Viscosupplementation for Osteoarthritis of the Knee

Introduction

- Hyaluronic acid (HA), also known as sodium hyaluronate or hyaluronan, is a viscoelastic substance composed of long-chain polymers of repeating Na-glucuronate-N-acetylglucosamine disaccharide units. HA is found naturally in synovial fluid and is believed to lubricate and protect articular cartilage.\(^1\)
- Hyalgan\textsuperscript{\textregistered}, Supartz\textsuperscript{\textregistered}, Synvisc\textsuperscript{\textregistered}, Orthovisc\textsuperscript{\textregistered}, and Euflexxa\textsuperscript{\textregistered} are FDA-approved as medical devices. As intra-articular injections, they are indicated for treating pain for osteoarthritis (OA) of the knee in patients not responding to nonpharmacologic therapy or analgesics.\(^2\), \(^3\), \(^4\), \(^5\), \(^6\)

What is the role of viscosupplementation for treating osteoarthritis of the knee?

- Viscosupplementation should be limited to patients who are:
  1. refractory or intolerant to all other methods of non-operative treatment* (exercise, physical therapies, intra-articular corticosteroids, non-steroidal anti-inflammatory drugs and/or analgesics), \textbf{AND} \(^2\), \(^3\), \(^4\), \(^5\), \(^6\)
  2. not candidates or not wishing to pursue joint replacement surgery or other operative interventions.

(* Also consider the use of complementary & alternative medicines (CAMs) prior to using viscosupplementation)

How does viscosupplementation compare with other treatment modalities?

- For the short-term relief of pain for osteoarthritis (OA) of the knee, viscosupplementation:
  - is superior to placebo.
  - is equivalent to NSAIDs and/or analgesics.
  - has not been proven to be more effective than intra-articular corticosteroids (IACs).
  - has not been proven to be more effective than physical therapy (PT).
  - has not been proven to delay total joint replacement for knee OA or decrease its frequency.
  - has not been studied as a “rescue” in patients with pain refractory or intolerant of NSAIDs, analgesics, PT, IACs, complementary & alternative medicines (CAM), or exercises.
  - has not been studied for the long-term relief of knee OA.
  - is an invasive and costly therapy, especially in terms of expert physician utilization.

How do the different hyaluronan products compare with each other?

- Based on available, published literature, \textit{there is no evidence to suggest that the clinical efficacy of one hyaluronan product is superior to another}.
- Hyalgan, Supartz, Orthovisc, and Euflexxa are “non-modified” hyaluronans with molecular weights (MW) lower than that of endogenous HA.\(^2\), \(^3\), \(^5\), \(^6\), \(^7\) In contrast, Synvisc is composed of cross-linked hyaluronic acids referred to as “hylan polymers”, making its MW comparable to that of endogenous HA.\(^4\)
- With its high MW and elastoviscosity, Synvisc may be associated with better efficacy outcomes and longer residence time in the joint, as evidenced by animal models.\(^8\), \(^9\) \textit{However}, conclusive clinical evidence to support a correlation between high MW and clinical efficacy is lacking.

What does the Cochrane Review tell us about the efficacy of viscosupplementation?

- Updated in 2006, the Cochrane Review included 76 randomized controlled trials that studied the treatment of knee OA, comparing HA products to placebo, IACs, NSAIDs, other hyaluronans, and PT.\(^10\)
- \textbf{Comparison vs. placebo:} The Cochrane Review found hyaluronans as a class are generally effective at reducing pain and improving physical function. In particular, the 5-13 week post-injection period showed the greatest percent improvement from baseline: 28-54% for pain, and 9-32% for function.\(^10\)
- \textbf{Head-to-head comparison:}
  - \textbf{Orthovisc vs. Synvisc:} Based on six head-to-head RCT’s, the efficacy of Orthovisc and Synvisc could not be clearly differentiated. No statistically significant differences were detected in the Western Ontario MacMaster (WOMAC) OA Index pain, physical function, and stiffness, the Lequesne Index, and patient global assessment for any time period.\(^10\)
- **Hyalgan vs. Synvisc**: A trial comparing Hyalgan to Synvisc was discontinued due to an increased frequency of acute inflammatory reactions seen in the Synvisc group.\textsuperscript{R10}

