Canadian Agency for Drugs and Technologies in Health

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Intra-Articular Hyaluronic Acid (Viscosupplementation) for Knee Osteoarthritis

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Summary

- ✓ **In viscosupplementation, a glycosaminoglycan (GAG) called hyaluronic acid (HA) is administered via intra-articular (IA) injection for patients with knee osteoarthritis (OA).**
- ✓ **Evidence suggests modest short-term reductions in pain and improvements in function, and no superiority among HA products.**
- ✓ **Adverse events are rare, benign, temporary, and likely associated with the IA injection.**
- ✓ **Economic analyses of mixed quality suggest that HA may be cost effective compared with usual care.**
- ✓ **Clinical practice guidelines and evidence suggest that this approach is most suitable for patients with mild to moderate knee OA, and in those for whom other approaches are contraindicated, or have failed.**

The Technology

HA (hyaluronic acid or hyaluronan) is a glycosaminoglycan (GAG) composed of glucuronic acid and glucosamine in a polysaccharide of varying lengths and molecular weights. At high molecular weights, HA is viscoelastic, aiding weight-bearing joints in lubrication, shock absorption, and fluid retention during movement.[1] Its mechanism of action is poorly understood, but its effects may be due to regulation of cartilage synthesis, inhibition of inflammatory cytokines and nociception, and stimulation of natural HA synthesis. These effects may depend on the molecular weight of the HA.[1]

Regulatory Status

Durolane® (Q-Med AB) was licensed for sale in Canada in 2003, NeoVisc® (Stellar Pharmaceuticals) in 1999, Orthovisc® (Rivex Pharma Inc.) in 1999, Ostenil® (Garvinci International) in 2005, Suplasyn® (Bioniche Life Sciences Inc.) in 1999, and Synvisc® or Hylan G-F 20 (Genzyme Corp.) in 1992. All are regulated as class III or IV medical devices, and sold as pre-filled single-use 2 mL (3 mL for Durolane) syringes. Approved indications are mild to moderate knee OA (Durolane), knee OA after arthrocentesis (NeoVisc, Suplasyn), symptomatic knee OA (Orthovisc), pain and restricted mobility in the knee (Ostenil), and temporary replacement of synovial fluid (Synvisc). Synvisc and Durolane are of a higher molecular weight.[2]

Patient Group

OA is the most common joint disorder leading to disability. Among adults >55 years old, 30% have radiographic evidence of knee OA, 10% have symptomatic knee OA, and 2.5% have severely disabling knee OA.[3] Suspected risk factors include overuse, trauma, obesity, and heredity.[3] Though the pathogenesis of knee OA is incompletely understood, decreased concentrations and molecular weights of HA may be implicated.[4]

The clinical features of knee OA include regional pain, joint tenderness, decreased range of motion, crepitus, effusion, and inflammation.[3] These symptoms may lead to decreased function, impaired activities of daily living, and partial or total disability.[3] Radiologic findings include joint space narrowing, osteophytes, subchondral sclerosis, and bony cysts. The radiographic findings correlate poorly with clinical symptoms, which often fluctuate.

Current Practice

Non-pharmacological, pharmacological, intra-articular (IA), and surgical therapies are available.[3] Non-pharmacological treatments include education, exercise, weight loss, physical therapy, walking aids, and nutritional supplements. Pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and other analgesics, including opioids. IA treatments include corticosteroid injections, tidal irrigation, and HA. Surgical treatments include arthroscopy, osteotomy, and unicompartmental or total joint replacement.[5,6]

Clinical practice guidelines recommend a combination of non-pharmacological and pharmacological treatments that is based on risk factors, level of pain intensity, signs of inflammation, and degree of structural damage. Treatment

progresses from acetaminophen to NSAIDs or COX-2 inhibitors, opioid analgesics, IA corticosteroids, and joint replacement.[3] Other guidelines recommend opioids, IA steroids, or IA HA in patients who do not improve after exercise, lifestyle changes, analgesics, NSAIDs, topical creams, and selective COX-2 inhibitors.[7] Adherence to clinical practice guidelines in Canada is unknown.

The Evidence

Although systematic reviews and meta-analyses reviewed many of the same RCTs, differences in methods led to heterogeneous conclusions. Most reviews reported a lack of comparative RCTs to establish evidence of superiority among HA products, and pooled the results from all products. The results of seven reviews, some of which are meta-analyses, are noted below.

