Letters to the Editor

Send letters to Kenneth W. Lin, MD, Associate Deputy Editor for *AFP* Online, e-mail: afplet@aafp.org, or 11400 Tomahawk Creek Pkwy., Leawood, KS 66211-2680.

Please include your complete address, e-mail address, and telephone number. Letters should be fewer than 400 words and limited to six references, one table or figure, and three authors.

Letters submitted for publication in *AFP* must not be submitted to any other publication. Possible conflicts of interest must be disclosed at time of submission. Submission of a letter will be construed as granting the American Academy of Family Physicians permission to publish the letter in any of its publications in any form. The editors may edit letters to meet style and space requirements.

Denosumab Is an Option for Treatment of Osteoporosis

Original Article: Denosumab (Prolia) for Treatment of Postmenopausal Osteoporosis

Issue Date: February 15, 2012

Available at: http://www.aafp.org/afp/2012/0215/p334.html

TO THE EDITOR: This drug review deserves a response. Safety data for denosumab (Prolia) are available from studies with five years of follow-up (an international, randomized, double-blind, placebo-controlled phase 3 trial[1,2]) and six years of follow-up (a phase 2 extension study[3]). Overall, there was no difference in the rate of infections between the treatment and placebo groups during the first three years of the trial, although serious adverse events of cellulitis were more common in the treatment group (4.1 versus 3.4 percent). However, in the phase 2 extension study, the rate of serious infections in years 4 through 6 was similar to that in the placebo group in years 1 through 3 (1.3 per 100 subject-years).

In addition to meeting the primary end point of reduced vertebral fractures at three years, study participants who received denosumab had a 61 percent reduction in their risk of vertebral fracture at one year, and a persistent reduction of vertebral fractures through five years (1.1 percent incidence).[1,2]

The price of denosumab varies. One must consider the issue of compliance with therapy and the medical costs that occur because of nonadherence to a prescribed regimen (including treatment of fractures). A longitudinal cohort study of osteoporosis therapy showed that patients who reported greater satisfaction with treatment were more likely to continue osteoporosis therapy.[4] The 24-month Denosumab Adherence Preference Satisfaction randomized crossover study reported that 92 percent of women preferred denosumab to alendronate (Fosamax), and that 93 percent of participants receiving denosumab were compliant with treatment for one year, compared with 63 percent of those receiving alendronate.[5]

The article notes that denosumab can be used in patients with renal impairment. Women who are at highest risk of hip fractures—those 80 years and older who have osteoporosis—have a 54 percent incidence of severe renal compromise (creatinine clearance less than 35 mL per minute per 1.73 m^2 [0.58 mL per second per m^2]).[5]

Consistent with the American Association of Clinical Endocrinologists guideline,[6] I suggest that denosumab is an appropriate first-line choice for the treatment of postmenopausal osteoporosis, especially in women with impaired renal function.

CHRISTINE SIMONELLI, MD
Woodbury, Minn.
E-mail: msciao@comcast.net

Author disclosure: Dr. Simonelli is on the speaker's bureau for and has received research support from Amgen, the manufacturer of Prolia, as well as from Novartis and Eli Lilly and Company.

REFERENCES

1. Cummings SR, San Martin J, McClung MR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis [published correction appears in *N Engl J Med.* 2009;361(19):1914]. *N Engl J Med.* 2009;361(8):756-765.
2. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. *J Bone Miner Res.* 2012;27(3):694-701.
3. Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab.* 2011;96(2):392-402.
4. Wade SW, Curtis JR, Yu J, et al. Medication adherence and fracture risk among patients on bisphosphonate therapy in a large United States health plan. *Bone.* 2012;50(4):870-875.
5. Freemantle N, Satram-Hoang S, Tang ET, et al.; DAPS Investigators. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012;23(1):317-326.
6. American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. https://aace.com/files/osteo-guidelines-2010.pdf. Accessed November 12, 2012.

