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Viscosupplementation for Osteoarthritis of the Knee: A Key Opinion Leader Panel Discussion

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SUMMARY

With a sharp rise in the prevalence of osteoarthritis of the knee (OAK) in a younger population, new management strategies are needed to preserve mobility, improve patients' quality of life, and reduce the effects of potential disease-related comorbidities. Viscosupplementation with the use of hyaluronic acid (HA) injection is a treatment option for OAK that can provide lubrication and elastic shock absorption, leading to potential pain relief, improved function, and reduced stiffness. A key opinion leader (KOL) panel discussion was held December 3, 2016, with the objective of sharing opinions, ideas, information, and trends regarding OAK and the potential treatment and management offered by viscosupplementation. The panel concluded that viscosupplementation with HA injections presents a viable, cost-effective, and safe alternative for the treatment of OAK.

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A live key opinion leader (KOL) panel discussion was held December 3, 2016, in New York City, New York. In attendance were the following 11 KOLs with varying titles and specialties in the field: 4 pharmacists, 3 orthopedic surgeons in clinical practice, 1 rheumatologist, 1 medical officer for a pharmacy benefits manager, 1 professor of orthopedic surgery, and 1 sports medicine physician. With a sharp rise in the prevalence of osteoarthritis of the knee (OAK) in a younger population, new management strategies are needed to preserve mobility, improve patients' quality of life, and reduce the effects of potential disease-related comorbidities. Viscosupplementation with the use of hyaluronic acid (HA) injection is a treatment option for OAK that can provide lubrication and elastic shock absorption, leading to potential pain relief, improved function, and reduced stiffness. The objective of this panel was to share opinions, ideas, information, and trends regarding OAK and the potential treatment and management offered by viscosupplementation. The panel concluded that viscosupplementation with HA injections presents a viable, cost-effective, and safe alternative for the treatment of OAK.

Background

OAK, a degenerative form of arthritis, is the most common type of arthritis in the knee, affecting 14 million individuals in the United States.¹ OAK is associated with degradation of the cartilage in the knee joint space, which leads to symptoms such as pain, stiffness, and crepitus.² The condition can be mechanically driven and age-dependent, but it is biochemically mediated.³ Factors such as obesity, mechanical axis malalignment, and macrotrauma may lead to biophysical changes that ultimately result in the degradation of articular cartilage.³ In

patients without osteoarthritis, HA aids in the lubrication and cushioning of the synovial joint and may play a role in reducing toxic catabolic oxidative synovial chemokines and potentially improve the viscosity of synovial fluid.⁴⁻⁶ In osteoarthritis, however, HA is observed to have a reduced molecular weight and lower concentration, which results in a decreased viscosity and elasticity of the synovial fluid, potentially contributing to the pain, stiffness, and loss of mobility.^{6,7} Viscosupplementation with HA is a procedure during which HA is injected into the knee joint, which has been shown to provide lubrication and elastic shock absorption, leading to pain relief, improved function, and reduced stiffness.⁴⁻⁷ However, HA injections are typically reserved for clinical cases in which patients are no longer able to manage their condition with traditional treatments such as physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs).⁷

Epidemiology

Although OAK has generally been associated with advanced age, the patient demographics of OAK are changing, with a sharp rise in prevalence among the younger population, likely due to the increase in obesity rates.¹ During the 1990s, the average age at OAK diagnosis was 72 years; however, as of 2016, more than half of those with symptomatic OAK were aged younger than 65 years, allowing for substantial time for greater disability to occur.¹ Of the 14 million people living with OAK in the United States, about 6 million are between the ages of 45 and 64 years and about 6 million are aged 65 years and older.¹

Patient Burden

The most common reason for knee replacement surgery is to relieve the pain and disability caused by osteoarthritis, which is predicted to be the fourth-leading cause of disability by the year 2020.⁸ The results of a 2011 study demonstrated that patients with osteoarthritis of the knee or hip have a higher risk of all-cause mortality, which is likely due to concomitant risk factors, including diabetes, cancer, cardiovascular disease, and reduced functional activity levels.⁹ It is evident that proper management strategies are needed for this patient population in order to preserve mobility, maintain and improve patients' quality of life, and reduce the impact of potential disease-related comorbidities.

