)	<0.001
		060-079		0.45 (0.37-0.53)	<0.001
		080-099		0.63 (0.53-0.75)	<0.001
Race	<0.001	Asian	White	1.19 (0.99-1.44)	0.069
		Black		1.03 (0.93-1.15)	0.552
		Hispanic		1.23 (1.10-1.37)	<0.001
		Unknown		1.19 (1.07-1.32)	0.001
Region	<0.001	Midwest	South	0.66 (0.61-0.71)	<0.001
		Northeast		1.47 (1.34-1.61)	<0.001
		West		0.83 (0.76-0.91)	<0.001
Injection of CS at the same visit as HA	<0.001	Yes	No	0.70 (0.60-0.81)	<0.001
Use of fluoro imaging for HA	0.002	Yes	No	0.59 (0.42-0.82)	0.002
Use of ultrasound imaging for HA	<0.001	Yes	No	1.34 (1.19-1.50)	<0.001
Use of fluoro/ultrasound imaging for HA	<0.001	Yes	No	1.38 (1.25-1.52)	<0.001
Sex	0.069	Female	Male	1.06 (1.00-1.12)	0.069
Year of HA	<0.001			1.04 (1.03-1.06)	<0.001

CS = corticosteroid; HA = hyaluronic acid; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs; Rx= prescription; OA = osteoarthritis; PT = physical therapy; fluoro = fluoroscopic.

[a]Level refers to the subcategory within the factor (variable).

[b]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.

injection at the same visit as the HA injection was associated with lower risk by 30%. Hispanic patients also had greater risks by 23% compared with white patients. Fluoroscopic imaging with HA appeared to be associated with lower risks (AHR = 0.59), but the opposite was true for ultrasound imaging (AHR = 1.34). The only factor that was associated with knee OA–related ER visits for the hylan G-F 20 patients was the use of CS injection at the same

Table 3. Risk Factors for ER Visits (with Knee OA Diagnosis) within 3 Days Post-HA Injection for Hylan G-F 20 Cohort.

Factor/Variable	*P*	Level[a]	Reference Level	HR[b] (Lower HR-Upper HR)	*P*
Age (years)	0.139	40-44	<40	0.63 (0.19-2.08)	0.453
		45-49		1.55 (0.62-3.88)	0.349
		50-54		0.60 (0.22-1.61)	0.312
		55-59		0.54 (0.20-1.43)	0.214
		60-64		0.63 (0.24-1.66)	0.349
		65-69		0.83 (0.33-2.13)	0.704
		70-74		0.73 (0.27-1.97)	0.532
		75-79		0.61 (0.20-1.80)	0.369
		80+		0.77 (0.28-2.14)	0.616
Charlson Comorbidity Index (CCI)	0.343	CCI 1-2	CCI 0	—[c]	
		CCI 3-4		—[c]	
		CCI 5+		1.77 (0.54-5.76)	0.343
1 week prior arthroscopy		Yes	No	—[c]	
1 week prior CS injection	0.573	Yes	No	1.50 (0.37-6.15)	0.573
12 mo. prior arthroscopy		Yes	No	—[c]	
12 mo. prior CS injection		Yes	No	—[c]	
12 mo. prior NSAID Rx		Yes	No	—[c]	
12 mo. prior opioid Rx		Yes	No	—[c]	
12 mo. prior PT		Yes	No	—[c]	
Provider HA volume	0.932	001-024	150+	1.54 (0.35-6.88)	0.570
		025-049		1.14 (0.26-5.03)	0.866
		050-074		1.31 (0.30-5.78)	0.725
		075-099		1.77 (0.37-8.43)	0.475
		100-124		1.05 (0.40-2.74)	0.920
		125-149		0.61 (0.22-1.70)	0.346
Provider Synvisc volume	0.064	001-019	100+	0.36 (0.08-1.56)	0.170
		020-039		0.18 (0.04-0.79)	0.023
		040-059		0.23 (0.05-0.93)	0.039
		060-079		0.15 (0.03-0.71)	0.017
		080-099		0.08 (0.01-0.75)	0.027
Race	0.257	Asian	White	0.34 (0.05-2.49)	0.291
		Black		—[c]	
		Hispanic		—[c]	
		Unknown		0.59 (0.26-1.34)	0.205
Region		Midwest	South	—[c]	
		Northeast		—[c]	
		West		—[c]	
Injection of CS at the same visit as HA	0.041	Yes	No	0.13 (0.02-0.92)	0.041
Use of fluoro imaging for HA	0.997	Yes	No	0.00 (0.00-7989.84)	0.997
Use of ultrasound imaging for HA		Yes	No	—[c]	
Use of fluoro/ultrasound imaging for HA		Yes	No	—[c]	
Sex		Female	Male	—[c]	
Year of HA				—[c]	

CS = corticosteroid; ER = emergency room; HA = hyaluronic acid; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs; Rx = prescription; OA = osteoarthritis; PT = physical therapy; fluoro = fluoroscopic.