A meta-analysis of 22 RCTs with 2,927 patients compared HA to IA placebo, and reported a small pooled effect size of 0.32 (0.17 to 0.47) for change in pain from baseline, after two to four months follow-up.[1] Analysis without the three RCTs of high molecular weight HA, with 252 patients, reduced the effect size 40% to 0.19 (0.10 to 0.27). The review suggested publication bias, and identified two unpublished trials with a pooled effect size of 0.07 (–0.15 to 0.28) for the same outcome. The authors concluded that HA had modest efficacy for knee OA, and that high molecular weight HA may be superior to low molecular weight HA. Many methodological weaknesses were reported among the included RCTs, including dropout rates of 26% to 40%.

HA was compared with IA placebo in a meta-analysis of 20 RCTs (with 1,647 knees). It noted a pooled sum of pain index difference of 7.9% (4.1% to 11.7%) in favour of HA.[8] There was significant study heterogeneity with higher efficacy reported in RCTs of cross-linked (i.e., high molecular weight) HA, and in RCTs with lower methodological quality. Lower efficacy was reported in RCTs that permitted acetaminophen as a rescue medication in patients >65 years old, and in patients with complete loss of joint space.

Improvements in pain, function, and activity were reported in a review of 13 RCTs and five observational studies, with 2,747 patients.[9] Results from studies with high Molecular weight HA were mostly positive, whereas results from studies with low molecular weight HA were conflicting. The authors suggested that although the onset of benefits is slower with IA HA than with IA corticosteroids, the effect of HA may last longer, so this would be an appropriate therapy for patients with refractory knee OA who cannot tolerate other treatments.

A review of 22 RCTs with 3,222 patients reported a 3.8 mm (–1.4 mm to 9.1 mm) mean improvement in visual analogue scale (VAS) pain during movement after two to six weeks, 4.3 mm (0.9 to 7.6 mm) after 10 to 14 weeks, and 7.1 mm (2.4 to 11.8 mm) after 22 to 30 weeks. The minimum clinically important difference was 15 mm.[10] Most RCTs used poor methods, which likely overestimated treatment effects. The authors suggested that the effectiveness of HA had not been proven for knee OA.

No difference in WOMAC scores between HA and control groups was noted in a review of seven RCTs; however, this same review showed an advantage for HA over controls in the Lequesne index up to, but not beyond, six months.[11] The authors suggested that HA offers transient improvement in older patients with knee OA, and that there was insufficient evidence on which to base a recommendation for the use of HA.

A review of six systematic reviews reported a small but significant effect on pain and function, similar to that of corticosteroids at one month, but superior after a few months, with benefits similar to those of NSAIDs, and with fewer gastrointestinal-related adverse events.[12] It concluded that the onset of efficacy with HA was delayed by two to five weeks, reached maximum efficacy at five to 13 weeks, and maintained efficacy for six months. This study found conflicting evidence that efficacy was related to molecular weight. The authors suggested that HA had higher efficacy in patients <65 years old with mild to moderate effusion and pain.

Finally, in a review of 76 RCTs reported that overall pooled effects supported the efficacy of HA compared to placebo, with heterogeneity in effects based on products, outcome measures, and timepoints.[13] The greatest efficacy was pain reduction of 28% to 54%, and improved function of 9% to 32% at five to 13 weeks. Efficacy was generally comparable to that of NSAIDs, and the duration of efficacy was longer than that of corticosteroids.

Adverse Effects

Reviews have concluded that HA for knee OA seems well tolerated and safe,[14] is associated with few AEs,[8] generates minor side effects,[9] leads to more AEs than controls,[10] is safe with repeated treatments,[15] has a risk of acute painful reactions with high molecular weight products,[12] and seems safe.[13] The prevalence of AEs from clinical studies was approximately 2% to 5% of injections, and 5% to 10% of patients, comparable to the rate observed with IA saline placebo. Rare but serious AEs, including severe acute inflammatory reaction (SAIR), infection, allergic reaction, and anaphylaxis, have been reported with

Synvisc.[16] A Canadian post-marketing surveillance study of 1,537 Synvisc injections given to 336 patients with knee OA reported 28 local AEs.[17] A study of 4,253 patients receiving 12,699 IA injections of Synvisc for knee OA from 840 physicians in Germany reported 365 AEs, including one serious AE.[18] The most frequent AEs were local effusion (2.4%), swelling (1.3%), arthralgia (1.2%), warmth (0.6%), and erythema (0.3%). Over 60% were mild to moderate.