Diagnosis and Treatment Goals

Diagnosis of OAK involves a clinician assessment of the nature and severity of the pain, often in addition to a measurement of movement in the joint.¹⁰ Clinicians will often rely on X-rays to

illustrate knee-narrowing of the joint space, which indicates OAK, and bony spurs.¹⁰ Magnetic resonance imaging (MRI) is employed in some cases to add clarification and accuracy to the diagnosis.¹⁰

Following diagnosis, clinicians and patients will work together to determine an appropriate and manageable treatment regimen. Treatment goals generally focus on alleviating OAK-associated pain, increasing range of motion, increasing overall functional strength, and improving physical fitness levels and mobility.¹⁰⁻¹² Attainment of these treatment goals is often attempted by a combination of nonpharmacological and pharmacological treatment modalities, commonly including acetaminophen, aspirin, and NSAIDs; once these options are exhausted and the condition worsens, surgical options are commonly employed.¹⁰⁻¹² Nonpharmacological treatment options often include weight reduction, avoiding activities that exert stress on the joint, physical therapy, and rehabilitation.¹⁰

■ Treatment Considerations in the Management of OAK, Including Use of HA Injections

Major treatment guidelines for the pharmacological management of OAK in the United States are published by the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Rheumatology (ACR).^{13,14} Additionally, although not classified as a treatment guideline, the American Medical Society for Sports Medicine (AMSSM) published a scientific statement supporting viscosupplementation injections for OAK in 2015.¹⁵

The AAOS treatment guidelines recommend oral NSAIDs, topical NSAIDs, or tramadol for the management of symptomatic OAK.¹³ The AAOS notes that it cannot recommend using HA for patients with symptomatic OAK because meta-analyses allowed for its review group to determine that the overall effect of HA did not provide minimum clinically important improvement (MCII) and minimum and minimal clinically important difference (MCID) to patients in this population, using their own interpretation; levels of MCII and MCID are typically defined according to the patient's perceptions of what signifies an important improvement or difference.¹³ For patients with OAK, the ACR recommends the use of acetaminophen, oral NSAIDs, topical NSAIDs, tramadol, or intra-articular corticosteroid injections for initial management.¹⁴ The ACR indicates that the organization has no recommendations for or against the use of intra-articular hyaluronates as part of a pharmacological regimen for the initial management of OAK; instead, the ACR conditionally recommends the use of HA injections for patients who have had an inadequate response to initial therapy, including corticosteroid injections and oral or topical NSAIDs.¹⁴

AMSSM noted in its scientific statement that it recommends the use of HA injections in appropriate patients with OAK, citing high-quality evidence demonstrating benefit to patients 60 years of age or older; AMSSM suggests the use of HA

injections in patients under the age of 60 years, citing moderate-quality evidence demonstrating benefit in this age group.¹⁵ Additionally, some providers use HA injections to postpone total knee arthroplasty (TKA) when conservative measures do not relieve symptoms or improve quality of life. TKA is indicated for patients who experience significant, disabling pain caused by advanced arthritis, whose quality of life has significantly been reduced, and whose pain and dysfunction persist despite use of conservative treatment.¹⁶

■ Gaps in Care/Guidelines

While TKA has generally resulted in successful outcomes, satisfaction rates of this surgical invention vary.¹⁷⁻¹⁹ In a prospective study of patients who underwent TKAs, 39% of patients reported that the expectations they had regarding the results of the TKA had not been fulfilled, and multiple studies suggest that up to 20% of patients receiving TKAs are dissatisfied with their results.¹⁷⁻¹⁹ Despite TKA outcomes not meeting some patients' expectations, the rate of TKA procedures is increasing. One published study projected that by the year 2030, the demand for TKAs is estimated to increase by 673%, to 3.48 million procedures annually.²⁰ This projected increase is based on 2003 estimates coupled with the aging population and the desire to maintain an active lifestyle.

The longevity of TKAs is typically greater than 10 years; however, the rate of TKA failures requiring revision varies from 2%-5.7% within the first 5 years to 5%-6.8% within the first 10 years.²¹⁻²³ The rising demand for primary TKAs will inevitably correspond with an increasing demand for revisions of TKAs, and it was projected that demand for revision TKAs would grow by 601% from 2005 to 2030.^{20,24} The increase in TKAs in combination with dissatisfaction rates, younger age of diagnosis, and rates of TKA revisions point to the need for alternative OAK therapy and management.

