

[Sports Physical Therapy]

Viscosupplementation During Rehabilitation

Holly J. Silvers, MPT*^{†‡}

Context: Viscosupplementation (VS) and physical therapy are both used to treat pain associated with knee osteoarthritis (OA).

Evidence Acquisition: PubMed and EMBASE searches were performed to July 2013. Search terms included *hyaluronic acid* OR *hylan*, *physical therapy* OR *exercise*, AND *osteoarthritis*.

Study Design: Clinical review.

Level of Evidence: Level 4.

Results: The efficacy and safety of VS in painful knee OA is well documented, as are the appropriate candidates for this intervention. Studies suggest that adding VS to physical therapy and therapeutic exercise may lead to improved pain reduction and increased functionality compared with physical therapy alone.

Conclusion: Appropriately selected patients undergoing physical therapy for knee OA may benefit from VS.

Keywords: viscosupplementation; hyaluronic acid; knee osteoarthritis; anterior cruciate ligament surgery; physical therapy

Arthritis is the leading cause of disability in the United States,¹⁰ and osteoarthritis (OA) is the most common form of arthritis.¹⁵ Twelve percent of adults at least 60 years of age have symptomatic knee OA,²⁰ and 1 in 2 individuals may develop symptomatic knee OA within their lifetimes.¹⁶

Intra-articular injection of hyaluronic acid (HA), also known as viscosupplementation (VS), has demonstrated efficacy in the treatment of painful knee OA.^{8,11} Seven VS products are available in the United States, consisting of sodium hyaluronate/hyaluronan/hyaluronic acid^{23,26,32,45,55} or hylan G-F 20.^{54,56} Viscosupplements have been approved by the US Food and Drug Administration for use in patients whose painful knee OA has responded inadequately to conservative nonpharmacologic measures and simple analgesics (eg, acetaminophen).^{23,26,32,45,54-56}

While OA has been typically regarded as a disease in older age, posttraumatic OA frequently occurs in a younger population.¹⁴ More than half of individuals with an anterior cruciate ligament (ACL) or meniscal tear are diagnosed with OA within 10 to 20 years.⁴² Currently, 12% of those with

symptomatic OA have posttraumatic OA, and treatments cost more than \$3 billion in the United States alone.³³

Pain and decreased function can hinder a patient's ability to fully participate in, and therefore benefit from, physical therapy. To the degree that VS reduces pain and improves patient function, it may facilitate participation and adherence to a physical therapy protocol. Increased activity and physical therapy, in turn, are likely to improve the OA patient's functional outcome. Data support the benefit of adding VS to physical therapy or exercise for painful knee OA.^{52,58}

EFFICACY AND SAFETY IN KNEE OSTEOARTHITIS

A Cochrane review⁸ and pooled analysis of data from 76 randomized controlled trials supported the efficacy (ie, reduced pain and improved function) of VS in knee OA (see Appendix, available at <http://sph.sagepub.com/content/suppl/1-3,9,13,17,19,21,22,28,31,34,35,41,44,46,50,53,57,66>). Pain improved from 28% to 54% and function from 9% to 32% at 5 to 13 weeks

From the [†]Santa Monica Orthopaedic and Sports Medicine Research Foundation, Santa Monica, California, and [‡]Department of Biomechanics and Movement Science, University of Delaware, Newark, Delaware

*Address correspondence to Holly J. Silvers, MPT, Director of Research/Physical Therapist, Santa Monica Orthopaedic and Sports Research Foundation, 2020 Santa Monica Boulevard, 4th Floor, Santa Monica, CA 90404 (e-mail: hollysilverspt@aol.com).

The author declared potential conflicts of interest: Sanofi provided financial support to Precise Publications to assist in the writing of this article.

DOI: 10.1177/1941738114539911

© 2014 The Author(s)

postinjection compared with baseline.⁸ The most recent review found a moderate benefit of VS for pain reduction (effect size [ES], -0.37; 95% CI, 0.46 to -0.28) compared with placebo or no intervention.⁴⁹ A 2012 meta-analysis found a 40% to 50% reduction in pain when using VS compared with a placebo.¹⁸ Comparing by time point in a previous meta-analysis, VS was found to be efficacious as early as 4 weeks (ES, 0.31; 95% CI, 0.17-0.45), peak at 8 weeks (ES, 0.46; 95% CI, 0.28-0.65), and still be effective at 24 weeks (ES, 0.21; 95% CI, 0.10-0.31).⁷

