

Ultralow-Dose Estradiol Aids Some Over Others

BY ALISON PALKHIVALA
Contributing Writer

MONTREAL — Postmenopausal women with extremely low levels of bioavailable estradiol may benefit most from the bone-building effects of ultralow-dose hormone therapy, according to a study presented at the annual meeting of the International Bone and Mineral Society.

It remains unclear, however, whether these women are also more vulnerable to

the negative effects of hormone therapy. Although estrogen therapy has been shown to suppress bone turnover in postmenopausal women, the Women's Health Study revealed in 2002 that it may increase cardiovascular risk. Experts are exploring the possibility that a dose of estrogen exists, at least for some women, that is high enough to improve bone parameters but too low to affect cardiovascular risk.

Dr. Alison Huang, of the University of California, San Francisco, and colleagues

explored whether an ultralow dose of estradiol—only 0.014 mg/day delivered transdermally—could help postmenopausal women with very low or even undetectable estradiol levels. This group has a lower bone mineral density (BMD), increased bone turnover, and are at an increased risk for hip and vertebral fractures.

For the trial, 417 postmenopausal women were randomized to a 0.014-mg/day transdermal estradiol patch or placebo for 2 years. Bioavailable estradiol

levels were calculated as the ratio of total estradiol to sex hormone-binding globulin.

The investigators measured the levels of serum osteocalcin and bone-specific alkaline phosphatase (BSAP), markers of bone turnover, at 12 months. They also measured total hip and lumbar spine BMD at 24 months in women who adhered at least 80% to the study protocol.

Women in the lowest quintile of bioavailable estradiol had significantly greater drops in osteocalcin and BSAP than women in the highest quintile of bioavailable estradiol in response to therapy. In women in the lowest quintile, there was also a trend toward greater improvement in total hip BMD, versus women in the highest quintile. Spine BMD was unaffected. "Measurement of bioavailable estradiol levels identifies women for whom the ultralow-dose 0.014-mg/day transdermal estrogen therapy may have significant reductions in bone turnover," wrote the authors

During a press conference, however, Dr. Huang warned it is still not clear whether the women who appear to have the most to gain from estradiol therapy—those with very low baseline bioavailable estradiol levels—may also be the most vulnerable to the effects of hormone therapy on cardiovascular health. ■

Antiresorptives Cut Low-Trauma Fracture Risk

MONTREAL — Antiresorptive drugs reduce the risk of low-trauma, nonvertebral fractures in women over 50, and women with a prevalent fracture or frank osteoporosis have most to gain from these drugs, according to a study presented at the annual meeting of the International Bone and Mineral Society.

Dr. Suzanne Morin, of McGill University, Montreal, and colleagues obtained data from the Canadian Multicentre Osteoporosis Study (CaMos), in which more than 6,000 women over age 50 were randomly selected from across Canada. Demographics, medical history, and bone mineral density (BMD) were collected.

The researchers conducted a case-control analysis of the data. Women with self-reported incident low-trauma fractures, excluding fractures of the head, hands, feet or vertebrae, were matched with controls with respect to time in study, age, prevalent osteoporosis, prevalent vertebral deformity, prior clinical low-trauma fracture, and baseline BMD availability; 477 cases and 1,377 controls were included. Among cases, 37% were current users of antiresorptive agents (estrogen, bisphosphonates, selective estrogen receptor modulators [SERMs], and calcitonin) versus 41% of controls. Antiresorptive drug use was tied to an adjusted odds ratio of 0.68 for risk of a low-trauma fracture. Among those with a prevalent fracture or a BMD indicative of osteoporosis, OR was 0.58, versus 0.88 for women with neither of these risk factors.

—Alison Palkhivala

SYNVISC
HYLAN G-F 20

UNIQUE NATIONAL
HCPCS CODE

Q4084

BRIEF SUMMARY FOR THE PHYSICIAN (CONSULT PACKAGE INSERT FOR FULL PRODUCT INFORMATION)

CAUTION: Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

INDICATIONS Synvisc is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS • Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations. • Do not inject Synvisc in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

WARNINGS • Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence. • Do not inject Synvisc extra-articularly or into the synovial tissues and capsule. Local and systemic adverse events, generally in the area of the injection, have occurred following extra-articular injection of Synvisc. • Intravascular injections of Synvisc may cause systemic adverse events.