■ Overview of HA Injections and Role in Treatment

Intra-articular viscosupplementation with the use of HA injections has been approved by the U.S. Food and Drug Administration (FDA) exclusively for use in treating pain associated with OAK in the United States since 1997.²⁵ Per FDA labeling, HA injections are indicated for the treatment of pain in OAK in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen). Since HA is a natural component of synovial fluids, HA injections replace this substance and restore the protective effect of healthy synovial fluid by increasing the viscosity of synovial fluid in knee joints affected by OA and potentially reducing and/or counteracting the effects of inflammatory mediators.²⁶ HA injections include avian-/nonavian-based, cross-/noncross-linked, and single/multi-injection formulations. Cross-linking increases the half-life up to 8.8 days, which can increase residence time

in trace amounts up to 26 weeks.²⁷ Additionally, research has evaluated the effect of molecular weight on the effectiveness of HA injections. Low-molecular-weight preparations have been shown to achieve maximum concentration into the joint but have lower elastoviscosity compared with native HA.²⁸ Evidence found clinically important reductions in pain with high-molecular-weight formulations, which offer an improved increase in fluid retention into the joint.²⁹ In the Panel Insights section of this paper, KOLs' comments are shared regarding the conflicting results of studies that have compared the effectiveness of HA injections with different molecular weights for the treatment of OAK.³⁰⁻³² Adverse events associated with HA injections are minimal and typically limited to injection site pain, joint stiffness, and, possibly, swelling; however, avian-based preparations may potentially elicit more adverse allergic reactions than nonavian-based preparations.³³

Numerous studies, including observational studies and a few randomized, head-to-head trials, have evaluated the effects of intra-articular HA injections; however, these studies were noted to have poor study design, perceived inherent bias, and lack of consistency.³⁴ These poor-quality studies resulted in an inability for guideline-issuing organizations to develop a high-quality meta-analysis necessary for an evidence-based assessment of efficacy.^{13,14} Ong et al. (2016) demonstrated that HA injections were associated with longer time (8.7 months) to TKA in patients with OAK.³⁵ Another study showed that among patients with OAK, those who received HA injections showed a significantly longer time to TKA compared with those who received none (0.3 years vs. >1.0 years, respectively).³⁶ The ACR and AAOS treatment guidelines were last updated in 2012 and 2013, respectively.^{13,14}

More recently, the AMSSM systematic literature search reported that there are multiple recent randomized controlled trials that indicate that there is evidence to support the use of HA injections for appropriate patients with OAK.¹⁵ Specifically, the AMSSM recommends HA injections for Kellgren and Lawrence (a classification that is a commonly used clinical tool for the radiographic diagnosis of OAK) grade II-III OAK in patients older than 60 years of age based on high-quality evidence demonstrating clinical benefit.¹⁵ Due to the treatment response in patients above 60 years of age, the AMSSM also suggests HA injections for patients with OAK who are younger than 60 years of age based on moderate-quality evidence.¹⁵

Moreover, since HA injections are used as an alternative to corticosteroid injections, viscosupplementation may also minimize the need for corticosteroid injections; corticosteroid injections can cause additional local damage to joint cartilage if used repeatedly long-term or systemic issues such as hyperglycemia in diabetic patients.^{37,38} A 2-year study assessed the impact of intra-articular triamcinolone injections on patients with symptomatic knee osteoarthritis; the results showed significantly greater cartilage volume loss and no significant difference in

knee pain in patients receiving triamcinolone injections compared with saline injections.³⁹ The results of a trial comparing the safety and efficacy of NSAIDs and HA injections for OAK demonstrated that HA injections are as effective as continuous NSAID use at 5 weeks of treatment and are associated with a more favorable safety profile.⁴⁰ As prolonged NSAID utilization is often associated with gastric complications, ulcers, increased risk for hospitalization, and other adverse effects, HA injections present a safe and equally effective treatment alternative.^{10,34} Additionally, viscosupplementation may offer the benefit of longer duration of effectiveness, with some HA injections offering up to 6 months of relief compared with up to 3 months with the use of corticosteroid injections.^{25,41-43}

