National Major Science and Technology Project

Sub-topic 4: Study on the Intervention Effect of Denosumab on High-Risk Patients with Osteoporotic Fractures in Type 2 Diabetes

Study Protocol

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1. Background

In recent years, the global population has gradually entered an aging phase, and China has already become an aging society. According to the seventh national population census, the population aged 65 and above has reached 13.5%. Large-scale and rapid aging has become a major challenge for China's public health and an important livelihood issue. As important age-related diseases, type 2 diabetes and osteoporosis will become an important part of promoting the construction of "healthy aging" in China by comprehensively improving their prevention and treatment levels.

The prevalence of osteoporosis in China's population aged 50 and above is 19.2%. Osteoporotic fractures, which are serious consequences of osteoporosis, are one of the main causes of disability and death in the elderly. The prevalence of type 2 diabetes in Chinese adults is as high as 11%, and it exceeds 20% in the population aged 60 and above. Various chronic complications of diabetes are the main causes of all-cause mortality in Chinese adults. In recent years, with the sharp increase in the number of people with diabetes, diabetic osteoporotic fractures have gradually attracted attention and have become an important complication of diabetes. Foreign research data suggest that the risk of hip fractures or vertebral fractures in people with type 2 diabetes is 1.4-1.7 times and 1.3-1.4 times that of the non - diabetic population, respectively. Compared with non-diabetic patients, diabetic patients have a worse prognosis after hip fractures. In 2015, there were about 2.69 million new cases of osteoporotic fractures in China, with medical expenses amounting to 72 billion RMB. It is projected that this figure will reach 132 billion yuan by 2035. Meanwhile, the direct medical expenditure on diabetes every year is as high as 621 billion yuan. Therefore, with the intensification of the aging process, type 2 diabetes and osteoporosis have become two major chronic metabolic diseases in China. While posing a serious threat to the health of the nation, they also bring a heavy economic burden to society and families. It is urgent to comprehensively improve the prevention, control, and disease management of osteoporotic fractures in people with diabetes.

Over the past three decades, China has made significant progress and remarkable

achievements in the prevention and treatment of diabetes, conducting a large number of high-level epidemiological surveys, basic scientific research, and prospective clinical studies that widely cover the occurrence, development, and outcomes of diabetes. However, in terms of the prevention, treatment, and management of osteoporotic fractures in people with type 2 diabetes, there is still a considerable gap between China and Western countries. Western countries began to pay attention to the association between type 2 diabetes and osteoporosis and fractures 20 years ago. Through cross - sectional and prospective studies, they found that people with type 2 diabetes have higher bone density than non - diabetic individuals, but their risk of osteoporotic fractures is significantly higher than that of non-diabetic people. Therefore, in 2018, the International Osteoporosis Foundation's Bone and Diabetes Working Group recommended using dual - energy X-ray absorptiometry (DXA) to measure the T-score of lumbar spine or hip bone density, with a threshold of - 2.0 for intervention in people with diabetes. They also pointed out that this cut - off point may be more suitable for European populations. They have also focused on the impact of hypoglycemic drugs on fractures and found that sodium - glucose cotransporter 2 (SGLT-2) inhibitors, thiazolidinediones (TZDs), and insulin all increase the risk of fractures. Given the serious harm of osteoporotic fractures (fragility fractures) to people with diabetes, the 2024 American Diabetes Association's "Standards of Medical Care in Diabetes" for the first time specifically added an independent section on diabetic bone health, calling on more clinicians to pay attention to the bone health of people with diabetes. In view of the great significance of maintaining the bone health of people with diabetes, it is urgent to carry out systematic clinical research to improve the early screening, diagnosis, treatment, and management of the disease and effectively reduce the serious harm of osteoporotic fractures in people with type 2 diabetes.

Compared with Western developed countries, China has relatively limited clinical research data on osteoporosis and fractures in type 2 diabetes, which seriously restricts the effective prevention and control of osteoporotic fractures in type 2 diabetes in China. This project will focus on the major needs in the prevention and

control of osteoporosis and fractures in type 2 diabetes, establish precise diagnosis and treatment and effective management plans that are in line with national conditions, and provide important clinical research evidence for comprehensively improving the level of disease prevention and control, effectively reducing the harm of the disease, and formulating national health policies.