[a]Level refers to the subcategory within the factor (variable).

[b]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.

[c]Limited incidence.

visit as the HA injection. Those patients who had CS injection during HA injection had a lower risk of ER visits by 87% (95% CI 8%-98%; $P = 0.041$) (**Table 3**). Prior CS injections within 1 week and 12 months before HA were associated with greater risk of CS injections post-HA by 255% (95% CI 132%-444%; $P < 0.001$) and 36%

Table 4. Risk Factors for CS Injections (with Knee OA Diagnosis) within 3 Days Post-HA Injection for Hylan G-F 20 Cohort.

Factor/Variable	*P*	Level[a]	Reference Level	HR[b] (Lower HR-Upper HR)	*P*
Age (years)	<0.001	40-44	<40	0.53 (0.29-0.96)	0.037
		45-49		0.87 (0.54-1.41)	0.578
		50-54		0.84 (0.54-1.32)	0.445
		55-59		0.75 (0.48-1.17)	0.207
		60-64		0.55 (0.34-0.88)	0.012
		65-69		0.46 (0.28-0.75)	0.002
		70-74		0.54 (0.33-0.90)	0.017
		75-79		0.29 (0.15-0.54)	<0.001
		80+		0.26 (0.14-0.48)	<0.001
Charlson Comorbidity Index (CCI)	0.218	CCI 1-2	CCI 0	1.03 (0.83-1.27)	0.819
		CCI 3-4		0.54 (0.30-0.98)	0.041
		CCI 5+		0.99 (0.43-2.24)	0.972
1 week prior arthroscopy		Yes	No	—[c]	
1 week prior CS injection	<0.001	Yes	No	3.55 (2.32-5.44)	<0.001
12 mo. prior arthroscopy	0.124	Yes	No	0.78 (0.56-1.07)	0.124
12 mo. prior CS injection	0.004	Yes	No	1.36 (1.10-1.69)	0.004
12 mo. prior NSAID Rx	0.506	Yes	No	1.08 (0.86-1.37)	0.506
12 mo. prior opioid Rx	0.158	Yes	No	0.86 (0.70-1.06)	0.158
12 mo. prior PT	0.377	Yes	No	1.10 (0.89-1.36)	0.377
Provider HA volume	<0.001	001-024	150+	1.13 (0.52-2.45)	0.750
		025-049		1.28 (0.64-2.55)	0.479
		050-074		0.38 (0.17-0.86)	0.019
		075-099		0.96 (0.53-1.73)	0.895
		100-124		0.46 (0.26-0.81)	0.007
		125-149		0.40 (0.22-0.74)	0.003
Provider Synvisc volume	<0.001	001-019	100+	0.27 (0.13-0.58)	<0.001
		020-039		0.22 (0.11-0.46)	<0.001
		040-059		0.42 (0.22-0.79)	0.007
		060-079		0.35 (0.18-0.67)	0.002
		080-099		0.84 (0.49-1.43)	0.518
Race	0.070	Asian	White	0.95 (0.49-1.86)	0.887
		Black		0.64 (0.41-0.98)	0.039
		Hispanic		1.10 (0.79-1.54)	0.581
		Unknown		1.36 (0.98-1.87)	0.062
Region	<0.001	Midwest	South	0.37 (0.28-0.50)	<0.001
		Northeast		1.48 (1.09-2.00)	0.012
		West		1.23 (0.96-1.57)	0.099
Injection of CS at the same visit as HA	<0.001	Yes	No	2.91 (2.21-3.82)	<0.001
Use of fluoro imaging for HA	0.472	Yes	No	0.69 (0.25-1.90)	0.472
Use of ultrasound imaging for HA	0.094	Yes	No	0.69 (0.45-1.07)	0.094
Use of fluoro/ultrasound imaging for HA	0.042	Yes	No	1.40 (1.01-1.94)	0.042
Sex	0.124	Female	Male	1.17 (0.96-1.43)	0.124
Year of HA	0.015			1.05 (1.01-1.09)	0.015

CS = corticosteroid; HA = hyaluronic acid; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs; Rx = prescription; OA = osteoarthritis; PT = physical therapy; fluoro = fluoroscopic.
[a]Level refers to the subcategory within the factor (variable).
[b]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.
[c]Limited incidence.