Panel Insights and Recommendations

Before the 2013 publication, AAOS treatment guidelines indicated that the AAOS recommendation for or against the use of HA injections in the treatment of OAK was inconclusive. Of note, this recommendation has since been updated to reflect a recommendation against such usage.¹⁴ However, the AAOS did not determine utility based on OA severity, but rather, osteoarthritis in general. Despite the AAOS and ACR treatment guidelines regarding the use of HA injections in this setting, the panelists' perceptions regarding the utility of HA injections for the management of OAK were aligned with those of the AMSSM, which recommends the use of these products based on previously published studies. The KOLs cited evidence from a clinical study showing HA injections may be most beneficial in earlier grades of OAK, as 91% and 80% of patients in radiographic grade I and II OAK, respectively, reported feeling better after injection compared with 76% and 58% of patients in grades III and IV, respectively.⁴⁴ Overall, KOLs perceive HA injections as alternative treatments that may provide their patients with an option to delay TKA.⁴⁵ Provider KOLs noted that HA injections are an effective alternative to corticosteroid injections as the therapies show equal efficacy in the short term, yet evidence shows HA injections to be superior in duration of pain relief.⁴⁶ KOLs also recommended HA injections be used in patients who experience transient improvement from corticosteroid injections but seek additional relief.

In addition to the discussion regarding the benefits associated with HA injections, KOLs discussed the potential benefits associated with the different formulations of HA products. KOLs referenced evidence in animal studies that suggests that the cross-linking of HA molecules in viscosupplements may increase the half-life of these products, thereby increasing residence time of molecules in the joint space and potentially increasing the production of endogenous hyaluronan in the knee; however, there is some debate regarding the impact of molecular weight on the effectiveness of HA injections.^{27,47-49} KOLs discussed the controversial data that indicate that it is not molecular size—but rather, cross-linking of HA

molecules—that impacts the effectiveness of these products. Evidence suggests that studies evaluating cross-linked formulations achieved clinically significant reduction in pain in patients with OAK.²⁹ The consensus among KOLs was that cross-linking appears to have a benefit in allowing for single-injection administration rather than the multiple injections required with noncross-linked formulations, and most patients consider single-injection products to be more convenient than multiple-injection products.

Best Practice Considerations

KOLs identified various considerations that should be defined in order to better indicate HA and properly manage OAK with HA injections. From clinical experience, including private and hospital practice, the 4 provider KOLs concluded that an MRI should not be required to determine a patient's eligibility status for HA injections. Rather, an appropriate radiographic (i.e., weight-bearing film) and clinical evaluation of the grade of OA is necessary to determine whether a patient is a candidate for treatment with HA injections.

In some cases, providers may choose to perform ultrasound-guided HA injections to increase accuracy and clinical outcomes. KOLs noted that if a patient is morbidly obese and the proper injection site is difficult to locate, an ultrasound may help to ensure the safe and effective administration of the viscosupplement. To prevent the misuse of ultrasound-guided HA injections, KOLs suggested the implementation of a limitation on the use of ultrasound for patients who have a body mass index (BMI) greater than 30 kg/m² or who have anatomic variations that render normal landmark-based injection technique a challenge. While KOLs noted that this method may often be an unnecessary precaution, evidence suggests that the enhanced accuracy associated with ultrasound guidance often improves patient-reported clinical outcomes and cost-effectiveness.⁵⁰

The panel also discussed the utility of HA injections, particularly in patients with medical comorbidities. In patients who have comorbidities, especially obesity and diabetes, HA injections may be a more desirable choice than corticosteroid injections due to the corticosteroid-associated risks of additional weight gain and hyperglycemia.^{38,51} Additionally, chronic use of NSAIDs may not be a viable treatment option for some patients due to cardiovascular risk or potential to destabilize blood pressure.⁵² KOLs noted that it may be beneficial for coverage policies to include a list of comorbidities for which HA injections may be an appropriate treatment option; however, the list should be used as a guide, not as a substitute for medical advice, to ensure that a patient-centered treatment selection can still be made.

