Weill Cornell Medicine

Cross-Linked Sodium Hyaluronate combined with Triamcinolone Hexacetonide

Lisa R. Witkin, M.D

Site Director of Pain Medicine

New York-Presbyterian/ Lower Manhattan Hospital

Assistant Professor of Anesthesiology

New York-Presbyterian/ Weill Cornell

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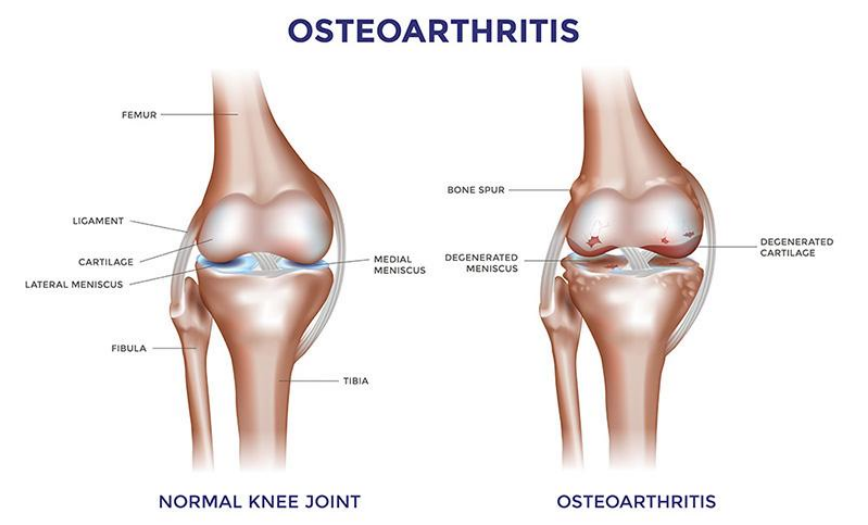
Introduction- Osteoarthritis

- Osteoarthritis (OA) is the most common joint disorder globally, affecting over 27 million people in the US
- It is characterized by a decreased concentration of hyaluronic acid (HA) in synovial fluid and a slow degradation of cartilage, resulting in joint pain and functional limitations.
- The economic burden of OA is high, with health care expenditures of over $185 billion annually in the US due to OA.
- Almost 50% of people are projected to develop symptomatic knee OA by age 85



Introduction- OA Treatments

- Intraarticular corticosteroid injections to treat knee OA are recommended in multiple clinical practice guidelines.
  - **potent anti-inflammatory effects can reduce pain quickly and improve motion; however, the effects are typically short lived**
  - a review of 28 trials found statistically significant short-term pain reduction for up to 3 weeks

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;(2):CD005328.

  - **Corticosteroids have not been shown to slow the progression of OA and may cause additional joint damage or joint destruction when intraarticular steroid injections are given repeatedly over a long period of time**
- Intraarticular HA injections are also used to reduce OA pain and improve joint function by supplementing the synovial fluid with exogenous HA (“viscosupplementation”)
  - **improves the elasticity and function of the synovial fluid**
  - **provides lubrication and mechanical support as well as protects the surface of articular cartilage.**

Introduction- OA Treatments

- Injections of HA can deliver long lasting pain relief, but the patient does not typically experience the peak effects until several weeks after the final injection (up to 8 wks)
- **A meta-analysis of 54 RCT of intraarticular HA versus placebo to treat knee OA pain demonstrated that HA was efficacious between 4 weeks and 6 months.**

Bellamy N, Campbell J, Robinson V, et al. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005328.

- Several small RCT have shown that the combination of a corticosteroid and HA versus HA alone results in significant short-term pain relief from the corticosteroid with the longer term pain relief from the HA.

