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New FDA Labeling Suggests Stopping bisphosphonates after 3 to 5 years in low risk patients

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Osteoporosis is a disease associated with a reduction in bone mass and an increase in skeletal fragility. It affects 10 million Americans; another 34 million are considered at risk.[1]

Bisphosphonates have been shown to be effective in reducing the risk of osteoporotic fragility fractures, and are widely prescribed for that purpose. During the period from 2005 to 2009, 150 million prescriptions were dispensed in the United States outpatient setting for three popular oral bisphosphonates: alendronate (Fosamax®), risedronate (Actonel®) and ibandronate (Boniva®) in the US. Of these 150 million prescriptions, 5.1 million patients over the age of 55 received a prescription for bisphosphonates in 2008.[2]

The long-term safety and efficacy of bisphosphonate therapy for osteoporosis was evaluated by the FDA Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management committee. Rare but serious adverse events associated with long-term bisphosphonate use have been identified in post-marketing surveillance reports. Cases have included atypical femur fractures, osteonecrosis of the jaw, and esophageal cancer. The Committees jointly recommended that bisphosphonate labeling be updated.[1]

It is worth noting that bisphosphonates significantly accumulate in skeletal binding sites because the receptors are essentially unsaturable. A reservoir is formed and drug is continuously released for months to years, even after the drug is discontinued. This makes it possible for clinicians to consider a 'drug holiday' for patients on bisphosphonate therapy after a certain period of time.[3]

In September of 2011, the FDA held a hearing to review the long term safety and efficacy of bisphosphonates. Consequently, they recommended that clinicians reevaluate the need for continued bisphosphonate therapy beyond 3-5 years. They also stated that in patients at high risk, a drug holiday may not be advisable.[3] Currently, all bisphosphonates approved by the FDA for the treatment of osteoporosis contain the following "Important Limitation of Use" statement: "The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis." FDA scientist Theresa Kehoe, MD, testified that the agency's own analysis concluded that there was no clear benefit or evidence of harm in women who continued bisphosphonate therapy after five years, nor was there a "clear and consistent" reduction in fracture risk.[4]

The committee recommended that the decision to continue treatment with bisphosphonates should be based on individual assessment of risks and benefits and patient preference. They indicated that patients that are at low risk for fractures, meaning those that are younger and without a history of fracture and a bone mineral density (BMD) near normal range, may be good candidates for bisphosphonate therapy lasting for 3-5 years. On the other hand, patients at increased risk of fractures, such as older patients with a history of fractures, or bone mineral density in the osteoporotic range, may benefit from continued bisphosphonate therapy.[2]

A double-blind, randomized, placebo-controlled trial called the Fracture Intervention Trial (FIT) was conducted to study the effects of alendronate treatment on fracture risk among 6459 postmenopausal women with low BMD. FIT enrolled 3236 women on alendronate who were followed for an average of 3.8 years. The investigators sought to determine if additional therapy with alendronate beyond this period would result in preservation or further gains in BMD following alendronate discontinuation.

Subsequently, they conducted a follow-up, double-blind, placebo-controlled extension trial to FIT, [FIT long-term extension (FLEX)] in which 1099 (39%) women from the FIT trial who had used alendronate for an average of 5 years were re-randomized. To be eligible for the FLEX study, women had to have been on alendronate for at least 3 years. Women were randomly assigned to alendronate 10 mg/day (30%) (n=333), alendronate 5 mg/day (30%) (n=329) or placebo (40%) (n=437) for a duration of 5 years. Randomization was stratified by fracture risk; women with at least one radiographic morphometric vertebral deformity identified by the end of FIT and/or who experienced a clinical fracture during FIT were

