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A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee[1]

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Summary

Objective: To compare the safety and effectiveness of a high molecular weight hyaluronan produced by biological fermentation (Bio-HA) with those of avian-derived hyaluronan that uses cross-linking to achieve high molecular weight (CL-HA).

Design: This was a prospective, multicenter, randomized, double-blind trial evaluating patients with confirmed osteoarthritis of the knee. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Index) pain subscale was the primary effectiveness measure (visual analog scale). Both products were administered via three weekly injections, with follow-up evaluations at weeks 3, 6 and 12. Acetaminophen was permitted as rescue medication and quantitated by pill counts.

Results: Analyses were performed on the intent-to-treat population, defined as all patients receiving at least one injection. Of the 321 patients randomized to treatment, 314 patients (98%) completed the final study assessment. Improvement in the average WOMAC Index pain score was 29.8 mm (−61.6%) for Bio-HA and 28.8 mm (−54.9%) for CL-HA, meeting the prospective criteria for non-inferiority. For the secondary outcome measures, statistically significant differences favored Bio-HA for the number of patients requiring acetaminophen ($P = 0.013$) and patient global satisfaction evaluations ($P = 0.03$). Local reactions differed between the products in that 15 effusions were reported in 13 CL-HA patients (8.1%) after injection, compared to one effusion (0.6%) after Bio-HA injection ($P = 0.0015$).

Conclusion: The effectiveness of Bio-HA was not inferior to that of CL-HA. The significantly higher incidence of post-injection effusion in the CL-HA group provides a safety advantage for Bio-HA. These data suggest that Bio-HA has an improved benefit-risk profile compared with CL-HA.

Key words: Osteoarthritis, Viscosupplementation, Hyaluronan.

Introduction

Intra-articular hyaluronan (IA-HA) injections are now licensed worldwide for the treatment of osteoarthritis (OA). In the United States, IA-HA is indicated for pain relief in patients with OA of the knee who fail to respond to conservative non-pharmacologic therapy or simple analgesics (e.g., acetaminophen), and is included in the guidelines of the American College of Rheumatology and the American Academy of Orthopedic Surgery. The goal of therapy is to reduce pain and improve physical function by temporarily supplementing the viscosity and elasticity of synovial fluid, which are reduced in OA[1]. A course of treatment consists of a series of three to five weekly intra-articular injections with a viscoelastic solution of hyaluronan or its derivatives. Efficacy trials comparing IA-HA injections with saline injections demonstrate a statistically significant difference over a 3–6-month period, depending on the trial design[2–5]. In clinical practice, patients can experience symptomatic benefits for a year or longer[6–8].

Commonly referred to as viscosupplementation, the therapeutic benefits of IA-HA injections are believed to be dependent on the viscoelastic properties of the hyaluronan injected[9]. It is widely believed that higher molecular weight hyaluronan preparations will provide improved clinical benefits[10,11]. Questions regarding the importance of molecular weight for IA-HA products are of particular clinical relevance, because products can differ substantially in this parameter. Four IA-HA products are currently available in the United States: Hyalgan® (Fidia SpA, Padua, Italy), Supartz® (Seikagaku Corporation, Tokyo, Japan), Orthovisc® (Anika Therapeutics, Woburn, MA) and Synvisc® (Genzyme Corporation, Cambridge, MA). Supartz, Hyalgan and Orthovisc contain unmodified hyaluronan derived from chicken combs, with molecular weight ranges specified on their respective labels as 0.62–1.2 million Daltons for Supartz, 0.5–0.72 million Daltons for Hyalgan, and 1–2.9 million Daltons for Orthovisc[12–13]. Synvisc is composed of two cross-linked derivatives of hyaluronan (CL-HA): solid hylan gel particles and soluble hylan molecules described as having a molecular weight of 6 million Daltons[14]. Several recent publications have noted acute local reactions after hylan CL-HA injection[15,16], particularly in patients receiving repeat treatment[17]. Inflammatory reactions around hylan gel particles have also been histologically observed in synovial

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biopsies[18,19]. These reports make it especially important to consider safety differences among IA-HA products, and alternate ways of producing high molecular weight hyaluronan for viscosupplementation.

All four of the IA-HA products currently available in the United States are produced from chicken combs and therefore require the removal of inflammatory and immunogenic impurities endogenous to the avian tissue source[20]. With the aim of producing hyaluronan from a non-avian source, methods have been developed to produce high molecular weight hyaluronan using biological fermentation (Bio-HA)[21,22]. EUFLEXXA™ bioengineered 1% sodium hyaluronate (Ferring Pharmaceuticals, Inc., Suffern, NY) is a high molecular weight IA-HA product produced by biological fermentation. It has been approved in the European Union since November 2000 and Israel since June 2001 and has a molecular weight range of 2.4–3.6 million Daltons. The high molecular weight of Bio-HA is achieved by careful control of the fermentation, recovery and purification processes and does not require the use of any cross-linking processes.