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Cross-linked sodium hyaluronate combined with triamcinolone hexacetonide

- Delivers the short-term pain relief of an approved corticosteroid, triamcinolone hexacetonide (TH), with the sustained pain relief of a commercial cross-linked HA viscosupplement
- sterile, single-use, 4-mL, for intraarticular injection, containing 88 mg HA and 18 mg of TH.
- First and only CE mark approved combination product

Advantages

- **Optimal molecular weight (MW) molecules strongly bind to cell surface receptors, maximizing stimulation of native HA biosynthesis**
- Low MW HA -requires treatment of up to 5 injections
- Excessively high MW HA- unable to bind to cell surface receptors, inhibiting their ability to stimulate HA biosynthesis
- **High concentration of HA mimics concentration in healthy synovial fluid.**
- **Lightly cross-linked extends the time of the HA molecules in the joint space, providing longer lasting pain relief**
- **Naturally sourced (by bacterial fermentation)- Other products contain HA from rooster combs, which increases patients' risk of developing allergic reactions to animal proteins**
- **Triamcinolone: rapid action and longer duration**
- Effects last for up to 21 days, other corticosteroids may only last for 8-14 days.
- **biocompatible and non-pyrogenic: the cross-linked HA and steroid do not physically or chemically interact, delivering maximum stability of each compound**

Osteoarthritis

Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial

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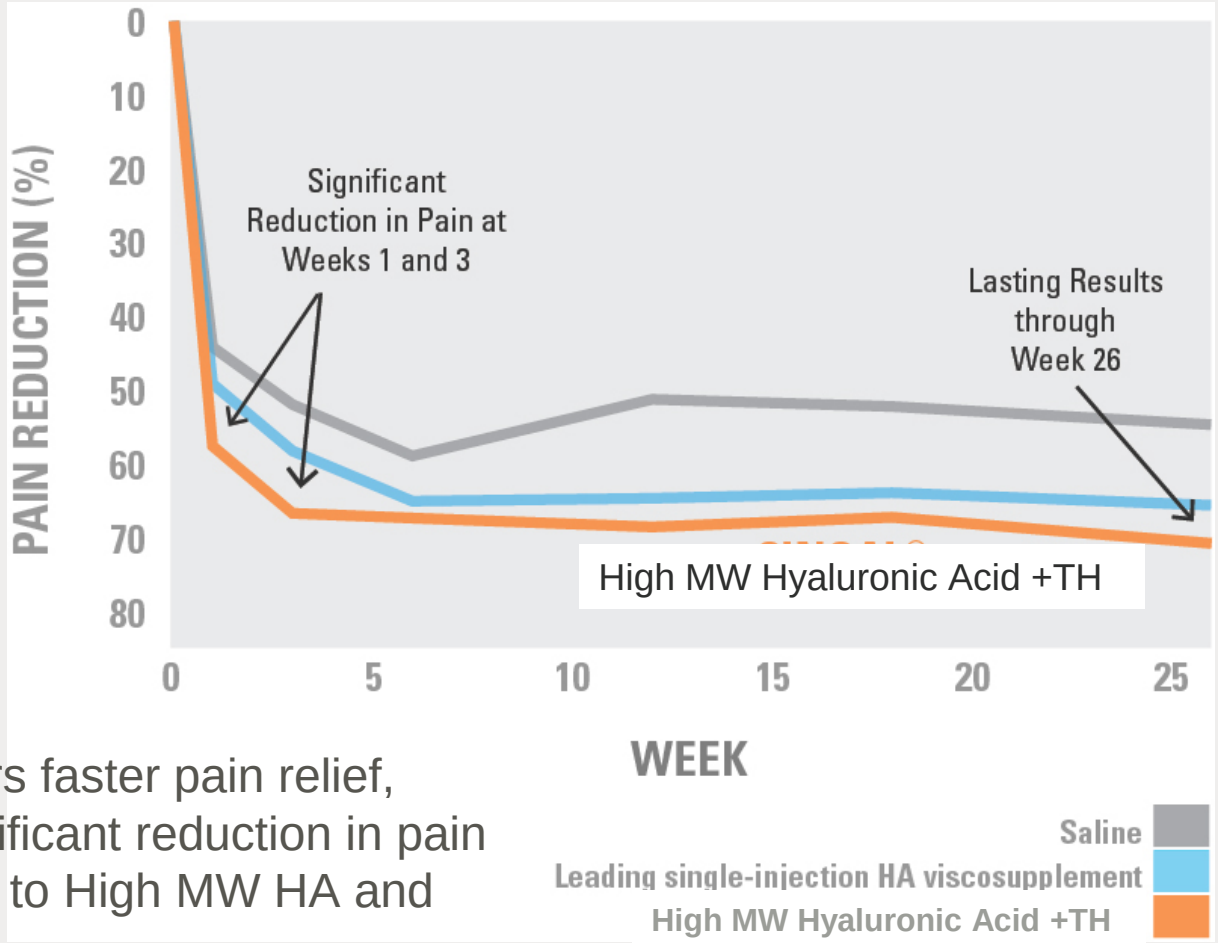
Laszlo Hangody[1], Robert Szody[2], Piotr Lukasik[3], Wojciech Zgadzaj[4], Endre Lénárt[5], Eva Dokoupilova[6], Daniela Bichovsk[7], Agnes Berta[1], Gabor Vasarhelyi[1], Andrea Ficzere[1], György Hangody[1], Gary Stevens[8], and Miklos Szendroi[9]