Efficacy of VS was comparable with that of nonsteroidal anti-inflammatory drugs (NSAIDs; 6 trials) and lasted longer than intra-articular corticosteroids (10 trials).⁸ While intra-articular corticosteroids generally have a more immediate effect, VS has a longer lasting effect.^{11,12,24}

Side effects with VS are predominantly local and transient, such as pain and/or swelling at the injection site or in the injected knee.^{11,38,62} The incidence of local side effects in 16 randomized, placebo-controlled studies evaluating the 5 VS products approved in the United States was 0% to 12.8% per patient and 0% to 2.8% per injection with HA compared with 0% to 11.8% per patient and 0% to 2% per injection for hylan G-F 20.¹¹

A large short-term safety study of 4253 patients with knee OA found that local, treatment-related side effects occurred in 4.2% of patients and 2.4% of hylan G-F 20 injections.³⁸ Most side effects were mild (21.4%) to moderate (40.3%) in severity.³⁸ One serious side effect was reported (severe swelling and synovial fluid accumulation).³⁸ Similarly, a longer term, 5-year retrospective review reported the incidence of local pain and swelling as 5.2% per patient and 1.2% per injection (n = 1047 patients, 1489 knees; hylan G-F 20, single practice).⁶² Most of the local side effects were mild to moderate in nature, with severe local events (pain and swelling) occurring in 1.2% of patients and 0.3% of injections.⁶² All local side effects resolved spontaneously or with aspiration and/or corticosteroid treatment.⁶²

In general, the incidence of local side effects with VS is comparable with that of intra-articular steroid therapy^{12,24} or saline injections.^{3,9,53} Rates of cardiovascular and gastrointestinal (GI) side effects with VS are also similar to those observed with controls.²⁷ Additionally, the incidence of GI side effects is lower with VS plus conventional therapy than with conventional therapy alone.⁴⁸ In a prospective health outcomes trial, patients with knee OA were randomized to conventional therapy alone or with hylan G-F 20.⁴⁸ Fewer patients in the VS + conventional therapy group took medications for the GI tract compared with patients in the conventional therapy alone group ($P > 0.01$).⁴⁸

Some systematic evaluations of local side effect incidence with repeat treatment do not show an increase in local pain and swelling with repeat courses of multiple- or single-injection therapy.^{17,47} However, a large case series⁶³ reported an increase in the incidence of local side effects with repeat courses of therapy.

Analysis of synovial fluid from the knees that developed swelling or pain after VS injection found no evidence that these local side effects were related to infection, inflammation, allergy,

or the formation/presence of crystals.⁶¹ No long-term clinical sequelae were associated with local side effects.⁶¹ Patients with skin diseases or infections in the injection area or those with known hypersensitivity to hyaluronan preparations should not be treated with VS.^{23,26,32,45,54-56} In addition, VS products derived from chicken combs should not be used⁴⁵ or should be used with caution^{55,56} in patients with allergies to avian or avian-derived products (eg, eggs, feathers, or poultry).

Finally, development of local side effects after injection does not appear to affect the clinical efficacy of VS.⁶² Knees in which local side effects developed and to which 3 injections of VS were administered (n = 50) showed the same pattern of physician-rated improvement (visual analog scale) as the overall treatment population.⁶²

A 2012 systematic review and meta-analysis analyzed safety as a secondary outcome.⁴⁹ While VS was associated with an increased risk for flare-ups (relative risk [RR], 1.51; 95% CI, 0.84-2.72), this risk was not statistically significant, but may be clinically significant. Significant increased risk with VS use was found with local side effects (RR, 1.34; 95% CI, 1.13-1.60) and serious side effects (RR, 1.41; 95% CI, 1.02-1.97).⁴⁹ No differences were noted between VS and placebo when comparing side effects.⁴⁹

PATIENT SELECTION

Viscosupplementation may be prescribed for those who have failed traditional medicinal management or have contraindications to the use of NSAIDs.^{5,43} Long-term NSAID therapy has been associated with cardiovascular, GI, and renal adverse events, limiting their usefulness in patients at elevated risk for these complications.^{4,25,37,40,67,68} Older age is a risk factor for NSAID-related GI adverse events,⁶⁷ and OA is more common among older adults. Other risk factors for GI adverse events with NSAIDs are a history of ulcer or GI complications; concomitant use of low-dose aspirin, oral corticosteroids, or anticoagulants; higher NSAID dose or use of more than 1 NSAID; and a serious concomitant condition.^{40,67}