IN REPLY: I appreciate Dr. Simonelli's comments regarding the drug review on denosumab for postmenopausal osteoporosis. The longest-term safety data available are from the use of denosumab in approximately 80 patients for a total of eight years in a phase 2 extension study.[1] Other long-term data are from use in approximately 2,000 patients for a total of six years.[2] The data from both of these studies showed continued increases in bone mineral density and a continued low incidence of vertebral and nonvertebral fractures.[1,2] Although it is reassuring that the incidence of serious adverse effects, such as infections and malignancies, did not increase with continued exposure to denosumab, these effects were consistently reported. The overall incidence of infection was similar between the denosumab and placebo groups, but the treatment group had more serious infections that required hospitalization, as well as endocarditis and skin, abdominal, urinary tract, and ear infections.[3] Additionally, four cases of osteonecrosis of the jaw were reported in the extension study.[2] Although this type of information is needed to determine the long-term effectiveness and safety of denosumab, it should be interpreted with caution. Rare but serious events need to be carefully followed because they may become more common with widespread use in a more heterogeneous population.

I do not find it surprising that the study referenced by Dr. Simonelli found better compliance with denosumab compared with the once-weekly oral bisphosphonate alendronate.[4] Annual intravenous zoledronic acid (Reclast) would have been a better comparison.

Renal impairment is not listed as a contraindication to denosumab use and no dose adjustment is required in patients with renal impairment. However, patients with creatinine clearance of 50 mL per minute per 1.73 m^2 (0.83 mL per second per m^2) or less have an increased risk of developing hypocalcemia.[5] Most bisphosphonates are not recommended in patients with creatinine clearance of less than 35 mL per minute per 1.73 m^2 because of limited data in this population. A recent study that examined the relationship between denosumab use and degree of renal impairment found that renal impairment was not associated with a decrease in effectiveness or an increase in adverse effects.[6] However, most patients in this analysis had an estimated glomerular filtration rate of at least 30 mL per minute per 1.73 m^2; only 73 of the 4,069 patients had an estimated glomerular filtration rate of 15 to 29 mL per minute per 1.73 m^2; and no patients had stage 5 chronic kidney disease.[6]

GRETCHEN L. JOHNSON, PharmD, BCPS
Winchester, Va.
E-mail: gjohnson@su.edu

Author disclosure: Dr. Johnson owns stock in Merck & Co.

REFERENCES

1. Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab.* 2011;96(2):394-402.
2. Brown JP, Bone HG, Chapurlat R, et al. Six years of denosumab treatment in postmenopausal women with osteoporosis: results from the first three years of the FREEDOM extension. https://acr.confex.com/acr/2011/webprogram/Paper24541.html. Accessed May 16, 2012.
3. Cummings SR, San Martin J, McClung MR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis [published correction appears in *N Engl J Med.* 2009;361(19):1914]. *N Engl J Med.* 2009;361(8):756-765.
4. Freemantle N, Satram-Hoang S, Tang ET, et al.; DAPS Investigators. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012;23(1):317-326.
5. Prolia [package insert]. Thousand Oaks, Calif.: Amgen Inc.; 2010. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf. Accessed April 9, 2012.
6. Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res.* 2011;26(8):1829-1835.

Effectiveness of Glucosamine and Chondroitin for Osteoarthritis

Original Article: Osteoarthritis: Diagnosis and Treatment

Issue Date: January 1, 2012

Available at: http://www.aafp.org/afp/2012/0101/p49.html

TO THE EDITOR: This article repeated a common misconception about the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), interpreting it as showing that the combination of glucosamine and chondroitin is effective for treating moderate to severe osteoarthritis.[1] The study found that glucosamine and chondroitin, separately or in combination, were not more effective than placebo. Only one of 10 subgroups showed statistically significant results, and these were for moderate to severe arthritis. With 10 subgroups, it is likely that chance alone would produce false-positive results in one of these groups. The authors of the study warned that it was not powered to differentiate among subgroups, and that no clinical recommendations should be made based on that finding.[1]

The *AFP* article recommends a combination of glucosamine and chondroitin as the third step in a stepped-care approach for the treatment of osteoarthritis. This is not justified by the evidence. In addition, the rationale is suspect because glucosamine and chondroitin are produced by the body. The amount added by taking supplements is only a minuscule fraction of what is already present. These are not essential nutrients like vitamins, of which taking a small amount is likely to make a large difference.