(95% CI 10%-69%; $P = 0.004$) (**Table 4**). Concomitant CS injection and HA injection was also associated with elevated risk of CS injections post-HA by 191% (95% CI 121%-282%; $P < 0.001$). Higher risk of arthrocentesis/aspiration post-HA was found for hylan G-F 20 patients who had CS injection within 1 week before HA (AHR = 2.47;

Table 5. Risk Factors for Arthrocentesis (with Knee OA Diagnosis) within 3 Days Post-HA Injection for hylan G-F 20 Cohort.

Factor/Variable	*P*	Level[a]	Reference Level	HR[b] (Lower HR-Upper HR)	*P*
Age (years)	<0.001	40-44	<40	0.91 (0.73-1.14)	0.426
		45-49		0.92 (0.75-1.12)	0.400
		50-54		0.97 (0.81-1.17)	0.767
		55-59		0.90 (0.75-1.08)	0.272
		60-64		0.90 (0.74-1.08)	0.249
		65-69		0.56 (0.46-0.69)	<0.001
		70-74		0.56 (0.45-0.70)	<0.001
		75-79		0.46 (0.36-0.59)	<0.001
		80+		0.45 (0.36-0.58)	<0.001
Charlson Comorbidity Index (CCI)	0.253	CCI 1-2	CCI 0	0.99 (0.91-1.09)	0.900
		CCI 3-4		0.82 (0.67-1.00)	0.045
		CCI 5+		0.96 (0.69-1.34)	0.830
1 week prior arthroscopy	0.772	Yes	No	1.24 (0.30-5.16)	0.772
1 week prior CS injection	<0.001	Yes	No	2.47 (1.95-3.13)	<0.001
12 mo. prior arthroscopy	<0.001	Yes	No	0.79 (0.70-0.90)	<0.001
12 mo. prior CS injection	<0.001	Yes	No	0.85 (0.79-0.92)	<0.001
12 mo. prior NSAID Rx	0.050	Yes	No	1.10 (1.00-1.21)	0.050
12 mo. prior opioid Rx	0.923	Yes	No	1.00 (0.92-1.08)	0.923
12 mo. prior PT	<0.001	Yes	No	1.16 (1.06-1.26)	<0.001
Provider HA volume	<0.001	001-024	150+	0.71 (0.51-0.99)	0.047
		025-049		0.80 (0.58-1.09)	0.160
		050-074		0.67 (0.48-0.92)	0.014
		075-099		0.76 (0.57-1.00)	0.051
		100-124		0.38 (0.30-0.49)	<0.001
		125-149		0.21 (0.16-0.28)	<0.001
Provider Synvisc volume	<0.001	001-019	100+	0.24 (0.17-0.33)	<0.001
		020-039		0.23 (0.17-0.31)	<0.001
		040-059		0.18 (0.13-0.25)	<0.001
		060-079		0.17 (0.13-0.24)	<0.001
		080-099		0.59 (0.47-0.76)	<0.001
Race	<0.001	Asian	White	0.96 (0.74-1.24)	0.753
		Black		0.90 (0.78-1.05)	0.178
		Hispanic		1.25 (1.09-1.42)	0.001
		Unknown		1.23 (1.07-1.41)	0.003
Region	<0.001	Midwest	South	0.51 (0.46-0.57)	<0.001
		Northeast		1.38 (1.22-1.56)	<0.001
		West		1.05 (0.94-1.16)	0.372
Injection of CS at the same visit as HA	<0.001	Yes	No	0.53 (0.43-0.66)	<0.001
Use of fluoro imaging for HA	<0.001	Yes	No	0.22 (0.12-0.41)	<0.001
Use of ultrasound imaging for HA	0.028	Yes	No	1.19 (1.02-1.38)	0.028
Use of fluoro/ultrasound imaging for HA	<0.001	Yes	No	1.58 (1.39-1.80)	<0.001
Sex	0.287	Female	Male	1.04 (0.96-1.13)	0.287
Year of HA	<0.001			1.07 (1.06-1.09)	<0.001

CS = corticosteroid; HA = hyaluronic acid; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs; Rx = prescription; OA = osteoarthritis; PT = physical therapy; fluoro = fluoroscopic.