Patients with a history of, or other risk factors for, cardiovascular or renal disease may be more likely to develop NSAID-associated side effects affecting these systems.^{4,25,37} Cyclo-oxygenase 2 selective inhibitors reduce the risk of GI side effects^{39,40} but are associated with increased risk of cardiovascular adverse events, including myocardial infarction, stroke, heart failure, and hypertension.⁴ Nonselective NSAIDs also have been associated with risk of myocardial infarction and other cardiovascular events.⁶⁰

Viscosupplementation may be prescribed for those who have failed therapy with intra-articular corticosteroids. Corticosteroid use has been associated with joint degradation.⁵¹ A systematic review of corticosteroids for knee OA found a benefit for corticosteroid use for 1 week, but after the first week, the benefit was not significant compared with placebo.²⁹ Corticosteroids are useful for short-term relief of knee OA pain, but other treatment options are needed for longer pain relief.²⁹

Viscosupplementation may be prescribed for those who are not candidates for, or who refuse, total knee replacement. There is some evidence to suggest that VS may delay total knee replacement.⁶⁴ In a report from a single center, among total knee replacement candidates (ie, Kellgren-Lawrence grade IV [severe] knee OA) who received hylan G-F 20, 75% of patients had not had a total knee replacement 3.8 years after hylan G-F 20; 19% (225/1187 knees) underwent total knee replacement within a median of 1.8 years.⁶⁴ All knees received 1 course of VS therapy (3 weekly injections of hylan G-F 20), with 44.9% receiving 2 courses of treatment and 14.3% receiving 3 courses.⁶⁴

A study compared patients who received HA injections for knee OA pain over 54 months for incidence and time to total knee replacement.⁵⁹ From a total of 183 patients, 72% (n = 131) responded to HA treatment and did not require total knee replacement for the study duration (mean follow-up, 45.6 months).⁵⁹ Delay to surgery was calculated at 7.7 months per cycle of HA injections.⁵⁹ The patients who did not require total knee replacement had 5.5 to 6.1 repeated cycles of HA injections, while patients who progressed to total knee replacement had 1.2 to 2.5 repeated cycles.⁵⁹ Also, a retrospective study of HA injections for knee OA pain found a delay to total knee replacement for up to 4 years, with some patients receiving 6 to 8 series of injections.⁶⁵ Importantly, the HA injections alleviated knee OA pain, with less than 1% of patients reporting side effects related to the HA injections.⁶⁵ Most of the side effects (20/26) were mild and resolved spontaneously without any medical intervention.⁶⁵

VISCOSUPPLEMENTATION COMPARED OR COMBINED WITH PHYSICAL THERAPY IN OSTEOARTHRITIS

Viscosupplementation and/or Physical Therapy as a Treatment for Osteoarthritis

Few studies have compared VS to physical therapy for painful knee OA. Patients were randomized to receive either 3 weekly injections of HA and a fourth injection at 6 months (n = 40) or physical therapy 5 times a week for 3 weeks (n = 42).⁶ Within the VS group, patients received either hylan G-F 20 (n = 20) or HA (n = 20).⁶ Outcomes were assessed at 1, 3, 6, 9, and 12 months.⁶ Pain and function improved compared with baseline in both groups.⁶ Change in range of motion and stiffness was similar in the 2 groups and not significantly different from baseline.⁶ Improvement in pain at night and at rest was significantly greater ($P < 0.05$) with physical therapy at 1, 3, and 6 months.⁶ Compared with baseline scores, Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain scores showed significantly greater ($P < 0.05$) improvement with HA at 12 months.⁶ Four patients from the VS group reported local side effects of mild swelling, warmth, and pain at the injection site that was relieved with cold pack application.⁶ Severe or systemic side effects were not observed throughout the study period.

Viscosupplementation During Rehabilitation Improves Outcomes

Adding hylan G-F 20 to rehabilitation/physical therapy significantly reduced ($P < 0.01$) pain and improved function in knee OA.⁵⁸ Patients were randomized to receive 15 days of daily physical therapy alone (n = 60 knees) or combined with 3 weekly injections of hylan G-F 20 (n = 60 knees).⁵⁸ Pain, stiffness, and function improved significantly ($P < 0.01$) at 3 and 12 weeks in both groups compared with baseline.⁵⁸ Improvement at 12 weeks was significantly greater ($P < 0.05$) with combined therapy.⁵⁸ No side effects were observed.