Following the publication of the 2013 AAOS treatment guidelines, which advised against the use of HA injections for the treatment of OAK, several payers subsequently eliminated coverage of HA products. Of note, Blue Cross Blue Shield of

Kansas City and Blue Cross Blue Shield of Kansas eliminated coverage for viscosupplementation in 2013 and 2014, respectively, and the Society of Actuaries issued a report that identified a nearly 6-fold increase in total knee surgery rates for new enrollees in Kansas during the first quarter of 2014.⁵³ While not conclusive, the results of this report may suggest a possible relationship between payers' restrictive coverage policies and the utilization of alternative management strategies, particularly TKA surgical procedures. This may not be the desired outcome payers seek, as TKAs are associated with significantly higher costs compared with HA injections.⁵⁴ As of 2016, Blue Cross Blue Shield of Kansas still considers HA injections not medically necessary, citing evidence that suggested larger treatment effects in small trials than in large-scale trials, and concluding that there is a lack of definitive treatment benefit.⁵⁴ In response to this issue, the panelists referenced the 2015 data released by the Osteoarthritis Research Society International, which confirms that treatment with HA injections can result in a delay in the need for TKA by up to 3.6 years.⁵⁵ KOLs noted that delaying the need for TKA in patients for a number of years may result in fewer revision TKAs and costly complications throughout the course of the patient's lifetime, and such delays have the potential to result in substantial cost savings for payers.

KOLs pointed to evidence demonstrating that HA injections offer a cost-effective alternative in the management of OAK.^{56,57} A 2014 analysis used analytic models to compare HA treatments with corticosteroid treatments, and the results indicated that HA was both less costly and more effective than corticosteroids with NSAIDs and analgesics and is the dominant treatment strategy.⁵⁷ Studies comparing cost outcomes of HA injections to conventional care, including analgesics, NSAIDs, and assistive devices, showed that HA injections were shown to be a cost-effective treatment strategy.^{56,57}

Regarding product preference, provider KOLs referenced the barrier they currently face with highly restricted or nonexistent access to HA injectable products. Although some providers indicated that they have specific agents they prefer to use in practice, the panelists emphasized that having access to any high-molecular-weight HA injectable products was preferable to having no access. If access must be restricted to one product type, the panelists leaned toward single-injection products. The rationale for preferring single-injection products is because patients prefer fewer injections and value the convenience of a single office visit as opposed to multiple visits. Additionally, concerning avian-based and nonavian-based products, providers noted that aside from potential allergic reactions to avian-based preparations, there is no significant difference in overall clinical effectiveness; however, payer KOLs suggested that the formulary should include access to both product types, especially where patients have allergies or sensitivity to certain products.³³ A study showed that while both avian- and

nonavian-based products improved pain in patients with OAK, a significantly greater number of adverse events was observed in patients treated with avian HA products.⁵⁸

Future Needs and Considerations

In the future, it would be beneficial to have prospective, controlled studies to establish the effectiveness of HA injections as a treatment option for OAK and additional comparative studies for the various types of HA products. Both types of studies may be of value in treatment selection and coverage decision-making processes for providers and payers. Additionally, there may be an opportunity for patient education surrounding the benefits and risks associated with HA products for the treatment of OAK to allow for a well-informed treatment decision-making process and clinical algorithm. The lack of information and product inaccessibility may contribute to suboptimal management of OAK or patient requests for earlier TKA.

The development of a comprehensive policy that permits the coverage of at least 1 avian-based, cross-linked, single-injection formulation and 1 nonavian-based, multi-injection HA product for candidates may benefit both payers and patients. The policy should incorporate a mechanism (i.e., exceptions request process) by which providers can request a nonpreferred product based on individual patient clinical presentation and response to prior therapies. This policy should also allow for the transition between covered products to account for potential suboptimal responses to other viscosupplementation products. The policy should include certain coverage criteria, such as a list of comorbidities for which the use of HA injections is preferable, an age range age for which coverage is permitted, and a minimum BMI requirement for the use of ultrasound-guided HA injections. In conclusion, the provider and payer panelists agree with the conclusions of the AMSSM regarding the advantages of HA injections in patients with OAK and recommend the inclusion of HA injections on the formularies of managed care organizations.

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Supplement