Oral Alendronate Vs. Three-Monthly Iv Ibandronate In The Treatment Of Postmenopausal Osteoporosis

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A. Study Purpose and Rationale

More than 70% of fractures in people after the age of forty-five are thought to be due to osteoorosis. Osteoporotic fractures are estimated to contribute to 44 million patient days in nursing homes in the United States yearly. Health care costs from osteoporosis are estimated to exceed 13.8 billion dollars yearly in the U.S. alone.(1) Additionally, the physical and social consequences of these fractures can be severe, causing many women to become functionally dependent.

The first line drug for the prevention and treatment of osteoporosis in postmenopausal women is hormone replacement therapy (HRT). This therapeutic approach has been demonstrated to increase bone mineral density (BMD), and to reduce fracture risk by 50%. However, many women cannot or will not take HRT because of unpleasant side effects or the fear of breast cancer. As a result, bisphosphonates are commonly used to treat postmenopausal women with osteoporosis.

The bisphosphonates were first synthesized in the nineteenth century and were used as antiscaling agents to prevent calcium carbonate deposition in washing powders. In more recent times, their utility 'in preventing bone resorption has been discovered. Etidronate, the first bisphosphonate used to treat osteoporosis, has been shown to increase BMD and to reduce fracture risk. Initially there were concerns that etidronate would lead to osteomalacia due to impaired bone mineralization, but this problem was corrected by using this medication in a cyclical therapeutic regime. However, approximately 20% of postmenopausal women in large therapeutic studies were found to be non-responders.(2)

Accordingly, attention has turned to alendronate, a second generation bisphosphonate, that differs from etidronate in its side chain composition (amino group vs. alkyl group). In the first large placebo controlled double blind study of alendronate, performed by Liberman et al (3), 994 women with postmenopausal osteoporosis were randomized to receive a placebo, alendronate 5 mg daily, alendronate 10 mg daily, or alendronate 20 mg daily. The BMD (the strongest predictor of fracture risk) was found to increase an average of almost 10% in the 10 ing alendronate group and over 96% of patients in this group showed an increase in BMD over three years. There were significant gains in total body BMD and in BMD in the hip and wrists. Following this study, the Food and Drug Administration (FDA) approved alendronate 10 mg daily for the treatment of postmenopausal osteoporosis. More recently, a larger trial, the Fracture Intervention Trial (FIT), (4), was undertaken to assess the effect of alendronate on fracture risk. In a subgroup of 2023 women with low femoral neck BMD and one or more vertebral fractures, the incidence of '"Tist fractures decreased 48%, hip fractures decreased 51 %, and vertebral fractures decreased 55% over three years. In a second arm of this study (5), 4432 post-menopausal women with low BMD and without vertebral fractures were randomized to treatment with alendronate (5mg daily for two years followed by 10mg daily for two years) or placebo. Alendronate significantly reduced the incidence of hip fractures by 56% in women with an initial femoral neck BMD T-score of -2.5 or less, but not in those with a higher BMD T-score. As well, the overall incidence of fractures was decreased in women with a BMD T-score of -2.5 or less.

The oral ingestion of alendronate is associated with possible side effects and problems of absorption. There is a risk of erosive esophagitis with aminobiphosphonates such as alendronate, possibly in the range of 10 to 15%. Accordingly, alendronate must be prescribed with strict instructions to drink 6 to 8 ounces of water at the time of ingestion, and to remain upright for one half hour afterwards. Alendronate absorption is compromised by food in the stomach and the medication must therefore be taken on an empty stomach.

Ibandronate, a potent third generation bisphosphonate, can be given by intravenous injection every three months, and, therefore, has the potential to eliminate the problems associated with the oral ingestion of alendronate and with the compliance required for daily drug intake. This drug was initially studied for the treatment of hypercalcemia associated with metastatic malignant bone disease, but more recently has been studied for use in postmenopausal osteoporosis(6). Thiebaud et al (7) randomized 125 postmenopausal women with osteoporosis to receive either a placebo, or ibandronate in a dose of 0.25mg, 0.5mg, ling, or 2 ing intravenously every three months. The BMD increased in all groups receiving ibandronate. After one year, BMD measurements in the spine increased by 2.4%, 3.5%, 3.7%, and 5.2% respectively with increasing doses of ibandronate. The improvement achieved statistical significance in all treatment groups, except the 0.25 mg. group, compared to placebo, with no significant difference in the number of adverse effects.

Although alendronate and ibandronate have been studied independently in the treatment of postmenopausal osteoporosis, the efficacy of these drugs has not been compared in a single randomized drug trial. This study proposes that ibandronate intravenously will be equally effective to alendronate in increasing BMD in postmenopausal women with osteoporosis, with fewer side effects. BMD has been shown to be a strong predictor of fracture risk in previous studies.(8,9)

B. Study Design and Statistical Analysis

A two-year randomized double blind trial is proposed, comparing changes in BMD and side effects in postmenopausal women taking either oral alendronate or intravenous ibandronate. The study will aim to enroll 900 women, aged 55 to 80, who are at least 5 years postmenopause, and have both a femoral neck and lumbar spine BMD of at least 25 standard deviations below the mean of young normal women (T-score less than -2.5). Women with diseases that could alter bone metabolism, such as liver or renal disease, malabsorption, hyperthyroidism, hyperparathyroidism, malignancy, Paget's disease, or osteomalacia will be excluded. Patients treated with estrogen, calcitonin, or steroids at any time during the last 12 months and patients who have been treated with bisphosphonates at any time 'in the past will also be excluded. Due to file need to monitor for erosive esophagitis, women with dyspepsia or peptic ulcer disease will not be included.