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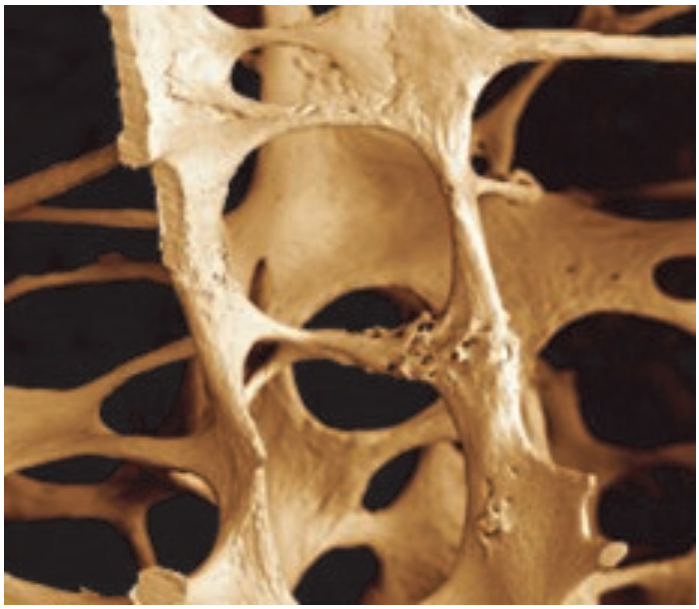
assigned to the high-risk stratum. All participants were strongly encouraged to take a daily supplement containing calcium (500 mg) and vitamin D (250 IU). The percentage of participants receiving the supplement was 97.5%.[5]

BMD of the total hip and its sub-regions, together with the posterior-anterior lumbar spine, and the total body was measured at the FLEX baseline using DXA and then repeated at 36 months using the same densitometers. At FLEX baseline, the average age was 73 years and 97% of participants identified themselves as white. The average duration of alendronate treatment was 5 years. The mean BMD at the total hip corresponded to a T score of -1.9, mean BMD at the femoral neck corresponded to a T score of -2.2, and mean BMD at the lumbar spine corresponding to a T score of -1.3. Thirty-eight percent of participants were assigned to the high fracture risk stratum.[5]

The study showed lumbar spine BMD increased in the alendronate group compared to the placebo group (5.26% vs. 1.52%), a mean difference of 3.74% (95% CI, 3.03%-4.45%; P<0.001). Similarly, in terms of total body and forearm BMD, there was a statistically significant mean difference between the alendronate (1.28%) and placebo group (2.01%) with (P<0.001 for both). In regards to nonvertebral fractures, no significant difference was found between the pooled alendronate group and the placebo group. The percentage of fractures was 19% with placebo vs 18.9% with alendronate. Although there was a statistically significantly lower risk of clinical vertebral fractures in the alendronate group (5.3% with placebo vs 2.4% with alendronate; RR, 0.45; 95% CI, 0.24-0.85), post hoc subgroup fracture analysis did not indicate any significant trends with lower BMD or prevalent vertebral fractures at FLEX baseline for either nonvertebral or clinical vertebral fractures. However, both nonvertebral and clinical fractures were increased with lower baseline BMD or prevalent fractures. The RR reduction in those who continued to take alendronate was 55% and the absolute risk reduction was 2.9%. It is clinically significant to note that women with a history of vertebral fractures or very low BMD are at much higher risk of future vertebral fractures and have a higher absolute benefit for prevention of vertebral fractures. The authors of the study report that gains in BMD appeared to be better maintained after discontinuation of drugs in the bisphosphonate class, including alendronate, risedronate, pamidronate and eidronate than with seen in patients treated with estrogen, raloxifene or intermittent parathyroid hormones.[6]

Some of the limitations of this study include 1) limited power to detect modest differences in fracture rates, as reflected in wide CIs for fracture outcomes, 2) many FLEX participants were not diagnosed as having osteoporosis, either because they entered the FIT trial without osteoporosis or because they experienced gains in BMD during FIT trial; thus further reducing the power to detect a difference between groups, if one exists, 3) dose and duration was not consistent throughout the trial, 4) the average age of the participants at baseline was 73 years, causing the results to be non-generalizable to the general population (i.e. younger women, men or the very elderly).



During the trial, there were no reports of osteonecrosis of the jaw. There were no significant between-group differences in upper gastrointestinal tract or serious upper gastrointestinal adverse events.