- Prospective, multicenter, double-blind, RCT
- subjects with mild-moderate knee osteoarthritis (Kellgren-Lawrence grades I-III) were given a single injection of :
- **4 mL, 88 mg [HA] plus 18 mg triamcinolone hexacetonide [TH],**
- **High MW HA (4 mL, 88 mg HA),**
- **or saline (4 mL, 0.9%).**
- The primary efficacy outcome was change in WOMAC (Western Ontario and McMaster Universities Arthritis Index) Pain Score through 12 wks vs saline.
- Secondary outcomes: Patient and Evaluator Global Assessments, OMERACT-OARSI Responder index, and WOMAC Total, Stiffness, and Physical Function scores through 26 wks.

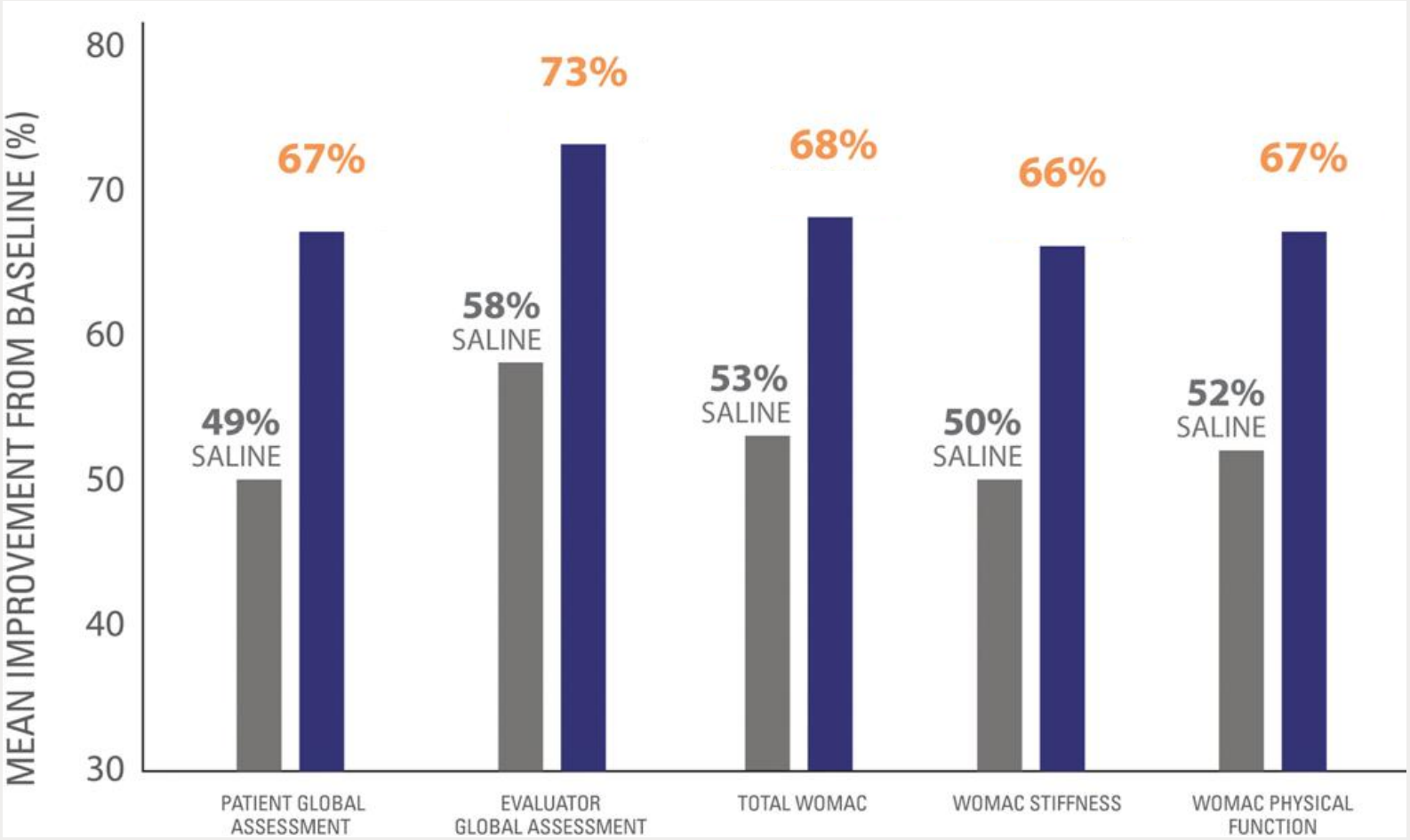
Study Results

- 368 patients were treated (High MW HA +TH, *n* = 149; High MW HA, *n* = 150; saline, *n* = 69).
- High MW HA+TH improvement from baseline was significantly greater than saline through 12 weeks (*P* = 0.0099) and 26 weeks (*P* = 0.0072).
- WOMAC Pain was reduced by 70% at 12 weeks and by 72% at 26 weeks with High MW HA+TH.
- Significant improvements were found in most secondary endpoints for pain and function at most time points through 26 weeks.



- High MW HA+TH delivers faster pain relief, providing statistically significant reduction in pain at Weeks 1 and 3 relative to High MW HA and saline
- High MW HA +TH patients experienced long lasting pain relief, demonstrating statistically significant reduction in pain at week 6-26 relative to saline (similar to High MW HA)

Highly statistically significant improvement compared to saline at all secondary endpoints at 26 weeks.



Safety

- A low incidence of related adverse events (*n* = 6)
- There were no statistically significant differences among the groups for type or rate of events.
- The most common AEs were:
  - **headache (15.7%),**
  - **arthralgia (12.9%),**
  - **spinal pain (8.3%),**
