Informed Consent

Dear Patient:

We invite you to participate in "***Efficacy and safety of minodronate in the treatment of postmenopausal osteoporosis with low back pain: a single-centre and randomized controlled trial***". Before you decide whether to participate in this study, please read the following as carefully as possible. It can help you understand the procedure, duration, benefits, and risks of this study. If you wish, you can also discuss it with your relatives or friends or ask your doctor for an explanation to help you make a decision.

Background:

The prevalence of osteoporosis in China is as high as 36%, and it has become the fourth largest chronic disease in China after hypertension, diabetes and coronary heart disease. According to the Chinese Guidelines for the Diagnosis and Treatment of Primary Osteoporosis (2017), bisphosphonates are recommended as the first choice for osteoporotic fractures, among which minodronate is a new generation of nitrogenous bisphosphonates, and minodronate 1mg/ day is the first-line treatment for osteoporosis. Low back pain is one of the most common symptoms in patients with osteoporosis.

Minodronate can effectively inhibit the bone resorption function of osteoclasts, thereby reducing the bone metabolism and circulation, so as to play a therapeutic effect on osteoporosis and reduce the symptoms of low back pain. Minodronate was administered at significantly lower doses than comparable drugs (10mg/day for alendronate and 1mg/day for minodronate), which improved patient compliance and reduced gastrointestinal adverse effects commonly associated with oral bisphosphonates. In addition, bone metabolism markers, bone mineral density, fracture incidence and bone pain of osteoporosis will also change with the increase of age, making the quantitative relationship between bone metabolism markers and bone mineral density different between the elderly and the general elderly.

Therefore, this study will compare the pain relief and gastrointestinal side effects of minodronate and alendronate in postmenopausal osteoporosis patients, and compare the bone turnover markers (BTMs) and bone mineral density (BMD) of minodronate and alendronate in Chinese postmenopausal elderly subjects with osteoporosis of different ages. To explore the efficacy and safety of minodronate in the treatment of low back pain in postmenopausal patients with osteoporosis, and to evaluate the efficacy and safety characteristics of minodronate in elderly postmenopausal patients with osteoporosis in China, so as to provide guidance for the clinical application of minodronate.

Objectives

Primary objectives

To explore the efficacy and safety of minodronate in the treatment of low back pain in postmenopausal OP patients.

Secondary objectives

To evaluate the BTMs, BMD and safety characteristics of minodronate in Chinese postmenopausal OP patients of different ages.

Study design

This study will be conducted at Peking University Third Hospital. A total of 72participants are expected to volunteer. Subjects will be randomized at a 1:1 ratio to receive either minodronate (1 mg/day) or alendronate (10 mg/day) every day, senior women (≥75 years old) and older women (< 75 years old) will be at a ratio of 1:2.

Outcomes

The primary outcome is the time required for the Visual Analogue Scale (VAS) score to decline by ≥10 from baseline, and the secondary outcomes are changes in the VAS score from baseline after medication, the usage of rescue medication, the BTMs and BMD of minodronate and alendronate in Chinese postmenopausal OP patients of different ages, and variations in upper gastrointestinal (GI) symptom scores from baseline (including heartburn, pain, and bloating).

Safety evaluation

Safety will mainly be assessed by monitoring adverse events and serious adverse events caused by oral minodronate and alendronate during the study.

Who is needed for this study?

(1) Chinese postmenopausal patients with a diagnosis of OP;

(2) Patients with low back pain of at least 3 months and a VAS score ≥30;

(3) The value of lumbar L1-4 or total hip bone density measured by DXA is < -2.5;

(4) Serum 25-hydroxyvitamin D (25-OHD) concentration ≥20 ng/mL;

(5) Patients with full capacity for civil conduct and understanding of the research process and methods voluntarily participated in this study and signed the informed consent form.

Who is not suitable to participate in the study?