Viscosupplementation is Comparable With Home Exercise Therapy

A randomized study comparing the effects of HA with home exercise therapy on pain and function in knee OA (n = 102 females) found that both therapies yielded significant improvement from baseline at 24 weeks, with no significant difference between the treatments, although with the small sample size, statistical differences may not have been achievable secondary to a lack of power.³⁶ Patients with early-stage OA at baseline showed significantly greater improvement on some scales than those with late-stage OA.³⁶ Patients received 5 weekly HA injections, followed by a monthly injection until 24 weeks.³⁶ While safety was not analyzed in this study, no severe side effects were reported.

Viscosupplementation Combined With Exercise Improved Outcomes

Adding HA (weekly injections for 5 weeks) to isokinetic exercise and ultrasound (each 3 times a week for 8 weeks) for knee OA (n = 140 patients, 280 knees) led to significantly greater ($P < 0.05$) improvement than exercise or exercise + ultrasound.³⁰ Patients were randomized to isokinetic exercise only; exercise + ultrasound; exercise, ultrasound and VS; or to a control group.³⁰ At 1 year, range of motion, pain, disability, ambulation speed, and muscle power showed significantly greater improvement with triple therapy compared with controls and the other treatment groups.³⁰ Of the 140 patients, 12 patients withdrew from the study; 9 withdrew because of intolerable knee pain from the prescribed exercises and leg muscle weakness.³⁰

VISCOSUPPLEMENTATION ADDED TO CONVENTIONAL OSTEOARTHRITIS CARE

A prospective, randomized trial examined the impact of adding VS to conventional care of painful knee OA and supported a multipronged approach to treating OA.⁴⁸ Patients (n = 255) from 14 practices received conventional care as determined by the treating physician (eg, analgesics, NSAIDs, exercise, weight loss, intra-articular corticosteroids).⁴⁸ They were randomized to inclusion or exclusion of VS (3 weekly injections, hylan G-F 20) as an option.⁴⁸ Outcomes at 1 year were superior in the group receiving VS, with clinically and statistically significantly greater reductions in the WOMAC pain scale (primary endpoint; 38% vs

13% improvement, $P < 0.01$).⁴⁸ Health-related quality of life measures (WOMAC stiffness, physical function, Short Form-36 aggregate physical component, and Health Utilities Index) all significantly favored the group including VS with superior scores ($P < 0.0001$).⁴⁸ Patients in the VS group were significantly less likely to use NSAIDs ($P = 0.0062$) or to receive intra-articular corticosteroid injections in the knee ($P < 0.0001$).⁴⁸ While the majority of patients had a side effect in both groups, only 1 serious side effect occurred in the conventional care group. A total of 38 patients in the VS plus conventional care group reported 82 local side effects within 48 hours of the VS injection.⁴⁸ Significantly fewer patients in the VS + conventional care group had GI side effects ($P < 0.05$).⁴⁸

CONCLUSION

Viscosupplementation may serve as an effective adjunct to physical therapy or exercise. The pain reduction and functional improvement associated with VS may facilitate participation in postinjection rehabilitation.

