Hylan Versus Corticosteroid Versus Placebo for Treatment of Basal Joint Arthritis: A Prospective, Randomized, Double-Blinded Clinical Trial

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Purpose Conservative, nonsurgical therapies for basal joint osteoarthritis, such as thumb spica splinting and intra-articular corticosteroid injections, remain the mainstays for symptomatic treatment. This study compares intra-articular hylan, corticosteroid, and placebo injections with regard to pain relief, strength, symptom improvement, and metrics of manual function in a randomized, controlled, double-blinded study.

Methods Sixty patients with basal joint arthritis were randomized to receive 2 intra-articular hylan injections 1 week apart, 1 placebo injection followed by 1 corticosteroid injection 1 week later, or 2 placebo injections 1 week apart. Patients were evaluated at 2, 4, 12, and 26 weeks and assessed with Visual Analog Scale pain scores, strength measures, difference scores, Disabilities of the Arm, Shoulder, and Hand (DASH) scores, and range of motion measurements.

Results All groups reported pain relief at 2 weeks. The steroid and placebo groups had significantly less pain at week 4 compared with baseline, but this effect disappeared by week 12. Only hylan injections continued to provide pain relief at 12 and 26 weeks compared with baseline. There were no significant differences in pain between groups at any time. At 12 and 26 weeks, the hylan group had improved grip strength compared with baseline, whereas the steroid and placebo groups were weaker. At 4 weeks, the steroid group reported in the difference score a greater improvement in symptoms (68%) compared with the hylan (44%) and placebo (50%) groups. Whereas at 26 weeks the hylan group reported the largest improvement in symptoms (68%), this was not statistically different from the placebo (47%) and steroid (58%) groups. There were no significant differences in Disabilities of the Arm, Shoulder, and Hand scores or range of motion among the groups. There were no complications from any injection.

Conclusions There were no statistically significant differences among hylan, steroid, and placebo injections for most of the outcome measures at any of the follow-up time points. However, based on the durable relief of pain, improved grip strength, and the long-term improvement in symptoms compared with preinjection values, hylan injections should be considered in the management of basal joint arthritis of the thumb. *(J Hand Surg 2008;33A:40–48. Copyright © 2008 by the American Society for Surgery of the Hand.)*

Type of study/level of evidence Therapeutic I.

Key words Basal joint arthritis, corticosteroid, hylan, osteoarthritis, viscosupplementation.

Osteoarthritis (OA) of the first carpometacarpal joint, or basal joint of the thumb, is a common, painful, and debilitating disease. It has been reported that up to 25% of women and 8% of men eventually show radiographic evidence of basal joint arthritis,[1] many of whom are symptomatic, with the most common presenting complaints being pain and limitations in gripping and pinching objects. Conservative, nonsurgical therapies are the mainstay of initial treatment of basal joint OA. Surgery is a last-resort treatment for those patients whose debilitating symptoms persist despite the usual rehabilitation strategies of rest, splinting, occupational therapy, and intra-articular steroid injection.

Hylan is a synthetic polymer made from hyaluronan, or hyaluronic acid (HA), the natural complex sugar of the glycosaminoglycan family that is normally found in the synovial fluid of joints. A wealth of laboratory evidence has demonstrated that HA contributes to the rheologic and elastoviscous properties of the synovial fluid, enhancing its functions of cushioning and lubricating the joint. Literature reporting decreased amounts of HA in the synovial fluid of joints affected by OA also suggests that the disease hastens

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the breakdown of HA.[2,3] Compounds of HA derivatives are therefore commonly used today with few adverse effects as injectable, intra-articular viscosupplementation devices, a concept introduced in 1993 by Balazs and Denlinger,[4] and are designed to improve the symptoms of pain and decreased function in osteoarthritic joints. In addition to the proposed enhancement of physical properties provided by the increased concentration of HA in the synovial fluid, studies have shown other beneficial mechanisms of action as well, such as chondroprotective effects,[5–8] inhibition of immune cells and inflammatory mediators,[9–11] stimulation of chondrocyte synthesis of proteoglycans and endogenous HA,[12,13] and antinociceptive effects.[14–16] Although HA-derivative products have been in use for more than a decade, the majority of existing literature has focused on the effect of HA derivatives on knee OA, but the implications for treatment of OA in other joints are largely unknown. Moreover, the clinical trials that have been performed for the knee have found conflicting results with regard to the benefit of hylan compared with placebo and other treatment modalities,[17–21] leaving the question of the relative efficacy of this therapy still in doubt.