(1) Patient who are allergic to minodronate, alendronate, or other bisphosphonate drug or any other component of the drug under evaluation;

(2) Patients with a diagnosis of secondary OP;

(3) The following drugs affecting bone metabolism were used before the screening:

- Received injections of bisphosphonate and denosumab within 3 years;
- Received oral bisphosphonate, parathyroid hormones or analogues, strontium, or fluoride within 6 months;
- Received glucocorticoids, steroids, immunosuppressants, calcitonin, calcitriol or its

analogues, thiazide diuretics, and ng-acting oestrogen/progesterone replacement therapy within 3 months;

(4) Patients with a diagnosis of diseases affecting bone metabolism (e.g., osteogenesis imperfecta, malignancy, progressive diaphyseal dysplasia, Paget's disease, rheumatoid arthritis, osteosclerosis, osteoporosis with a slipped disc and spinal stenosis, and liver and kidney failure);

(5) Patients are participating or have participated in an investigational drug study within 3 months before signing the informed consent form;

(6) Patients under 75 years old with a creatinine clearance rate < 60 mL/min and those > 75 years old with a creatinine clearance rate < 45 mL/min;

(7) Serum calcium levels < 2.0 mmol/L (8 mg/dL) or > 2.7 mmol/L (11.0 mg/dL);

(8) Patients with fever, severe infection, severe trauma, or major surgery within 30 days;

(9) Patients with a QTc interval of > 480 ms;

(10) Patients are undergoing or planning to undergo invasive dental treatment;

(11) Smoking history in the past six months;

(12) Patients with a history of alcohol abuse (> 15 g of alcohol per day, equivalent to 350 mL of beer or 150 mL of wine, more than twice per week) and drug abuse;

(13) Patients with a prior history of cerebral infarction, ischaemic or haemorrhagic stroke;

(14) Patients with implants and/or fractures in the lumbar spine or hip that interfere with BMD testing;

(15) Received pain relievers (e.g., nonsteroidal anti-inflammatory drugs, central analgesics) or life interventions to relieve pain within 1 week before screening.

How long will this study last?

This clinical study lasted for 24 weeks and was divided into two phases. The first phase was continuous administration of drug for 12 weeks, and the second phase was cessation of drug administration for 12 weeks. During this period, you may need to complete a total of 5 visits to Peking University Third Hospital. You can opt out of the study at any time without losing any of the benefits you would have received. However, if you decide to withdraw from the study during the study, in consideration of your safety, it is possible that a relevant examination will be conducted after your withdrawal.

Costs

Participation in this study will not incur additional costs beyond your usual treatment,examination, or operation costs.

If you experience any discomfort during the study or any unexpected circumstances, even if not related to the drug, you should promptly notify your physician who will make a

judgement and decide medical treatment. You must visit on time during the study, which may be an inconvenience to you.

Minodronate is a drug that has been marketed. The most common adverse reactions are gastrointestinal adverse reactions, such as nausea, vomiting, dyspepsia, acid reflux, anorexia, mild diarrhea, epigastric pain, and epigastric discomfort.

Calcium and vitamin D supplements will be provided during the study. In addition, during the follow-up period, if you have a significant decrease in bone mineral density, the necessary treatment will be taken for you.

Is my personal information confidential?

All your medical records will be kept at the hospital where you are attending. Researchers and ethics committees will be allowed access to your medical records. Your identity will not be disclosed in any public report of the results of this study. We will make every effort to protect your privacy within the scope of the law.

What compensation can I get?

You will be compensated 200 RMB per visit when you complete all follow-up visits. If you drop out of the study, you will be compensated in part, and the amount of compensation will be based on the number of visits you complete. We have also purchased insurance for you to protect your rights and interests

Do I have the right to participate in or withdraw from the study voluntarily?

Participation in the study is entirely up to you. You may refuse to participate in or withdraw from the study at any time without affecting your relationship with your physician. However, all unused investigational drugs should be returned.Your continued participation in this study may be discontinued at any time by the doctor or the investigator for your best interest. You may also be required to undergo a laboratory and medical examination if your doctor deems it necessary.

How can I get more information?

You can ask any questions about this study at any time and get answers accordingly. If, during the course of the study, you have any questions related to your own rights or you want to express your dissatisfaction and concerns, please contact the Comprehensive Office of Research Ethics of Peking University Third Hospital.

Statement of doctor

I confirm that the patient has been informed in detail about the trial, including background, objectives, trial design, and potential benefits and risks, and that I have given him or her a copy of the informed consent to sign.

Doctor's signature	Tel	Date

Statement of Subject

I have read the above introduction to this study and have had the opportunity to ask my doctor questions about this study. All my questions have been satisfactorily answered. I know there may be risks and benefits to participating in this study. I take part in the study on a voluntary basis. I confirm that I have had sufficient time to consider this decision, and I know that I can always consult my doctor to obtain more information. I can withdraw from this study at any time without discrimination or retaliation, and my rights and interests will not be affected. I grant access to my research materials to research management or ethics committees. In the end, I have decided to take part in the study and promise to follow my doctor's advice as much as possible.

Subject's signature	Tel	Date