PRECAUTIONS General • The effectiveness of a single treatment cycle of less than three injections of Synvisc has not been established. • The safety and effectiveness of Synvisc in locations other than the knee and for conditions other than osteoarthritis have not been established. • Do not inject anesthetics or other medications into the knee joint during Synvisc therapy. Such medications may dilute Synvisc and affect its safety and effectiveness. • Use caution when injecting Synvisc into patients who are allergic to avian proteins, feathers, and egg products. • The safety and effectiveness of Synvisc in severely inflamed knee joints have not been established. • Strict aseptic administration technique must be followed.

• **STERILE CONTENTS.** The syringe is intended for single use. The contents of the syringe must be used immediately after its packaging is opened. Discard any unused Synvisc. • Do not use Synvisc if package is opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). **DO NOT FREEZE.** • Remove synovial fluid or effusion before each Synvisc injection.

• Synvisc should be used with caution when there is evidence of lymphatic or venous stasis in that leg. **Information for Patients** • Provide patients with a copy of the Patient Labeling prior to use. • Transient pain, swelling and/or effusion of the injected joint may occur after intra-articular injection of Synvisc. In some cases the effusion may be considerable and can cause pronounced pain; cases where swelling is extensive should be discussed with the physician. • As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged weight-bearing activities such as jogging or tennis following the intra-articular injection.

Use in Specific Populations • Pregnancy: The safety and effectiveness of Synvisc have not been established in pregnant women. • **Nursing mothers:** It is not known if Synvisc is excreted in human milk. The safety and effectiveness of Synvisc have not been established in lactating women. • The safety and effectiveness of Synvisc have not been established in children.

ADVERSE EVENTS

Adverse Events Involving the Injected Joint

Clinical Trials: A total of 511 patients (559 knees) received 1771 injections in seven clinical trials of Synvisc. There were 39 reports in 37 patients (2.2% of injections, 7.2% of patients) of knee pain and/or swelling after these injections. Ten patients (10 knees) were treated with arthrocentesis and removal of joint effusion. Two additional patients (two knees) received treatment with intra-articular steroids. Two patients (two knees) received NSAIDs. One of these patients also received arthrocentesis. One patient was treated with arthroscopy. The remaining patients with adverse events localized to the knee received no treatment or only analgesics.

Postmarket Experience: The most common adverse events reported have been pain, swelling and/or effusion in the injected knee. In some cases the effusion was considerable and caused pronounced pain. In some instances, patients have presented with knees that were tender, warm and red. It is important to rule out infection or crystalline arthropathies in such cases. Synovial fluid aspirates of varying volumes have revealed a range of cell counts, from very few to over 50,000 cells/mm³. Reported treatments included symptomatic therapy (e.g., rest, ice, heat, elevation, simple analgesics and NSAIDs) and/or arthrocentesis. Intra-articular corticosteroids have been used when infection was excluded. Rarely, arthroscopy has been performed. The occurrence of post-injection effusion may be associated with patient history of effusion, advanced stage of disease and/or the number of injections a patient receives. Reactions generally abate within a few days. Clinical benefit from the treatment may still occur after such reactions.

The clinical trials described above included 38 patients who received a second course of Synvisc injections (132 injections). There were twelve reports in nine patients (9.1% of injections, 23.7% of patients) of knee pain and/or swelling after these injections. Reports of two additional clinical trials in which patients received repeated courses of Synvisc treatment have appeared during the post-marketing period. One of these trials included 48 patients who received 210 injections during a second course of Synvisc treatment; the other contained 71 patients who received 211 injections during a second course of Synvisc treatment. A total of 157 patients have received 553 injections in the three clinical trials of repeated courses of Synvisc treatment. The reports in these trials describe a total of 48 reports of adverse events localized to the injected knee in 35 patients that occurred after injections that patients had received during their second course of treatment. These adverse events accounted for 6.3% of injections in 22.3%

of patients as compared to 2.2% of injections in 7.2% of patients in a single course of Synvisc injections. In addition, reports of two retrospective studies during the post-marketing period have described adverse events localized to the injected knee that have occurred after 4.4% and 8.5% of injections that patients had received during one or more repeated courses of Synvisc treatment.^{2,3} Intra-articular infections did not occur in any of the clinical trials and have been reported only rarely during clinical use of Synvisc.

