

# Updates on Intra-Articular Hyaluronic Acid Therapy for Knee Osteoarthritis

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**O**steoarthritis (OA) is the most common form of arthritis in the United States. Prevalence in the United States was estimated at 27 million in 2008, an increase from 21 million in 1995.<sup>1</sup> OA results from inflammatory and mechanical factors in susceptible individuals leading to joint pain,

stiffness, and loss of range of motion.<sup>2</sup> No therapies have been shown to alter the natural history of OA. In the absence of disease modifying osteoarthritis drugs (ie, DMOADs), treatment of OA is focused on controlling symptoms, especially pain. Non-pharmacologic therapies include weight loss, low-impact exercise, and physical therapy.<sup>2,3</sup> Medical options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and opioids in selected patients.<sup>2,3</sup> Topical therapies include capsaicin, methylsalicylate, and NSAIDs.<sup>2,3</sup>

Intra-articular (IA) injections provide an additional non-operative strategy for OA management when non-pharmacologic and medical therapies provide inadequate relief of symptoms. IA corticosteroids and hyaluronic acids (HA) are available for the treatment of OA, though the latter are approved by the US Food and Drug Administration solely for osteoarthritis of the knee.<sup>2</sup> Both IA corticosteroids and HAs are recommended in guidelines for the management of knee OA.<sup>3,4</sup> Joint replacement surgery should be reserved for those patients who fail pharmacologic and non-pharmacologic modalities, including an adequate trial of injection therapy.

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The efficacy of IA hyaluronates for the treatment of symptomatic knee OA has been previously reviewed.<sup>2,5</sup> Similar to the findings for IA corticosteroids for knee OA, a Cochrane analysis of viscosupplementation for the treatment of knee OA found HA derivatives as a class to be effective.<sup>5,6</sup> There is increasing interest in the use of HAs for OA at sites other than the knee. Though preliminary reports suggest efficacy for shoulder and hip OA, these indications are currently considered off label.<sup>7,8</sup>

Several questions remain regarding the use of HAs for OA. Should the initial injection for OA be a corticosteroid or an HA? Is there evidence to support use of a particular HA product over its competitors? Can injection therapies be combined for OA? This column will explore these concerns based on the currently available evidence and provide comments based on the author's practice.

## SELECTION OF INITIAL INTRA-ARTICULAR AGENT FOR KNEE OSTEOARTHRITIS

Corticosteroids and HAs are commonly used for the management of knee OA not responding to more conservative therapy. Few direct comparisons of IA corticosteroids to HA injections have been performed. Therefore, current guidelines make no recommendations as to which class should be initially employed once the decision is made to use injection therapy for knee OA.

In one of the largest comparison studies reported, Leopold and colleagues<sup>9</sup> randomized 100 patients with knee OA to receive a 3 injection series of Hylan G-F 20 or a corticosteroid injection. Both groups were followed for a total of 6 months and the corticosteroid group was allowed a second corticosteroid injection at any time during the study period. At study conclusion, there were no significant differences between the groups as assessed by 3 different pain scales commonly used to measure response in knee OA trials.

The Osteoarthritis Research Society International (OARSI) has examined treatment effects of both corticosteroids and HAs for knee OA in a review of research published through January 2009.<sup>4</sup> The effect size of corticosteroids on knee OA was estimated at 0.58, compared with 0.60 for HA derivatives (0.5 indicates a moderate effect). The number needed to treat (NNT) for each modality was

also similar: 5 for corticosteroids and 7 for HA injections. This analysis suggests IA corticosteroids and HA can be expected to deliver similar results in clinical practice.

Safety is an important consideration in choosing an initial agent for injection. In general, the rate of post-arthrocentesis septic arthritis is low and has been estimated at 1 in 14,000 to 1 in 50,000 following corticosteroid injections.<sup>10</sup> Albert and colleagues<sup>11</sup> described 2 cases of septic knee arthritis following intra-articular hyaluronate injection in elderly OA patients, but no estimates are currently available specifically for the rate of post-hyaluronate injection septic arthritis. Patients should be informed of the risk of infection when counseled about this procedure, because infection can occur following injection with either corticosteroid or HA.

In addition to septic arthritis, risks of HA injection include pseudoseptic injection reaction and flare of crystalline arthritis. Attacks of gout and calcium pyrophosphate dehydrate arthritis (ie, pseudogout) have been described following HA injection.<sup>12,13</sup> Noninfectious inflammatory reactions have also been described and are more common with hylan G-F 20 injections.<sup>14</sup> When HA injection results in acute joint inflammation, arthrocentesis with synovial fluid analysis is mandatory. Synovial fluid must be sent for Gram stain, culture, and cell count. Crystal analysis should also be performed to exclude gout or pseudogout. Empiric treatment for septic arthritis may be considered until results of these studies are available. Both crystalline arthritis and the pseudoseptic inflammatory reaction respond favorably to a corticosteroid injection once infection has been excluded.

Efficacy and safety for IA corticosteroids and HAs are similar. The author's approach is to perform an initial steroid injection for knee OA refractory to oral medication and adjunctive treatments based single dose convenience and more rapid clinical response.<sup>15</sup> If this approach is successful, corticosteroid injections are continued as frequently as every 3 months.<sup>16</sup> If the corticosteroid injection is not initially effective, or if it loses efficacy over time, the patient is switched to injected HA prior to referral for consideration of joint replacement surgery.