[a]Level refers to the subcategory within the factor (variable).

[b]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.

$P < 0.001$) (**Table 5**). Ultrasound imaging was also associated with greater risks of arthrocentesis/aspiration (AHR = 1.19; $P = 0.028$), but the opposite was true for fluoroscopic imaging (AHR = 0.22; $P < 0.001$). Similarly, concomitant CS injection and HA injection was associated with lower risk of arthrocentesis/aspiration by 47% (95% CI

Table 6. Risk Factors for Any Visit or Response (with Knee OA Diagnosis) within 3 Days Post-HA Injection for Hylan G-F 20 cohort.

Factor/Variable	*P*	Level[a]	Reference Level	HR[b] (Lower HR-Upper HR)	*P*
Age (years)	<0.001	40-44	<40	0.94 (0.80-1.10)	0.446
		45-49		0.90 (0.78-1.04)	0.158
		50-54		0.93 (0.81-1.06)	0.283
		55-59		0.83 (0.72-0.95)	0.008
		60-64		0.85 (0.74-0.98)	0.028
		65-69		0.61 (0.53-0.71)	<0.001
		70-74		0.60 (0.51-0.71)	<0.001
		75-79		0.47 (0.40-0.57)	<0.001
		80+		0.50 (0.42-0.60)	<0.001
Charlson Comorbidity Index (CCI)	0.073	CCI 1-2	CCI 0	1.02 (0.96-1.09)	0.572
		CCI 3-4		0.84 (0.73-0.97)	0.015
		CCI 5+		1.01 (0.80-1.27)	0.933
1 week prior arthroscopy	<0.001	Yes	No	3.89 (1.98-7.65)	<0.001
1 week prior CS injection	<0.001	Yes	No	1.84 (1.51-2.25)	<0.001
12 mo. prior arthroscopy	0.836	Yes	No	1.01 (0.93-1.09)	0.836
12 mo. prior CS injection	<0.001	Yes	No	0.84 (0.79-0.89)	<0.001
12 mo. prior NSAID Rx	0.064	Yes	No	1.07 (1.00-1.14)	0.064
12 mo. prior opioid Rx	0.320	Yes	No	1.03 (0.97-1.10)	0.320
12 mo. prior PT	<0.001	Yes	No	2.22 (2.09-2.35)	<0.001
Provider HA volume	<0.001	001-024	150+	0.79 (0.64-0.96)	0.016
		025-049		0.84 (0.70-1.01)	0.067
		050-074		0.73 (0.61-0.87)	<0.001
		075-099		0.72 (0.60-0.87)	<0.001
		100-124		0.72 (0.62-0.83)	<0.001
		125-149		0.53 (0.45-0.62)	<0.001
Provider Synvisc volume	<0.001	001-019	100+	0.45 (0.37-0.54)	<0.001
		020-039		0.45 (0.38-0.54)	<0.001
		040-059		0.43 (0.37-0.52)	<0.001
		060-079		0.45 (0.38-0.53)	<0.001
		080-099		0.66 (0.56-0.78)	<0.001
Race	<0.001	Asian	White	1.10 (0.91-1.32)	0.335
		Black		1.05 (0.94-1.16)	0.386
		Hispanic		1.25 (1.13-1.39)	<0.001
		Unknown		1.20 (1.09-1.33)	<0.001
Region	<0.001	Midwest	South	0.66 (0.61-0.71)	<0.001
		Northeast		1.38 (1.26-1.51)	<0.001
		West		0.99 (0.91-1.07)	0.773
Injection of CS at the same visit as HA	<0.001	Yes	No	0.65 (0.57-0.76)	<0.001
Use of fluoro imaging for HA	<0.001	Yes	No	0.58 (0.42-0.80)	<0.001
Use of ultrasound imaging for HA	<0.001	Yes	No	1.35 (1.21-1.50)	<0.001
Use of fluoro/ultrasound imaging for HA	<0.001	Yes	No	1.46 (1.33-1.60)	<0.001
Sex	0.045	Female	Male	1.06 (1.00-1.12)	0.045
Year of HA	<0.001			1.05 (1.04-1.06)	<0.001

CS = corticosteroid; HA = hyaluronic acid; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs; Rx = prescription; OA = osteoarthritis; PT = physical therapy; fluoro = fluoroscopic.