OTHER ADVERSE EVENTS

Clinical Trials: In three concurrently controlled clinical trials with a total of 112 patients who received Synvisc and 110 patients who received either saline or arthrocentesis, there were no statistically significant differences in the numbers or types of adverse events between the group of patients that received Synvisc and the group that received control treatments.

Systemic adverse events each occurred in 10 (2.0%) of the Synvisc-treated patients. There was one case each of rash (thorax and back) and itching of the skin following Synvisc injections in these studies. These symptoms did not recur when these patients received additional Synvisc injections. The remaining generalized adverse events reported were calf cramps, hemorrhoid problems, ankle edema, muscle pain, tonsillitis with nausea, tachyarrhythmia, phlebitis with varicosities and low back sprain.

Postmarket Experience: Other adverse events reported include: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with Synvisc injection. These medical events occurred under circumstances where causal relationship to Synvisc is uncertain. (Adverse events reported only in worldwide postmarketing experience, not seen in clinical trials, are considered more rare and are italicized.)

DETAILED DEVICE DESCRIPTION

Each syringe of Synvisc contains:

Hylan polymers (hylan A + hylan B)	16 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate	0.32 mg
Sodium dihydrogen phosphate monohydrate	0.08 mg
Water for injection	q.s. to 2.0 mL

HOW SUPPLIED

Synvisc is supplied in a 2.25 mL glass syringe containing 2 mL Synvisc.

Product Number: 58468-0090-1 3 disposable syringes

The contents of the syringe are sterile and nonpyrogenic.

DIRECTIONS FOR USE

Synvisc is administered by intra-articular injection once a week (one week apart) for a total of three injections.

Precaution: Do not use Synvisc if the package has been opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). **DO NOT FREEZE.**

Precaution: Strict aseptic administration technique must be followed.

Precaution: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.

Precaution: Remove synovial fluid or effusion before each Synvisc injection.

Do not use the same syringe for removing synovial fluid and for injecting Synvisc, but the same needle should be used.

Take particular care to remove the tip cap of the syringe and needle aseptically.

Twist the gray tip cap before pulling it off, as this will minimize product leakage.

Inject Synvisc into the knee joint through an 18 to 22 gauge needle.

To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

Precaution: Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the tip of the syringe.

Do not inject anesthetics or any other medications intra-articularly into the knee while administering Synvisc therapy. This may dilute Synvisc and affect its safety and effectiveness.

Precaution: The syringe containing Synvisc is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate syringe must be used for each knee. Discard any unused Synvisc.

This brief summary is based upon the current circular, 70230602, revised November 15, 2004.

References: 1. Raynaud JP, Bellamy N, Goldsmith CH, Tugwell P, Torrance GW, Pericak D, et al. (2002). An evaluation of the safety and effectiveness of repeat courses of hylan G-F 20 for treating patients with knee osteoarthritis. Osteoarthritis Research Society International, 2002 OARSI World Congress on Osteoarthritis, Sydney, Australia [Paper reference #PS128]. Presentation on File. 2. Leopold SS, Warne WJ, Pettis PD and Shott S. (2002). Increased frequency of acute local reaction to intra-articular Hylan G-F 20 (Synvisc) in patients receiving more than one course of treatment. *J Bone Joint Surg.* 2002;84-A(9): 1619-1623. 3. Waddell DD, Estey DJ and Bricker D. (2001). Retrospective tolerance of Hylan G-F 20 using fluoroscopically-confirmed injection and effectiveness of retreatment in knee osteoarthritis. Proceedings of the American College of Rheumatology Annual Meeting 2001. Presentation on File.

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