The authors concluded that continuation of alendronate therapy for 10 years maintained both bone mass and reduced bone remodeling compared with discontinuation after 5 years. With that being said, even those who discontinued therapy after 5 years saw their BMD remain at or above baseline values and bone turnover was still somewhat reduced. Discontinuation of alendronate after 5 years did not increase the risk of nonvertebral fractures over the next 5 years. However, the risk of clinically diagnosed vertebral fractures was significantly increased among those who discontinued therapy. These results suggest that women at high risk of clinical vertebral fractures, such as those with vertebral fractures or very low BMD, may benefit by continuing bisphosphonate therapy beyond 5 years; and that discontinuation of alendronate after 5 years in women at low risk of fractures does not significantly increase fracture risk.[6]

The results of this study mirrors the recommendations of the FDA that patients on bisphosphonate therapy should be reevaluated after 3-5 years of therapy. Appropriateness of continued therapy based on an individual's risks and benefits should be assessed during the reevaluation period. Patients at high risk of future vertebral fractures, such as patients with existing vertebral fractures, or patients with low BMD may benefit from continued bisphosphonate therapy.

<Click here for references>

For better or for not-worse: A primer on the non-inferiority study

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A patient is taking warfarin prophylactically for a stroke or an embolism. The treatment is working well; however the patient complains about how many visits they have to make to get their INR tested. You have heard of newer anticoagulation drugs with fewer monitoring parameters, but how can you know if they are as effective as warfarin?

Making a direct comparison: Non-inferiority trials (NI) compare a new drug to the current standard of care and determine whether it is no worse, within an acceptable margin. Directly comparing the two treatments allows researchers to determine if the new treatment works just as effectively, while simultaneously providing comparative data about the side effects, costs, and monitoring parameters.

The good and the bad: NI trials use an active control instead of placebo in the comparison. This method is useful because it enables investigators to study the efficacy of a new treatment or medication without denying necessary treatment to patients when an established treatment exists. However, there is a major caveat with removing the placebo group. In order to assume efficacy of the active control, the study population used in an NI trial must be as similar as possible to the populations used in historical data for the active control.

The most controversial aspect of the NI study is the non-inferiority margin, which serves as the threshold of allowable inferiority for the drug being studied. The margin is meant to represent the magnitude of statistical difference that can exist between the two drugs without having a significant clinical impact. Since NI trials are fairly new, no standard method for determining the NI margins exist. The researcher prospectively sets the margin (an educated opinion of acceptable confidence intervals), describes the process by which it was determined, and allows the reader to exercise their clinical judgment.

Conclusion: Non-inferiority trials are conducted more frequently in clinical research than ever before. New treatments are marketed as potential replacements for a standard of care by demonstrating 'non-inferior' efficacy and possessing other beneficial characteristics. Only through meticulous examination can an educated decision based on reliable results justify a promising change of therapy.

<Click for References>

Placebo-Controlled Superiority Trials	Active-Comparator Non-Inferiority Trials
Assumes treatments are equally effective; baseline characteristics of groups should be equal	Assumes treatments are inherently different; baseline characteristics of groups should be equal and similar to
ONE or TWO sided tests of the null hypothesis utilize basic biostatistical tests	ONE sided tests of the reversal of the null hypothesis requires pre-specified setting of the "margin of difference" which introduces potential bias
Attention to ethics of withholding effective treatment from one population of patients	No withholding of effective treatment in active control group

New treatment available for systemic juvenile idiopathic arthritis

Kevin Olivieri, PharmD Candidate; Michael Mueller, PhD

Until recently, no FDA approved treatment was available for systemic juvenile idiopathic arthritis (sJIA), a disease from which an estimated 250,000 children suffer in the US alone.[1] On May 10, 2013 the biologic interleukin-1 beta antagonist Ilaris®, (canakinumab) was approved for the treatment of sJIA in children aged 2 years and older. Canakinumab has been on the market since 2009 when it was approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children older than 4 years.[2,3]

Interleukin-1 beta is a cytokine and a potent mediator of response to infection and injury. It is produced mainly by monocytes and macrophages, and induces various inflammatory and immune responses.[4] Blocking this inflammatory pathway reduces the amount of pro-inflammatory mediators in the blood stream, decreasing the likelihood of fever, arthritis and rash.