Administration and Cost

Administration schedules consist of single injection (Durolane), three to five weekly injections repeated every six to eight months (NeoVisc), three weekly injections (Orthovisc, Ostenil), three to six weekly injections (Suplasyn), and three weekly injections up to a maximum of six injections every six months (Synvisc). Arthrocentesis is recommended before the use of NeoVisc and Suplasyn. HA products cost from C$300 to C$500 per course of treatment, and are not covered by public health insurance in Canada, although physician fee codes are used for the IA injections. Treatment is often repeated, despite a lack of evidence about multiple courses.

Economic analyses report that compared with conventional care from a public health care perspective in France, care with Synvisc means lower costs for drugs, non-pharmacological treatments, and hospitalizations.[17] Adding HA to standard treatment would result in savings of US$4,706 per patient over three years from a US-managed care perspective.[5] HA as an adjunct therapy to NSAIDs can achieve a 7 mm improvement in visual analogue scale at an incremental cost of US$1,070 from a US-managed care perspective.[19] Adding Synvisc to appropriate care results in higher costs and greater effectiveness, with a favourable cost-effectiveness ratio from a public health care perspective in Canada.[20] The methodological quality of these analyses is mixed, and some conclusions are based on unsupported hypotheses (e.g., that HA can delay the need for total replacement by a year).

Concurrent Developments

Manufacturers of other HA products that are approved in the US, Europe, and Japan may seek regulatory approval in Canada. By sponsoring additional comparative trials, manufacturers may develop advantages in dose (i.e., one versus three to five injections), in repetition of treatment, in duration of effect, or in rate and severity of AEs. There may be off-label use in the hip, ankle, foot, shoulder, elbow, and wrist.

Rate of Technology Diffusion

The six HA products that are sold in Canada may face additional competition from products being sold internationally. Such market saturation could lead to more visibility from increased marketing, and additional research. Although the rate of technology diffusion has been low relative to other treatments for knee OA, recommendations from clinical practice guidelines and systematic reviews, and a projected increase in the prevalence of knee OA, may accelerate uptake.

Implementation Issues

Reviews and practice guidelines show that HA is most suitable for patients <65 years old with mild to moderate pain, effusion, and radiographic findings, and in those for whom other approaches are contraindicated, or have failed. Demand for HA will likely be high, although eligibility criteria will decrease the size of the potential market. The repeated office visits required for administration by IA injection will increase demand for services from primary care physicians, rheumatologists, physiatrists, orthopedists, and specialists in rheumatic disease. The use of HA will also likely increase the demand for radiological and laboratory testing.

References

1. Lo GH, et al. *JAMA* 2003;290(23):3115-21.
2. *Medical devices active license listing* [database online]. Rev. Ottawa: Medical Devices Bureau, Therapeutic Products Directorate, Health Canada; 2006. Available: http://www.mdall.ca/ .
3. Jordan KM, et al. *Ann Rheum Dis* 2003;62(12):1145-55.
4. Lajeunesse D, et al. *Bone* 2003;33(4):703-10.
5. Waddell D, et al. *Am J Manag Care* 2001;7(10):981-91.
6. Torrance GW, et al. *Osteoart Cartil* 2002;10(7):518-27.
7. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis & Rheumatism* 2000;43(9):1905-15.
8. Wang CT, et al. *J Bone Joint Surg Am* 2004;86-A(3):538-45.
9. Aggarwal A, et al. *Can Fam Physician* 2004;50:249-56. Available: http://www.cfpc.ca/cfp/2004/Feb/_pdf/vol50-feb-cme-2.pdf .
10. Arrich J, et al. *CMAJ* 2005;172(8):1039-43.
11. Medina JM, et al. *J Fam Pract* 2006;55(8):669-75.
12. Gossec L, et al. *Best Pract Res Clin Rheumatol* 2006;20(1):131-44.
13. Bellamy N, et al. *Cochrane Database Syst Rev* 2006;(2):CD005321.

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14. Espallargues M, et al. *Int J Technol Assess Health Care* 2003;19(1):41-56.
15. Pagnano M, et al. *Osteoarthr Cartil* 2005;13(9):751-61.
16. Hamburger MI, et al. *Seminars in Arthritis & Rheumatism* 2003;32(5):296-309.
17. Hammesfahr JF, et al. *American Journal of Orthopedics* (Chatham, Nj) 2003;32(6):277-83.
18. Kemper F, et al. *Current Medical Research & Opinion* 2005;21(8):1261-9.
19. Mark D, et al. *Technol Eval Cent Assess Program* 2005;19(17):1-13. Available: http://www.bcbs.com/TEC/Vol19/19_17.pdf .
20. Torrance GW, Raynauld JP, Walker V, Goldsmith CH, Bellamy N, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. *Osteoarthritis Cartilage* 2002;10(7):518-27.

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