REFERENCES

- Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. *J Rheumatol*. 1998;25:2203-2212.
- Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. *Osteoarthritis Cartilage*. 2011;19:1169-1175.
- Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Semin Arthritis Rheum*. 2009;39:1-9.
- Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115:1634-1642.
- Arnold W, Fullerton DS, Holder S, May CS. Viscosupplementation: managed care issues for osteoarthritis of the knee. *J Manag Care Pharm*. 2007;13:3-19.
- Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. *Rheumatol Int*. 2006;26:873-878.
- Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthritis Cartilage*. 2011;19:611-619.
- Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006;(2):CD005321.
- Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. *Clin Orthop Relat Res*. 2001;385:130-143.
- Brault MW, Hootman J, Helmick CG, Theis KA, Armour BS. Prevalence and most common causes of disability among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009;58:421-426.
- Brzusek D, Petron D. Treating knee osteoarthritis with intra-articular hyaluronans. *Curr Med Res Opin*. 2008;24:3307-3322.
- Caborn D, Rush J, Lanzer W, Parenti D, Murray C. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. *J Rheumatol*. 2004;31:333-343.
- Carrabba MP, Paresse E, Angelini M, Re KA, Torchiana EEM, Perbellini A. The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusion. *Eur J Rheumatol Inflamm*. 1995;15:25-31.
- Centers for Disease Control and Prevention. *A National Public Health Agenda for Osteoarthritis*. Atlanta, GA, Centers for Disease Control and Prevention; 2010.
- Centers for Disease Control and Prevention. Estimates for specific forms of arthritis. Updated May 7, 2010. <http://www.cdc.gov/features/dsarthritis/index.html>. Accessed March 28, 2013.
- Centers for Disease Control and Prevention. Osteoarthritis and you. Updated February 9, 2012. <http://www.cdc.gov/features/osteoarthritisplan/index.html>. Accessed March 28, 2013.
- Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis*. 2010;69:113-119.
- Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs*. 2012;26:257-268.
- Day R, Brooks P, Conaghan PG, Petersen M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. *J Rheumatol*. 2004;31:775-782.
- Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol*. 2006;33:2271-2279.
- Dixon AS, Jacoby RK, Berry H, Hamilton EBD. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Curr Med Res Opin*. 1988;11:205-213.
- Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage*. 1993;1:97-103.
- Euflexxa (1% sodium hyaluronate) [Prescribing information]. Ferring Pharmaceuticals. http://www.euflexxa.com/assets/euflexxa_physician-8f7c5c8e9b6f9317c6cfd0b7df1b48c6.pdf. Accessed May 22, 2014.
- Frizziero L, Pasquali-Ronchetti I. Intra-articular treatment of osteoarthritis of the knee: an arthroscopic and clinical comparison between sodium hyaluronate (500-730 kDa) and methylprednisolone acetate. *J Orthop Traumatol*. 2002;3:89-96.
- Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. *J Intern Med*. 2003;253:643-652.
- Gel-One (cross-linked hyaluronate) [Prescribing information]. Seikagaku Corporation. Available at: http://www.zimmer.com/content/pdf/en-US/Gel-One_Pkg_Insert_Final.pdf. Accessed May 22, 2014.
- Goldberg VM, Goldberg L. Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis. *J Pain Res*. 2010;3:51-56.
- Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. *Pharmatherapeutica*. 1987;5:137-141.
- Hepper CT, Halvorson JJ, Duncan ST, Gregory AJ, Dunn WR, Spindler KP. The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J Am Acad Orthop Surg*. 2009;17:638-646.
- Huang MH, Yang RC, Lee CL, Chen TW, Wang MC. Preliminary results of integrated therapy for patients with knee osteoarthritis. *Arthritis Rheum*. 2005;53:812-820.
- Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)*. 1999;38:602-607.
- Hyalgan (sodium hyaluronate) [Prescribing information]. Sanofi-Aventis. http://www.hyalgan.com/download/hyalgan_pi.pdf. Accessed May 22, 2014.
- Jaquet GJ. EWI VIII: sequelae of combat injuries. *AAOS Now*. April 2013. <http://www.aaos.org/news/aaosnow/apr13/clinical2.asp>. Accessed May 22, 2014.
- Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *Int J Clin Pract*. 2003;57:467-474.
- Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology*. 2002;41:1240-1248.
- Kawasaki T, Kurosawa H, Ikeda H, et al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. *J Orthop Sci*. 2009;14:182-191.
- Kean WF, Rainsford KD, Kean IR. Management of chronic musculoskeletal pain in the elderly: opinions on oral medication use. *Inflammopharmacology*. 2008;16:53-75.
- Kemper F, Gebhardt U, Meng T, Murray C. Tolerability and short-term effectiveness of hylan G-F 20 in 4253 patients with osteoarthritis of the knee in clinical practice. *Curr Med Res Opin*. 2005;21:1261-1269.