HARRIET A. HALL, MD
Puyallup, Wash.
E-mail: harriet.hall@comcast.net

Author disclosure: No relevant financial affiliations to disclose.

REFERENCE

1. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med.* 2006;354(8):795-808.

IN REPLY: I appreciate Dr. Hall's thoughtful comments. She is correct that the GAIT trial did not demonstrate a beneficial effect of glucosamine combined with chondroitin in most patients with osteoarthritis of the knee. However, there was a statistically significant benefit in the subgroup of patients with moderate to severe osteoarthritis. Of the 1,583 patients in the trial, 354 (22 percent) fell into this subgroup.[1]

I find that forest plots are useful in helping me visualize the effectiveness of various treatments.[2] There is a set of forest plots in *Figure 2* of the GAIT trial article.[1] The figure shows that the combination of glucosamine and chondroitin was more effective than placebo for moderate to severe osteoarthritis based on two scoring systems: the Western Ontario and McMaster Universities Osteoarthritis Index, and the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International. These are well-accepted clinical measures, and the differences reached statistical significance in each case.[1]

Dr. Hall states that "with 10 subgroups, it is likely that chance alone would produce false-positive results." However, if statistical significance is defined as a *P* value of .05 or less, that corresponds to a rate of one in 20 being false-positive by chance alone, not one in 10.

Additional studies are needed to confirm the effectiveness of glucosamine and chondroitin for the treatment of osteoarthritis. For now, I stand by the recommendation for a brief trial of combined glucosamine and chondroitin in patients who have progressed to moderate or severe osteoarthritis, although the stepped-care approach in my article should state that this is only for osteoarthritis of the knee, per the evidence in the GAIT trial.

KEITH SINUSAS, MD
Middletown, Conn.
E-mail: ksinusas@midhosp.org

Author disclosure: No relevant financial affiliations to disclose.

REFERENCES

1. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med.* 2006;354(8):795-808.
2. Yeh J, D'Amico F. Forest plots: data summaries at a glance. *J Fam Pract.* 2004;53(12):1007.

Correction

Error in when to perform a test of cure after gonorrhea treatment. In *AAFP News Now: AFP* Edition (September 15, 2012, p. 497), the second item on page 498, "CDC Discourages Use of Cefixime in Update on Gonorrhea Treatment," contained an error in regard to when patients should be tested for cure after gonorrhea treatment. The statement incorrectly implied that all patients with gonorrhea should be tested for cure one week after treatment. However, the Centers for Disease Control and Prevention (CDC) guidelines indicate that a test of cure should be performed only when a treatment regimen other than the preferred regimen is used, or when patients continue to have symptoms despite treatment. The statement should have read: "Patients with persistent symptoms after treatment, and patients treated with an alternative regimen (i.e., cefixime plus azithromycin or doxycycline; or a single dose of azithromycin) should be tested for cure one week after treatment." The online version has been corrected.

Clarification

Update to HEADSS assessment. In the Curbside Consultation "Care of a Sexually Active Adolescent" (September 1, 2012, p. 457), the third line of the first paragraph under the "3. Address Emergent Issues" header (p. 458) mentioned the HEADSS assessment. In 2004, HEADSS was expanded to HEEADSSS, focusing on assessment of the home environment, education and employment, eating, peer-related activities, drugs, sexuality, suicide/depression, and safety from injury and violence. The online version of this Curbside Consultation has been updated. ■