Meniscectomy Associated With Knee Osteoarthritis

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SAN DIEGO — Patients who underwent meniscectomy had a 10- to 18-fold increased likelihood of developing tibiofemoral osteoarthritis in the operated knee at follow-up of 15-22 years, compared with a group of controls, results from a large Swedish study demonstrated.

Moreover, these patients were significantly more likely than controls to develop concomitant patellofemoral osteoarthritis (OA) in the index knee and tibiofemoral OA in the contralateral, nonoperated knee, Dr. Stefan Lohmander reported at a symposium sponsored by the International Cartilage Repair Society.

"A meniscus tear is not simply a meniscus tear," said Dr. Lohmander, of the department of orthopedics at Lund (Sweden) University Hospital. "We need to differentiate between a tear in a healthy meniscus in a normal joint and a tear in a degenerated meniscus in a joint that may already be developing OA. We suggest that a degenerative meniscus lesion is an early signal of OA susceptibility. As a consequence, postinjury OA as a catch-all term for the OA associated with this kind of meniscus injury is not correct. The same disease process that leads to cartilage damage in the OA joint can even earlier lead to a damaged meniscus, prone to a tear.'

He went on to speculate that patients with meniscus lesions "are actually young

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Gastritis

Metabolic and Nutritional Disc

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Dizziness Vertigo Nerve Root Lesion

patients with old knees. The symptoms of their OA actually start at the meniscus, and the meniscus tear is just a signal event in the development of OA."

In an effort to determine the long-term consequences of meniscal injury and repair, he and his associates studied a group of 319 patients with isolated meniscus lesions who had no radiographic OA at index arthroscopy and no previous surgery. Postoperative follow-up ranged from 15 to 22 years and included standardized radiographs, validated questionnaires, functional tests, and biomarkers.

The average patient age at assessment was 54 years, and most (79%) were men. The mean body mass index of patients was 26 kg/m², and most (80%) had undergone medial meniscectomy.

A control group of 68 age-matched, uninjured patients was used as a reference.

At 15- to 22-year follow-up, 45% of patients who underwent medial meniscectomy and 57% of patients who underwent lateral meniscectomy had tibiofemoral



Tibiofemoral OA developed in this contralateral, nonoperated knee.

OA in their index knee, which translated into adjusted odds ratios of 9.5 and 18.3,

In addition, 19% of patients who underwent medial meniscectomy and 27% of patients who underwent lateral meniscectomy had patellofemoral OA in their index knee at follow-up, which translated into adjusted odds ratios of 2.6 and 5.3, respectively.

Finally, 22% of patients who underwent medial meniscectomy and 21% of patients who underwent lateral meniscectomy had tibiofemoral OA in their nonoperated contralateral knee at the 15- to 22-year followup, which translated into adjusted odds ratios of 3.5 and 4.4, respectively. Dr. Lohmander noted that this increased risk of OA in the "other knee" may be another sign that these individuals have a higher-than-average risk for OA in general.

There was no major difference in the OA risk for those who had subtotal removal of their meniscus and those who had only a partial removal by surgery. There are no published randomized studies to support the suggestion that meniscal repair or retransplantation can prevent future OA development.

Dr. Lohmander called for more controlled, randomized, blinded prospective trials to evaluate the long-term outcome of meniscal injury and repair.

BONIVA® (ibandronate sodium) TABLETS BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

- CONTRAINDICATIONS

 Known hypersensitivity to BONIVA or to any of its excipients
 Uncorrected hypocalcemia (see PRECAUTIONS: General)
 Inability to stand or sit upright for at least 60 minutes
 (see DOSAGE AND ADMINISTRATION)

 (MARDINING)

Inability to stand or sit upright for at least 60 minutes (see DOSAGE AND ADMINISTRATION)

WARNINGS

BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS: General

Mineral Metabolism: Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects: Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment: BONIVA is not recommended for use in patients with severe renal impairment esteratinine clearance <30 mL/min).

Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients with postmenopausal osteoprosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, adoliberapy, corticosteroids), and co-morbid disorders (eg, anemis, cagalulopathy, infection, pre-existing dental disease). Most reported cases have been in patients with postmenopausal osteoprosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, adoliberapy, corticosteroids), and co-morbid disorders (eg, anemis, adaptions treated orally. For patients with disease). Most reported cases have been in patients treated orally. For patients with disease in patients treated orally. For patients with disease in the management

patient based on individual benefit/risk assessment. Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/ or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include BONINA (libandronate sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug, Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. In placebo-controlled studies with BONINA, the percentages of patients with these symptoms were similar in the BONINA and placebo groups.

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Information for Patients: Patients should be instructed to read the Patient Information Leaflet carefully before taking BONNA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

BONNA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medications containing multivalent cations (including natacids, supplements or vitaminis).

-To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONNA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or stitting in an upright position. Patients should not lie down for 60 minutes after taking BONNA.

-Patin water is the only drink that should be taken with BONNA Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.

-Patients should not chew or suck the tablet because of a potential for corpharyngeal ulceration.

oropharyngeal ulceration.

The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).

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If the once-monthly dose is missed, and the patient's bowlavi Su-villa guides with the patient's hould be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

-The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONIVA day is take their tablet. The patient must wait until their next scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule. Patients should receive supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.

absorption of BUNIVA.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such an ew or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

new or worsening dysphagia, pain on swallowing, retrostemal pain, or heartburn. **Drug Interactions**Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONINA BONIVA should be taken at least 50 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see **PRECAUTIONS: Information for Patients**).

Patients

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commonitories assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.

Impairment of Fertility: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended at an oral dose of 15 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

Pregnancy: Pregnancy Category C: In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (3 times human exposure at the recommended daily oral dose of 2.5 mg or 1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended doile, or 16 mg/kg/day (45 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). was likely related to maternal dysloca. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dysloca and periparturient mortality in any of the treated groups (16 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation loss was observed in rats breated from 14 days before mating through teaching were observed at doses scausing maternal dysloca and periparturient mortality, are observed at 16 days selfect related to inhibition of skeletal calcium mobilization resulting in hypocalc

of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis: Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIWA 2.5 mg daily group. The percentage of patients who withdrew from treatment due adverse events was approximately 17% in both the BONIWA 2.5 mg daily group and the placebo group. Overall, and according to body system, there was no difference between BONIWA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

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Table 1 lists adverse events from the Treatment and Prevention Studies reported in 2% of patients and in more patients treated daily with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality. Table 1: Adverse Events Occurring at a Frequency 2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Rocky System

Placebo

Unary Tract Infection 4.2 5.5

Once-Monthly Dosing: In a 1-year, double-blind, multicenter study comparing BONIWA 2.5 mg once daily and BONIWA 150 mg once monthly in women with postmenopausal esteoporosis, the overall safety and folierability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the BONIWA 2.5 mg daily group and 7.1% in the BONIWA 150 mg once-monthly group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the BONIWA 2.5 mg daily group and 7.8% in the BONIWA 150 mg once-monthly group. Table 2 lists the adverse events reported in 2% of patients without attribution of causality.

Table 2: Adverse Events with an Incidence of at Least 2% in Patients Treated with BONIWA 150 mg Once Monthly or 2.5 mg Daily

Body System/Adverse Event

BONIWA

2.5 mg daily

BONIWA

50 mg monthly

6 mg-395)

6 mg-396) Vascular Disorders 7.3 6.3

3.3

2.3

were noted for the 150 mg once-monthly administration in the 1-year study.

OVERDOSAGE: No specific information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspessia, esophagilis, gastritis, or ulcer. Milk or antacids should be given to bind BÖNIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dilaysis would not be beneficial.

Pharmaceuticals

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