2. Purpose of Study

Patients with type 2 diabetes have a significantly increased risk of fractures, but there are few studies on anti-osteoporosis drug interventions for type 2 diabetes. Receptor activator of nuclear factor-κB ligand (RANKL) plays a key regulatory role in the differentiation, maturation, and function of osteoclasts. Denosumab is a specific monoclonal antibody that inhibits the function of osteoclasts, thereby reducing bone resorption, increasing bone density, and lowering the risk of fractures. Eddie Calciferol is an active vitamin D analog that increases bone density and treats osteoporosis by promoting calcium absorption in the intestines, inhibiting bone resorption, and promoting bone formation. However, there is currently a lack of high-quality evidence on the effects of Denosumab and Eldecalcitol in patients with type 2 diabetes and high fracture risk. This study will conduct a randomized controlled trial in patients with type 2 diabetes and high fracture risk to evaluate the effects of Denosumab and Eldecalcitol on bone density, bone turnover markers, and the risk of new fractures, providing a scientific basis for clinical diagnosis and treatment..

3. Methods

This study will enroll patients with type 2 diabetes and high fracture risk, using stratified block randomization. All participants will be randomly assigned in a 1:1 ratio to either the intervention group or the control group.

Control Group: Administered denosumab 60 mg subcutaneously once every six months for one year.

Intervention Group: Administer denosumab 60 mg subcutaneously once every six months in combination with eldecalcitol 0.75 μg once daily for one year. Follow-up visits are scheduled at 1 week and 3, 6, 9, and 12 months post-treatment to collect data on bone mineral density, radiographs, bone turnover markers, incident fractures, and adverse events.

Primary Endpoint: The change rate of lumbar spine bone density at 12 months of treatment.

Secondary Endpoints:

- The occurrence of osteoporotic fractures at 12 months of treatment
- The change rate of bone density in the femoral neck and total hip at 12 months of treatment.
- The change rate of bone turnover markers (β-CTX and PINP) at 6 and 12 months of treatment。

4. Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

1）Confirmed diagnosis of type 2 diabetes (based on the diagnostic criteria in the "China Guidelines for the Prevention and Treatment of Diabetes (2024 Edition)")；

2）Men aged ≥50 years; women aged ≥ 45 years and postmenopausal for more than 2 years；

3）Duration of diabetes >10 years; or presence of at least one of the following conditions: ①diabetic retinopathy; ②urine albumin-to-creatinine ratio (UACR)≥ 30 mg/g; ③estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2; ④coronary atherosclerotic heart disease; ⑤ischemic stroke; ⑥transient ischemic attack; ⑦ atherosclerosis of the carotid, cerebral, or lower-extremity arteries with ≥50% luminal stenosis;

4）Glycated hemoglobin (HbA1c) ≤ 8.0 % measured within 1 month;

5）History of hip or vertebral fragility fractures; or history of fragility fractures at other sites (excluding the skull, feet, and hands) with a T-score of < -1.0 in the

femoral neck, total hip, or any lumbar spine site (L1-L4); or a T-score of < -2.0 in the femoral neck, total hip, or any lumbar spine site (L1-L4);

6）In the BMD measurement at lumbar vertebrae L1 – L4, at least two or more vertebral bodies must meet the evaluable criteria;

7）Sign the informed consent form and be willing to participate in the study.

4.2 Exclusion criteria

1）Presence of diseases causing secondary osteoporosis: a. Various metabolic bone diseases, such as osteomalacia, primary hyperparathyroidism, osteogenesis imperfecta, Paget's disease, etc.; b. Cushing's syndrome; c. Hyperprolactinemia; d. Others；

2）Having had malignant tumors within 5 years, except for tumors that are expected to be cured after treatment (such as completely resected in situ basal cell or squamous cell carcinoma of the skin, cervical cancer, or breast ductal carcinoma, etc.)；

3）Having received intravenous bisphosphonate treatment within the past 2 years or oral bisphosphonate treatment within the past 1 year;