### CHOICE OF INTRA-ARTICULAR HYALURONIC ACID

Five HA therapies of varying molecular weight are approved for the treatment of knee OA in the United States.<sup>2</sup> Comparative efficacy data are important to consider in the selection of HA for injection. Additional factors that should influence the clinician's choice of HA include safety and dosing schedule.

Several studies have compared the efficacy of HA preparations. A 2006 prospective study by Kotevoglou and colleagues<sup>17</sup> randomized 59 patients to treatment with low molecular weight hyaluronan (Orthovisc), high molecular weight hyaluronan (Synvisc), or saline. At 6 months, both HA groups showed significant improvement in WOMAC pain scores compared with placebo but there was no dif-

ference between the HA groups. In a 2007 meta-analysis of hylan versus HA that included the aforementioned trial, the pooled effect size favored hylan slightly, however, heterogeneity between the studies was high.<sup>14</sup> The most recent study compared low molecular weight HA (Hyalgan) to an intermediate weight HA (GO-ON) not available in the United States. At 6 months, GO-ON showed statistical superiority for several outcome measures, compared with Hyalgan.<sup>18</sup>

In the absence of superiority of one HA agent, factors such as safety and ease of dosing influence the selection of HA. HA injections are typically well tolerated and have a favorable safety profile.<sup>19</sup> Uncommon side effects of HA injection include pseudoseptic inflammatory reactions and flares of crystalline arthritis as described above. The majority of HA products are given as a 3-5 injection series.<sup>2</sup> A notable exception is Hylan G-F 20, which showed similar therapeutic effects in a single 6 mL injection compared to 3 weekly 2 mL injections.<sup>20</sup> However, a meta-analysis by Reichenbach and colleagues<sup>14</sup> suggested twice the risk of local reactions with Hylan G-F 20, compared with hyalruonic acid. The author has the most experience with low molecular weight products, largely due to formulary constraints and not personal preference.

### COMBINATION INTRA-ARTICULAR THERAPY FOR OSTEOARTHRITIS

The potential synergy between injected anti-inflammatory agents and HA injections has been considered as a mechanism to enhance therapeutic injections. Ozturk and colleagues<sup>21</sup> performed a 1 year, randomized, single blind trial of 40 patients with knee OA. Twenty-four patients were treated with a course of HA injections at 0 and 6 months and a group of 16 patients received the same HA regimen but with the addition of 40 mg triamcinolone acetonide injected just before the first HA injection of each series.<sup>21</sup> Both groups had the same magnitude and duration of response as assessed by standardized pain scores, however the steroid group had a more rapid response.<sup>21</sup> There was no difference in progression of OA as assessed by magnetic resonance imaging in either group at 1 year.<sup>21</sup>

A recent meta-analysis examined the trajectory of the clinical response to injected HA to corticosteroids in knee OA. In their study, Bannuru and colleagues<sup>16</sup> showed corticosteroids had a more rapid onset of action from baseline through week 4, compared with HA. At the fourth week, the effect of HA equaled corticosteroids, and after week 8, HA had a greater treatment effect.<sup>16</sup> These results set the stage for further examination of the potential synergistic effect of combination injections with corticosteroids providing rapid onset relief of symptoms, and HAs providing a durable response of approximately 6 months' duration.

The combination of NSAID and HA has also been considered as a way to enhance the effect of an injection for knee OA. In a study of 43 patients with knee osteoarthritis, 22 patients were randomized to a standard 5 injection series of HA, whereas the remaining 21 patients received 2

weekly intra-articular injections of ketorolac followed by 3 weekly injections of HA.<sup>22</sup> At 16 weeks of follow-up, there was a statistically significant improvement in pain scores in the ketorolac plus HA group, compared with the HA group.<sup>22</sup> Of note, the ketorolac group experienced post-injection pain for 8 hours in 5 of 21 subjects, compared with no post-injection pain in the HA group.<sup>22</sup> No major adverse effects were observed in either group.

## CONCLUSION

OA is the most common arthritis in the United States. Symptomatic treatment remains the standard of care using pharmacologic and non-pharmacologic modalities. Injections with corticosteroids or HAs are used for the treatment of knee OA when oral therapy does not provide adequate symptom control. Joint replacement surgery is reserved for those who fail more conservative therapies, including injections.

HA derivatives have an established track record of efficacy and safety in knee OA. With the exception of Hylan GF-20, a drawback to these injections compared to corticosteroids is the need for multiple weekly injections over 3 to 5 weeks. Preliminary studies of the use of HAs in combination with corticosteroids or injected NSAIDs for knee OA show encouraging results. There appears to be a rapid onset of symptomatic relief with the same durability of response as HA alone with no apparent increase in toxicity with the combination approach. Future studies should examine if HA preparations (except for hylan G-F 20) can provide equal efficacy with compressed dosing schedules compared to traditional multi-week dosing. Additional research will also better define the role combination anti-inflammatory and HA injections for the treatment of OA at the knee and other sites.

## AUTHOR'S DISCLOSURE STATEMENT

The author reports no actual or potential conflict of interest in relation to this article.

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, or the US Government.

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