  - **back pain (6.0%),**
  - **and nasopharyngitis (5.1%).**
- Over 99% of AEs were considered mild or moderate in severity
- All AEs resolved without sequelae

Re-treatment

- Secondary clinical study: participants from the primary clinical study who had received an initial injection of High MW HA+TH received a repeat injection after 6 months
- >95% of the patients tolerated it without any problems
- AE were all minor side effects typical of those associated with viscosupplements
  - **joint pain, injection site pain, swelling, erythema , or rash**
  - **all resolved without treatment**
- AE rate associated was found to be consistent across both first-time and repeat injection studies.

High MW Hyaluronic Acid+TH 13-02, an open-label, follow-on study to High MW Hyaluronic Acid+TH 13-01. Anika Therapeutics, Inc.: study sponsor, Dr. Laszlo Hangody: global principal investigator, SynteractHCR: CRO.

Conclusions

- High MW HA+TH is safe and effective to provide fast and long-term relief of OA-related pain, stiffness, and function, significant through 26 weeks.
- It is statistically superior to saline at every time point for measurements including pain, stiffness, physical function, and global assessment
- An ancillary corticosteroid provides a significant early pain relief additive to the long-term pain relief provided by a leading HA viscosupplement
  - **The advantage of pain reduction over High MW HA was a 17% relative improvement at 1 week and 15% relative improvement at 3 weeks.**
- Since it achieved its largest improvement in WOMAC Pain at 26 weeks, further investigation is warranted into the benefits over longer timeframes.

Conclusions (continued)

- In Canada, High MW HA+TH is approved for use in knees.
- In Europe and other parts of the world, it is given into any synovial joint with OA