[a]Level refers to the subcategory within the factor (variable).

[b]Hazard ratio is a measure of how often the event occurs in one group compared with the other group.

34%-57%; $P < 0.001$). For the collective risk of any visit or studied responses, patients with CS injection or arthroscopy within 1 week prior to HA had greater risks by 84% and 289%, respectively (both $P < 0.001$) (**Table 6**). Ultrasound imaging was also associated with greater risks of any clinical encounter (AHR = 1.35; $P < 0.001$), but

not for fluoroscopic imaging (AHR = 0.58; $P < 0.001$). Concomitant CS injection and HA injection was associated with lower risk of any clinical encounter by 35% (95% CI 24%-43%; $P < 0.001$).

Discussion

Case reports of inflammatory-type reactions or SALR have been described following the use of HA in knee OA patients. The present study's findings do not support the hypothesis that the risk of surrogate SALR measures is greater for hylan G-F 20 patients. Our study of almost 750,000 knee OA patients who had HA injections, of which about a quarter were only given hylan G-F 20, demonstrated that inflammation or infections were extremely rare within 3 days of the HA injection. Knee OA–related occurrences were 0.001% for hylan G-F 20 and 0.002% for non-hylan G-F 20 HA groups. Of the various surrogate SALR measures, CS injection rates within 3 days following HA were higher for the hylan G-F 20, but when combined with arthrocentesis/aspiration, appeared to be comparable between both patient groups. Overall, the collective occurrence of any visit or studied responses was lower for the hylan G-F 20 cohort. Moreover, the present study identified certain clinical characteristics, such as the use of CS injections within 1 week before HA, concomitant use of CS and hylan G-F 20, and use of fluoroscopic imaging, as being either positively or negatively associated with the risk of a number of surrogate SALR measures.

A number of researchers have raised questions about the incidence, diagnosis, treatment, and prevention of SALR-type reactions following the use of HA in the knee.[2-19] However, there is substantial inconsistency in which these reactions are diagnosed. Most analyze synovial joint fluid from patients who return with a reaction,[3,4,8,9,15,16,18] but even then, some do not do it consistently for all their patients. The absence of crystals in the fluid is intended to rule out pseudogout.[6,20] Culture reports from the aspirated fluid are also needed to detect whether infectious agents are absent, so as to rule out sepsis.[6,7] A high concentration of eosinophils from synovial fluid analyses may also be suggestive of an immunologic sensitization.[6] Moreover, it is also unclear if there are any differences in the clinical presentation or laboratory findings between reactions following use of various products.[10] The present study showed that inflammation or infections were extremely rare within 3 days of the HA injection. The occurrence was 1 out of 100,000 hylan G-F 20 patients and 2 out of 100,000 non-hylan G-F 20 HA patients for those events that had a corresponding knee OA diagnosis, and increased to 2 out of 10,000 for both cohorts when all inflammation or infections were included regardless of diagnosis.

Although no significant difference in the risk of inflammatory response or infection was observed between hylan G-F 20 and non-hylan G-F 20 HA cohorts, the risk of CS injection rates within 3 days following HA were significantly higher for the hylan G-F 20 patients. Conversely, the arthrocentesis/aspiration rates tended to be higher for the non-hylan G-F 20 HA patients. A possible explanation for this trend is that there may be greater belief that acute reactions occur more frequently following hylan G-F 20 use,[5-7] thus physicians are more aware and likely to treat the affected patients with CS injection since the reaction generally resolves fairly quickly. In contrast, since there may be less awareness around the potential for acute reactions with other HAs, there is a concern for infections when those patients present with a reaction and, hence, aspirations are performed more frequently. If the rates of CS injections and arthrocentesis/aspirations are combined, they appeared comparable between both groups of patients. Furthermore, based on the overall findings from the present study, the risk of surrogate SALR measures was not found to be greater for hylan G-F 20 patients. Although acute reactions have been reported following the use of hylan G-F 20,[3,4,9,12-15] these have also occurred for other HA products (Genvisc, Ostenil, and Curavisc).[3,8,16,18] FDA reports of potentially similar reactions have also been identified following use of Supartz and Hyalgan.[7,10]