Agreeable women meeting BMD criteria for osteoporosis as outlined above will be screened by blood tests and a questionnaire for exclusion criteria. Those still eligible will be asked to return for the first study visit. At that time informed consent will be obtained and the study protocol explained. Participants will be asked to complete a short questionnaire concerning demographic information and risk factors for osteoporosis, such as smoking, calcium intake, etc. Baseline height and weight will be measured. At this time participants will be randomized to treatment with oral alendronate or intravenous ibandronate. The use of placebo is not felt to be ethical. Women with daily calcium intake of less than 1000 mg. will receive calcium supplementation with Oscal + D (calcium 500 mg. + 250 IU of vitamin D) tablets daily. Women randomized to the intravenous ibandronate group will receive ibandronate injections (2mg.) every three months at NYPH, as well as daily placebo pills identical in appearance to alendronate. Patients receiving daily alendronate will receive alendronate 10 mg daily as well as intravenous saline injections at NYPH every three months. Both study participants and investigators will be blinded to treatment and results of BMD values. Women will be screened regarding side effects, illnesses, and compliance at their three-monthly visits for intravenous injections. The BMD of the femoral neck and lumbar spine will be measured every six months using a Hologic 4500 A or C bone densitometer.

The percent change in BMD will be compared in the two groups using t-tests. The analysis will be intention to treat. The aim is to enroll 900 patients in order to detect a 1.5% difference between the two groups with a power of 80% and alpha of 0.05.

C. Study Procedures

Patients will undergo dual energy x-ray absorptiometry (using a Hologic 4500 A or C bone densitometer) of the lumbar spine and femoral neck every six months for the two year duration of the study. This is more frequent than the usual yearly monitoring performed for patients receiving therapy for postmenopausal osteoporosis. The procedure, which lasts approximately 15 minutes, is painless and non-invasive. The only risk to the patient is exposure to very small amounts of radiation, estimated to be approximately one fifth of the radiation exposure during a chest x-ray.

D. Study Drugs

Alendronate is an aminobisphosphonate which has been shown in large, randomized, placebo controlled trials to increase bone mineral density and decrease fracture risk in women with postmenopausal osteoporosis (as outlined above). Alendronate 10 mg. daily, the dosage to be used in this study, has been FDA approved for the treatment of postmenopausal osteoporosis since 1995. Inflarnmation or ulceration of the upper gastrointestinal tract and gastrointestinal symptoms such as nausea and dyspepsia, may occur with oral administration of alendronate. In particular, these drugs may be very irritating to the esophagus and may cause erosive esophagitis (10 - 15% of patients in some studies). In order to minimize esophageal irTitation, study participants will be instructed to take both alendronate and placebo medication with 6-8 ounces of water, and to remain upright for at least one half hour after drug ingestion to minimize reflux.

lbandronate is a potent bisphosphonate which can be given orally or as an intermittent bolus injection. The drug is not yet FDA approved and is currently in phase III trials. The drug has been shown to be safe in animals, and Thiebaud et al have studied the drug intravenously in 125 postmenopausal women with osteoporosis. lbandronate was found to increase BMD, and there was no significant difference in the overall number of adverse events between the treatment and placebo groups. This drug has also been shown to be effective in the treatment of malignant hyperealcemia in humans. An IND will be obtained before using this drug in the study.

E. Medical Devices

There will be no medical devices used in this study.

F. Study Questionnaires

Participants will be asked to complete a brief questionnaire about their general health and about risk factors for osteoporosis (such as fracture history after age 40, age at menopause, dietary calcium intake, history of smoking, exercise).

G. Study Subjects

As outlined above, the study will enroll women aged 55 - 80. Subjects must be at least five years postmenopause and have a T-score of less than 2.5 at both the femoral neck and lumbar spine as measured by bone densitometry. Women with diseases that might alter bone metabolism, such as liver or renal disease, malasorption, hyperthyroidism, hyperparathyroidism, Paget's disease, or osteomalacia will be excluded. Participants will be screened for this during an interview with a nurse or physician and by screening blood tests (CBC, C7, liver function tests, Ca, Vit.D., PTH, TSH, SPEP). Women will also be ineligible if they have been treated with calcitonin, estrogen, or steroids during the previous 12 months, or if they were treated with bisphosphonates at any time. Women,xith contraindications to the use of alendronate, such as dyspepsia or peptic ulcer disease, will also excluded. Women of all races will be included.

H. Recruitment of Subjects

Subjects will be recruited from the osteoporosis and endocrinology clinics at CPMC. As well, residents at the AIM clinics will be asked to refer appropriate patients.

I. Confidentiality of Study Data

Data will be stored in a locked cabinet accessible only to the investigators. As well, patients' names will not be used at any time, and code numbers will be accessible only to the investigators.

J. Potential Conffict of Interest

None.

K. Location of Study

The study will be conducted at CPMC medical clinics.

L. Potential Risks

The risks involved in taking bisphosphonates have been described above.

M. Potential Benefits

Participants will receive counseling on prevention and treatment of osteoporosis while participating in the study.

N. Alternative Therapies

The major alternative therapy for treatment of postmenopausal osteoporosis is hormone replacement therapy (HRT). Women are often reluctant to take hormones because of side effects such as breast tenderness and return of menses. In addition, women are afraid of a possible increased risk of breast cancer with long term HRT. The risks and benefits of HRT will be discussed with potential study participants (including its possible cardioprotective effects). Women who wish to take HRT will not be included in the study.

O. Compensation/Costs to Subjects

Subjects will not be compensated or incur costs for participation.

P. Minors as Research SubLects

N/A

Q. Radiation

Women will be exposed to only very small amounts of radiation (estimates at one fifth that of a chest x-ray) while undergoing bone densitometry.

R. References:

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