4）Having had or currently having osteomyelitis or osteonecrosis of the jaw; unhealed dental or oral surgical wounds; acute dental or jaw diseases requiring oral surgery; or planned to undergo invasive dental surgery during the study period；

5）Having received treatment with denosumab, teriparatide, or romosozumab within the past six months;

6）Continuous use of calcitonin for more than three months within the past year;

7）Use of glucocorticoids (equivalent to >5mg/day of prednisone) for more than 10 days within the past 6 weeks；

8）25-hydroxyvitamin D <20ng/mL；

9) Presence of active infections requiring systemic treatment with 25-hydroxyvitamin D <20ng/mL；

10）Uncontrolled comorbidities, including heart failure classified as New York Heart Association (NYHA) functional class III or above, severe arrhythmias, severe hepatic insufficiency (alanine aminotransferase or aspartate aminotransferase>3 times

the upper limit of normal), and severe renal insufficiency (eGFR <30ml/min/1.73m2)；

11）Hypocalcemia, hypercalcemia, or hypercalciuria

(Note: hypercalciuria is defined as a urinary calcium/creatinine ratio > 0.5 mg/mg, or 24-hour urinary calcium > 7.5 mmol)；

12）Allergy to the study medications；

13）Currently participating in other drug clinical trials；

14）Participants whom the investigator deems unsuitable for enrollment in this study

5. Study procedure

5.1 Baseline evaluation

（1）Questionnaire survey: Basic information of the subjects, medication history, past medical history, family history, history of previous fractures, and fall situations, etc;

（2）Bone density examination: Dual-energy X-ray absorptiometry (DXA) was used to measure the bone density of the subjects' lumbar spine (L1-4), femoral neck, and total hip. The examination was conducted by a specific technician who had undergone professional training and obtained a qualification certificate. The technician read the results and issued a report. Bone density examinations were performed at baseline and after 1 year of intervention;

（3）Laboratory tests: The subjects underwent routine blood tests, liver and kidney function tests, bone turnover markers (β-CTX, P1NP), 25-hydroxyvitamin D, parathyroid hormone, glycated hemoglobin, urine albumin-creatinine ratio, routine urine tests, and 24-hour urinary calcium. Laboratory tests were performed at baseline, 3 months, 6 months, 9 months, and 1 year;

（4）Muscle strength testing: Muscle strength tests were conducted at baseline, after 6 months of intervention, and at 1 year; Detailed information as follows:

A. Grip strength: The subjects were seated and squeezed the handle of the grip strength measuring device as hard as possible, holding for 3 seconds. This was

repeated 3 times, with a rest of 30 seconds to 1 minute between each attempt. The grip strength values were recorded during the rest intervals.；

B. Sit-to-stand test: The subject sat in the middle of the chair and stood up and sat down continuously five times. One repetition was counted for each stand-up and sit-down action. Timing started when the command “begin” was given and ended when the subject was seated steadily for the fifth time. The test result was recorded as the time taken in seconds or the inability to complete the test；

C. Walking speed: The time taken to walk a distance of 4 meters at the subject's usual walking speed was measured. The subject stood behind the starting line before beginning, and the measurement was repeated three times.

（5）Thoracolumbar anteroposterior and lateral X-ray imaging: Anteroposterior and lateral X-ray films of the thoracic spine (T4-L1) and lumbar spine (T12-L5) were taken for the subjects. The X-ray films were centrally evaluated by two dedicated radiologists. Thoracolumbar anteroposterior and lateral X-ray images were performed at baseline and after 1 year of intervention.

5.2 Group

5.2.1 Randomization and blinding

Randomization: This study adopted stratified block randomization. Stratification was based on baseline lumbar spine bone density levels and centers. A third-party statistician generated the random number table. All subjects were randomly assigned to the intervention group and the control group at a 1:1 ratio.

Blinding was not applied to the subjects and doctors in this study. The imaging results were centrally evaluated. The statistical analysis was conducted by an independent third-party statistician, who was blinded to the group allocation of the subjects.