The cause of these acute reactions still remains unclear. High molecular weight, crosslinked HAs have been implicated in having greater risk of acute reactions.[1] A meta-analysis of randomized controlled trials comparing hylan to "standard" HA found that patients treated with hylan were approximately twice as likely as patients treated with "standard" HA to experience flares (relative risk of 2.04) and joint effusions (relative risk of 2.40).[23] On the other hand, Maheu *et al*.[11] compared the safety and efficacy of high molecular weight hylan GF-20 to medium molecular weight Structovial and found no difference in local reactions, with no reports of pseudoseptic arthritis in their study. Allergic reaction to avian proteins has been identified as a possible source of the reactions,[5,14] but this may be refuted by similar reactions following the use of non-animal derived HA.[3,8,16] Some have also speculated that the accumulation of HA material or sensitization may be involved due to patients tending to react after their second or later injection or course.[8,13] Leopold *et al*.[9] reported that acute local reactions occurred more than 8 times more frequently in the patients who had received more than 1 course of hylan GF-20 (21%; 4 of 19) than those treated only once (2%; 1 of 42) ($P = 0.029$). However, it has been shown that these reactions can occur after the first HA injection,[2,3,18] which contradicts the sensitization theory or points to other mechanisms that may also play a role. The use of sterile[2,17,19] or refined[6] techniques may help reduce the risk. In summary, the reactions seem to be unpredictable and symptoms are somewhat diverse, as well as following the use of different HAs, which suggest that multiple mechanisms are at play.

The role of intra-articular CS in the development of the acute reactions is somewhat unclear. While CS and HA injections may be used concomitantly to improve the overall functional response[24-26] or used 1 week apart to reduce the risk of pseudoseptic arthritis,[22] acute reactions have also been reported following intra-articular CS use.[17] Intra-articular CS injections given before or with HA have been suggested to promote infections.[2] The present study provided some additional insight into the potential role of CS injections. The use of CS injections within 1 week before HA was found to be associated with greater risk of a number of surrogate SALR measures (knee OA–related office visits, subsequent CS injection, arthrocentesis/aspiration, any visit/response) for hylan G-F 20 patients. The concomitant use of CS and hylan G-F 20 was also a risk factor for subsequent CS injection, although there were conflicting results because it was associated with reduced risks of subsequent arthrocentesis/aspirations, office visits, ER visits, and any visit/studied response. It is unclear why factors such as the use of fluoroscopic imaging during HA injection may help reduce the risk of SALR, although this may be related to providing more accurate needle placement. Morgan *et al*.[27] reported that fluoroscopy image-guided HA injections significantly improve clinical outcomes at 6 months for patients with mild, moderate, and severe knee OA. The present study found that fluoroscopic imaging was associated with lower risk of subsequent office visits, arthrocentesis/aspiration, and any visit or studied responses.

The present study had several limitations, most of which relate to the use of administrative claims data. The data set did not include laboratory results; nor was it known if the patients had undergone blood or synovial fluid tests. Instead, we relied on surrogate measures as potential indicators for SALR. Given the degree of variability in how SALR is diagnosed clinically and at times without laboratory tests, our reliance on more discernible diagnoses, treatments, and health resource utilization (e.g., emergency department visits) provided a more consistent approach to identifying a potential signal. The severity of OA was unknown in these patients, thus it is unclear to what extent the disease stage may have played a role in our findings. We attempted to control for differences in baseline conditions and other potential confounding factors, including patient demographics and other clinical factors, in our regression analysis. The role of any selection bias or other unexamined factors are unknown. Although we examined non-hylan G-F 20 HA patients, we did not further stratify that group by molecular weight or HA source, which could possibly help elucidate any differences between HA product type. The role of the number of HA injections and courses on the outcomes was also not evaluated. The cause-and-effect of the various factors in leading to the surrogate SALR measures cannot be examined due to the use of observational data, as well as the use of claims data. But this study of a large cohort of hylan G-F 20 and non-hylan G-F 20 HA patients provides compelling data that the risk of SALR is comparable between both groups. Despite these limitations, our data have the advantage of being from a real-world large sample size, which includes a population-based perspective of the risk of SALR.

The present study analyzed the potential risk of SALR, via surrogate measures, in a real-world setting of almost 750,000 knee OA patients who used intra-articular HA. In this cohort, the diagnosis of inflammation or infections within 3 days of the HA injection was extremely rare. The overall risk of surrogate SALR measures was not found to be greater for hylan G-F 20 patients.

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Ethical Approval

The data are publicly available for purchase and are exempt from institutional review board approval.

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