The purpose of this study was to investigate the effectiveness of hylan viscosupplementation therapy for treatment of basal joint arthritis of the thumb compared with corticosteroids and placebo.

MATERIALS AND METHODS

Study Site, Approval, Patients, Power Analysis, and Randomization

This study was conducted at a single tertiary care center and was approved by the institutional review board. This investigator-sponsored study was funded with a joint grant from Genzyme Corporation and Wyeth Pharmaceuticals. U.S. Food and Drug Administration (FDA) approval for the study was obtained for use of hylan G-F 20 in an "off-label" use. Over a 2-year period, study patients were recruited and enrolled from the practices of the 2 senior authors and included patients older than 40 years of age with symptomatic basal joint osteoarthritis (BJOA). The condition was diagnosed using standard radiographic and clinical criteria: basal joint tenderness, thumb or wrist pain at rest or with activity, joint stiffness, decreased mobility, deformity, instability, and decreased manual function. Because radiographic grade does not necessarily correlate with the symptoms of patients with basal joint arthritis,[1,22] patients were not excluded based on radiographic grade. Patients who had received previous corticosteroid injections were excluded if they had not experienced at least mild to moderate pain relief or functional improvement from the injections, if they had received more than 2 such injections in the affected joint in the past, or if they had received such an injection in the preceding 6 months. Those patients who received 1 or 2 prior injections with at least moderate improvement were included, because they would likely have another good response to a second or third injection. Other exclusion criteria included pregnancy, prior surgery on the affected thumb or wrist, history of infection in the affected joint, history of inflammatory arthritis, and skin disease or eruption at the joint injection site. Patients with a known allergy to eggs, feathers, avian proteins, or HA derivative products were also excluded, as hylan G-F is derived from rooster combs.

In designing this study, a power analysis was performed to determine the sample size required to detect differences the size of 1 SD in the Disabilities of the Arm, Shoulder, and Hand (DASH) outcome measure. A calculation of 16 patients per group was shown to demonstrate 80% power and a 5% 2-tailed type I error rate to detect DASH differences seen in previous studies investigating treatment of basal joint arthritis.[23] To safeguard against loss to follow-up and other unexpected variances, we determined that approximately 20 patients per group were needed to observe these clinically relevant differences.

A computer-based program was used to randomly assign each of the 60 patients to 1 of the 3 treatment groups: placebo, steroid, or hylan. Assignments remained unknown to both the patients and the clinical evaluators throughout the duration of their participation in the study.

Injections and Treatment Schedule

All patients who had been taking non-steroidal anti-inflammatory drugs (NSAIDs) in the period just prior to study enrollment were given a 2-week "washout period," in which they were asked not to take NSAIDs prior to their first injection as part of the study. This process was instituted to minimize any possible confounding effect that prior medication might have on the planned interventions.

The injection schedule was organized in the following manner for the 3 treatment groups: the hylan group received a 1-mL injection of hylan G-F 20 (Synvisc; Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA; Genzyme Corporation) at the time of the first injection (time = 0) and a second 1-mL injection of hylan G-F 20 1 week later (time = 1 wk); the steroid group received a 1-mL placebo injection of normal saline (0.9% sodium chloride) at time = 0 and a 1-mL injection of sodium betamethasone sodium phosphate–betamethasone acetate (Celestone Soluspan; Schering-Plough, Kenilworth, NJ) at time = 1 week; the placebo group received a 1-mL injection of normal saline at time = 0 and a 1-mL injection of normal saline at time = 1 week. To eliminate the confounding variable of injection of different volumes among groups, the researchers gave 1 mL injections for all subjects, following the senior author's standard protocol for steroid injections. Two, rather than 1, hylan injections were used, to more closely resemble the FDA-approved standard treatment schedule of 3 injections for the knee. However, 3 hylan injections were not used because 3 mL of injection material in the basal joint of the thumb would lead to a greater ratio of injection material to joint space when compared with the FDA-approved protocol used in the knee. Only 1 steroid injection was used because multiple steroid injections should not be performed