sJIA is characterized by an evanescent erythematous skin rash, and a fever > 39° C for longer than 2 weeks that appears either once or twice a day at approximately the same time each day. Diagnosis requires at least one of the following: lymphad-enopathy, pericarditis, pleuritis, or hepatosplenomegaly, in children aged 16 years or younger. The etiology of sJIA is unknown. There are no specific lab tests for sJIA, but patterns of abnormalities have been identified including high C-reactive protein, high erythrocyte sedimentation rates, neutrophilia, thrombocytosis, and a hypochromic, microcytic anemia.[5]

Previously treatment was 24-hour non-steroidal anti-inflammatory drugs (NSAIDs) coverage for mild sJIA, and

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corticosteroids in severe cases, Minimal efficacy has been demonstrated with disease modifying drugs, such as methotrexate and etanercept.[6,7]

Canakinumab was approved for sJIA based on two clinical trials. Eligible patients had a diagnosis of sJIA and were between the ages 2 to 19 years. Patients taking up to 1mg/kg/day of prednisone and stable doses of NSAIDs were included in the study. Exclusion criteria included use of another biologic agent or of a disease-modifying drug without the proper washout period of 5 half-lives. Other exclusion factors included active tuberculosis infection, live-virus activation within 3 months before enrollment, active or recurrent bacterial, fungal or viral infection, and diagnosis of macrophage activation syndrome. Patients who did not have a fever were also excluded from the trials.[5,8]

Trial 1 was a 29-day, single-dose, randomized double-blind, placebo-controlled study, with 84 participants. Patients who had a response to canakinumab at day 15 were automatically enrolled in trial 2 at day 29. Clinical responses were assessed according to an adaptation of the JIA American College of Rheumatology 30 response, which is defined as absence of fever plus 30% improvements in three or more of the JIA core set with no more than one variable worsening. Assessment was based on the number of participants whose condition improved more than 30% and had an absence of fever.[5] All patients treated with canakinumab were fever free at Day 3 compared to 87% of patients treated with the placebo. No patients discontinued the study due to an adverse event.[2,5]

Trial 2 was a randomized, double-blind, placebo controlled, withdrawal study of flare prevention. The first part was an open -label phase in which eligible patients were treated with canakinumab every 4 weeks for 12 to 32 weeks. The objective of the withdrawal phase of the trial was to observe the median time to flare event, comparing placebo and canakinumab. 74% of patients in the canikinumab group had no flare, compared to 25% of patients in the placebo group. The second part of this study was to determine whether patients previously using glucocorticoids could be tapered down by at least 25%. 45% of patients were able to taper steroid use from 0.24 mg/kg/day to 0.05 mg/kg/day, and 33% of patients were able to discontinue glucocorticoid use completely.[5] Overall six patients withdrew from the placebo group due adverse events, three due to serious immunologic events; three due to less severe side effects (vomiting, rash and uveitis).[5]

Careful consideration should be used before prescribing canakinumab to patients at an increased risk of infection. Patients should be counseled not to use any other Interleukin-1 blocking drug, or anti-tissue necrosis factor drug while taking canakinumab. Patients who have chronic or active infection, including HIV, hepatitis B or hepatitis C, were excluded from the trials and patients should be screened for tuberculosis infection before beginning canakinumab. Any patient considering canakinumab should consult their physician regarding their vaccination history. Patients should be informed of signs and symptoms of macrophage activation syndrome (MAS), which is a life-threatening disorder that must be aggressively treated. Eleven of the 201 sJIA patients in the trials who were treated with canakinumab experienced MAS.[2,5,8]

Most common side effects reported in phase three trials were abdominal pain, cough, headache, nasopharyngitis, pyrexia, upper respiratory tract infection, and vomiting.[6] No drug-drug interaction studies have been conducted on canakinumab, nor has any pregnancy data been reported.[2] To date, canakinumab is the only approved sJIA treatment with efficacy data from large scale clinical trials in this patient population.

<Click here for references>

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