39. Laine L. Gastrointestinal safety of coxibs and outcomes studies: what's the verdict? *J Pain Symptom Manage.* 2002;23(suppl 4):S5-S10.
40. Laine L. Gastrointestinal effects of NSAIDs and coxibs. *J Pain Symptom Manage.* 2003;25(suppl 2):S32-S40.
41. Lohmander LS, Dalén N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Ann Rheum Dis.* 1996;55:424-431.
42. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35:1756-1769.
43. McHughes M, Lipman AG. Managing osteoarthritis pain when your patient fails simple analgesics and NSAIDs and is not a candidate for surgery. *Curr Rheumatol Rep.* 2006;8:22-29.
44. Neustadt DH. Intra-articular injections for osteoarthritis of the knee. *Cleve Clin J Med.* 2006;73:897-898, 901-904, 906-911.
45. Orthovisc (sodium hyaluronate) [Prescribing information]. Anika Pharmaceuticals. <http://www.depuym.com/sites/default/files/products/files/OrthoviscNonAvianPIFinal2010.pdf>. Accessed on May 22, 2014.
46. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis Cartilage.* 1993;1:233-241.
47. Raynauld JP, Goldsmith CH, Bellamy N, et al. Effectiveness and safety of repeat courses of hylan G-F 20 in patients with knee osteoarthritis. *Osteoarthritis Cartilage.* 2005;13:111-119.
48. Raynauld JP, Torrance GW, Band P, 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 1 of 2): clinical results. *Osteoarthritis Cartilage.* 2002;10:506-517.
49. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:180-191.
50. Scale D, Wobig M, Wolpert W. Viscosupplementation of osteoarthritic knees with hylan: a treatment schedule study. *Curr Ther Res.* 1994;55:220-232.
51. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. *Am J Med.* 2005;118:1208-1214.
52. Stitik TP, Blacksin MF, Stiskal DM, et al. Efficacy and safety of hyaluronan treatment in combination therapy with home exercise for knee osteoarthritis pain. *Arch Phys Med Rehabil.* 2007;88:135-141.
53. Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2012;20:350-356.
54. Supartz (sodium hyaluronate) [Prescribing information]. Seikagaku Corporation. <http://supartzprofessional.com/docs/PackageInsert.pdf>. Accessed May 22, 2014.
55. Synvisc (hylan G-F 20) [Prescribing information]. Genzyme Biosurgery. http://www.synvisc.com/~media/SynviscOneUS/Files/synvisc_PI.pdf. Accessed May 22, 2014.
56. Synvisc-One (hylan G-F 20) [Prescribing information]. Genzyme Biosurgery. <http://synvisc.com/~media/SynviscOneUS/Files/Synvisc-OnePI-70240104.pdf>. Accessed May 22, 2014.
57. Tamir E, Robinson D, Koren R, Agar G, Halperin N. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled study. *Clin Exp Rheumatol.* 2001;19:265-270.
58. Tetik S, Ones K, Tetik C. Efficacy of intra-articular hylan G-F 20 on osteoarthritis of the knee. *Pain Clinic.* 2003;15:459-466.
59. Turajane T, Amphansap T, Labpiboonpong V, Maungsiri S. Total knee replacement following repeated cycles of intra-articular sodium hyaluronate (500-730 kDa) in failed conservative treatment of knee osteoarthritis: a 54-month follow-up. *J Med Assoc Thai.* 2009;92(suppl 6):S63-S68.
60. van der Linden MW, van der Bij S, Welsing P, Kuipers EJ, Herings RM. The balance between severe cardiovascular and gastrointestinal events among users of selective and non-selective non-steroidal anti-inflammatory drugs. *Ann Rheum Dis.* 2009;68:668-673.
61. Waddell DD. The tolerability of viscosupplementation: low incidence and clinical management of local adverse events. *Curr Med Res Opin.* 2003;19:575-580.
62. Waddell DD, Bricker D. Clinical experience with the effectiveness and tolerability of hylan G-F 20 in 1047 patients with osteoarthritis of the knee. *J Knee Surg.* 2006;19:19-27.
63. Waddell DD, Bricker DC. Hylan G-F 20 tolerability with repeat treatment in a large orthopedic practice: a retrospective review. *J Surg Orthop Adv.* 2006;15:53-59.
64. Waddell DD, Bricker DC. Total knee replacement delayed with hylan G-F 20 use in patients with grade IV osteoarthritis. *J Manag Care Pharm.* 2007;13:113-121.
65. Whitman C, Allen D, Comadoll JL, Thomason HC, Oweida SJ. A retrospective study of SUPARTZ and repeat treatment for osteoarthritis pain in the knee. *J Manag Care Med.* 2010;13:43-47.
66. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther.* 1998;20:410-423.
67. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1999;340:1888-1899.
68. Zhao SZ, Reynolds MW, Lejkowith J, Whelton A, Arellano FM. A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre safety database. *Clin Ther.* 2001;23:1478-1491.

For reprints and permission queries, please visit SAGE's Web site at <http://www.sagepub.com/journalsPermissions.nav>.