- **Supartz vs. Synvisc**: Supartz was compared to Synvisc in one trial, and no differences were seen in efficacy.\textsuperscript{R10}

- **Euflexxa vs. Synvisc**: There was one non-inferiority study comparing Synvisc with Euflexxa. Non-inferiority criteria were met, as both groups achieved statistically significant improvements from baseline in WOMAC OA Index pain scores.\textsuperscript{R10}

- **Comparison vs. NSAID**: Of the five FDA-approved HA products, only Hyalgan and Synvisc had trials using NSAIDs as an active control. Based on these trials, Hyalgan and Synvisc were found to be comparable in efficacy to NSAID therapy, as no statistically significant differences were found during any time period.\textsuperscript{R10}

- **Comparison vs. intra-articular corticosteroids**: The Cochrane Review included trials comparing Orthovisc, Hyalgan, and Synvisc to IAC’s. The HA products were generally as or more effective for controlling pain and improving function than IAC’s, but differences were not seen until 5-13 and 14-26 weeks post-injection. This suggests a faster onset of action for IAC’s but a longer duration of action for the HA products.\textsuperscript{R10}

- **Limitations of the Review**:
  - The majority of trials were manufacturer-sponsored.
  - There was significant heterogeneity among the studies. Most notably, there was wide variability in study quality, sample size, inclusion & exclusion criteria, outcomes measures, duration of follow-up, per-protocol vs. intent-to-treat analysis, and defining primary vs. secondary endpoints.
  - Information is lacking regarding long-term benefits associated with repeated therapy.

**What is the safety profile of viscosupplementation?**

- HA injections appear to be generally well-tolerated. As a class, the most common adverse reactions reported for HA products compared to placebo include injection site pain and local reactions (skin rash, pruritus, pain and swelling).\textsuperscript{R2, R3, R4, R5, R6}

- In a trial comparing Hyalgan to Synvisc, an increased frequency of acute inflammatory reactions, characterized by acutely hot, painful, and swollen knees, were noted in 6/29 (21%) of Synvisc patients, vs. 0/25 (0%) of Hyalgan patients. The trial was subsequently discontinued. Symptoms were relieved with rest, ice, and oral analgesics.\textsuperscript{R11}

- In a head-to-head trial of Euflexxa vs. Synvisc, the incidence of joint effusions was significantly higher in the Synvisc group vs. the Euflexxa group: 8% (13/161 patients) vs. 0.6% (1/160 patients).\textsuperscript{R12}

- A number of reports of pseudosepsis, also known as severe acute inflammatory reaction, have been reported in literature for Synvisc. Due to a lack of reports of pseudosepsis associated with non-modified HA products, it has been suggested that there is a link between pseudosepsis and hylan polymers.\textsuperscript{R13} Pain, swelling, and/or effusion of the injected knee requiring symptomatic treatment (ice, heat, rest, elevation, analgesics, and sometimes arthrocentesis) are the most commonly reported postmarketing adverse events for Synvisc, with symptomatic treatment required.\textsuperscript{R4}

- Transient increases in inflammation in the injected knee have occurred in Hyalgan-treated patients who have an inflammatory arthritis such as rheumatoid or gouty arthritis, and in Orthovisc-treated patients who have an inflammatory OA.\textsuperscript{R2, R5}

**Summary**

- Reserve viscosupplementation for patients who are refractory or intolerant to all other methods of non-operative treatment (exercise, PT, IACs, NSAIDs, analgesics) and who are either not candidates or not wishing to pursue joint replacement surgery or other operative interventions.

- Synvisc differs from other hyaluronans in that it has a higher MW and elastoviscosity, but a clinical advantage in efficacy has yet to be demonstrated in head-to-head trials. Additionally, there have been some clinical study associations of Synvisc with a higher rate of acute inflammatory reactions.

- Based on the current clinical evidence, consider Euflexxa, Hyalgan, Supartz, and Orthovisc to be equivalent hyaluronan products.
References

R2. Sanofi-Synthelabo I. Hyalgan Prescribing Information. 2001;
R3. Seikagaku Corporation. Supartz Prescribing Information. 2006;
R5. Anika Therapeutics. Orthovisc Prescribing Information. 2005;
R6. Ferring Pharmaceuticals. Euflexxa Product Information. 2006;