A small single-blind trial comparing Bio-HA with placebo in 49 patients was conducted to estimate the efficacy of the product. The results were favorable but the study was underpowered to declare statistically significant differences[23]. Randomized clinical trials (RCTs) comparing IA-HA products with placebo injections have not been uniformly positive, and recent meta-analyses have likewise reached divergent conclusions[3,24,25]. Because the "placebo" intra-articular intervention in these RCTs can be considered an active treatment in patients presenting with a synovial effusion[26], RCTs of IA-HA present methodological challenges that remain incompletely resolved. Despite any ongoing controversy, Food and Drug Administration (FDA) has recently accepted RCTs designed to test for non-inferiority as part of the marketing application for IA-HA products in the United States.

In addition to the above consideration regarding non-inferiority, it was also deemed unethical to conduct a placebo-controlled trial of Bio-HA in a setting where IA-HA products are used in routine clinical practice. Our primary objective was therefore limited to comparing the safety and effectiveness of Bio-HA with those of CL-HA. This particular IA-HA preparation was chosen for comparison because several recent meta-analyses noted that the effect size for IA-HA is greatest for the higher molecular weight preparations, and CL-HA is the highest molecular weight hyaluronan preparation currently available[3,24,25].

Methods

TRIAL DESIGN

This was a multicenter, prospective, randomized, controlled, double-blind (blinded patient/blinded evaluator) study conducted in adult patients with symptomatic OA of the knee. Patients were centrally randomized to receive either EUFLEXXA™ (Bio-HA, Bio-engineered HA, Ferring Pharmaceuticals, Inc., Suffern, NY) or Synvisc® (CL-HA, Hylan G-F 20, Genzyme Corporation, Cambridge, MA). For the blinding procedure, unmarked boxes containing three blister-packaged syringes of either Bio-HA or CL-HA were delivered to the investigational sites. A computer-generated randomization number was centrally assigned to each box, and the randomization code was centrally maintained by the sponsor and concealed from the study sites. Randomization was blocked within the sites in groups of four. The physician who performed evaluations was separate from the physician who performed injections in order to maintain double-blinding (blinded patient, blinded evaluator). All study-related case report forms recorded only the randomization number.

Both products were administered as a course of three 2 ml injections administered weekly. Before administration of each injection, any synovial fluid that was present in the knee was aspirated. Patients were advised to rest for 24 h following each injection, consistent with the label instructions for most IA-HA products. Assessments were performed at screening, at baseline (prior to the first injection), and at 1, 2, 3, 6, and 12 weeks after the initial injection. Only acetaminophen was permitted for rescue analgesia, up to 4 g daily, with usage quantitated by pill counts. Acetaminophen (as 500 mg tablets) was provided to study patients according to the following schedule: 28 tablets were provided at treatment initiation, week 1 and week 2; 84 tablets were provided at week 3; and 168 tablets were provided at week 6. Non-steroidal anti-inflammatory drugs (NSAIDs) and other non-acetaminophen pain medications were prohibited during the study, and patients taking such agents were considered dropouts from the point of medication usage. The study was carried out in accordance with the International Conference on Hormonization (ICH) Guidelines for Good Clinical Practice (May 1, 1996, amended September 1997) and the Declaration of Helsinki concerning medical research in humans (1966).

PATIENTS

Patients were enrolled at 10 sites across Germany. The study protocol and informed consent form were approved by the relevant ethics committees. The study was open to patients of either sex, age 50–80 years, with confirmed OA in one or both knees. OA diagnosis date and radiological diagnosis date for the study knee and other knee were recorded on the study case report form at baseline. In patients with bilateral OA, the more symptomatic knee was assigned as the study knee at the screening visit based on the investigator's clinical judgment. Patients were included regardless of whether the tibio-femoral or patello-femoral compartment was predominantly affected. Criteria for inclusion were as follows: clinical evidence of chronic idiopathic OA of the study knee according to the criteria of Altman; radiologically verified OA of the study knee of grade 2 or 3 according to a modification of the grading system of Kellgren and Lawrence (grade 2 defined as definite osteophytes with unimpaired joint space and grade 3 defined as definite osteophytes with moderate joint space narrowing[27]); symptoms in the study knee for at least 1 year; willingness to discontinue all OA treatments other than acetaminophen; and moderate-to-severe knee pain as reflected by a visual analog scale (VAS) pain score of 41–80 (on a scale of 0 mm [no pain] to 100 mm [worst pain]) for the average of the five pain questions of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC Index)[28], with only one pain parameter permitted to be below 20 mm or above 80 mm on the VAS. The five questions in the WOMAC Index pain scale are regarding pain during (1) walking on a flat surface, (2) going up and down stairs, (3) rest at night, (4) sitting or lying, and (5) standing upright.

Patients were excluded from the study if they had secondary OA originating from a known injury to the knee, rheumatoid arthritis, history of joint infection, dermatologic disorders or skin infection in proximity to the study knee, osteonecrosis, chronic active fibromyalgia, any inflammatory