5.2.2 Control and Intervention

The subjects included in this study will be randomly divided into the intervention group and the control group:

Control group:

Denosumab injection (Mai-Li-Shu), 60 mg subcutaneously once every 6 months for 1 year;

Intervention group:

Denosumab injection (Mai-Li-Shu), 60 mg subcutaneously once every 6 months, in combination with Eldecalcitol soft capsules (Gai-Sheng-Yuan), 0.75 μg/capsule, one capsule orally once daily, for 1 year.

Study-drug information:

Mailishu (denosumab injection):

- Manufacturer: Jiangsu Taikang Biopharm Co., Ltd.
- Description: recombinant fully human IgG2 monoclonal antibody against RANKL
- Approval No.: National Medical Products Administration (NMPA) S20233111
- Storage: 2–8℃, protected from light; do not freeze
- Presentation & use: pre-filled syringe, 60 mg/1.0 mL; administer by subcutaneous injection (upper thigh, abdomen, or outer upper-arm region) once every 6 months

Gaishengyuan (eldecalcitol soft capsules):

- Manufacturer: Henan Taifeng Biotechnology Co., Ltd.
- Approval No.: NMPA H20223700
- Storage: tightly closed, protected from light, ≤ 25 °C
- Presentation & use: 0.75 μg × 14 capsules per box; take one capsule orally once daily

5.2.3 Glycaemic control

Both the control and intervention groups will receive anti-diabetic therapy in accordance with the Chinese guidelines for the diagnosis and treatment of diabetes and routine clinical practice. The glucose-lowering regimen will be titrated according to blood-glucose measurements, with a recommended target glycated haemoglobin (HbA1c) of < 7.5 %.

5.2.4 Bone-health supplement therapy

Control group: daily, regular supplementation with vitamin D 800–2,000 IU (dose determined by the study physician) plus 600 mg elemental calcium;

Intervention group: daily, regular supplementation with vitamin D 800–2,000 IU (dose determined by the study physician).

5.2.5 Concomitant-medication restriction

Use of any other anti-osteoporotic agents is prohibited throughout the study period, including (but not limited to) bisphosphonates, teriparatide, romosozumab, estrogens, selective estrogen-receptor modulators (SERMs), and strontium salts.

5.2.6 Treatment-discontinuation criteria

1. Severe hypocalcaemia (albumin-corrected serum calcium < 2.0 mmol/L) or severe hypercalcaemia (albumin-corrected serum calcium > 2.7 mmol/L) at any visit: immediately stop all protocol-specified study drugs and manage as clinically indicated.

2. Urinary calcium/creatinine ratio > 0.5 mg/mg: repeat on a non-consecutive day.If the repeat value is still > 0.5 mg/mg: To Control group: discontinue calcium supplements while continuing denosumab and vitamin D. To Intervention group: discontinue eldecalcitol while continuing denosumab and vitamin D. Additional measures may be instituted at the investigator`s discretion.

3. Any new serious illness emerging during follow-up: discontinue protocol-specified therapy and treat as clinically appropriate.

Patients who discontinue study drugs for any of the above reasons remain in the study and continue all scheduled follow-up assessments.

6. Sample calculation

The primary endpoint is the 12-month percent change in bone mineral density (BMD). Based on prior data (*Tsvetov et al., Osteoporos Int 2020; 31:655–665; Cummings et al., N Engl J Med 2009; 361:756–765*), the expected mean ± SD lumbar-spine BMD gain is 6.8 % ± 2.1 % with combination therapy and 6.1 % ± 2.1 % with denosumab alone. For a two-sided $\alpha = 0.05$ and power = 0.8 with a 1:1 allocation, 143 participants per group (286 total) are required. The key secondary endpoint is the incidence of hypocalcaemia during the 12-month treatment period. Anticipated rates

are 14 % with denosumab monotherapy and 4 % with combination therapy. Using the same α and power, 125 participants per group (250 total) are needed.

The larger sample size (286) governs the study. Allowing for a 20 % dropout rate, we plan to enrol 358 subjects.

6.1 Statistical analysis plan

（1）The primary endpoint will be analyzed based on the Full Analysis Set (FAS) using a mixed-effects model to compare the differences in bone density change rates between the intervention group and the control group.

（2）The analysis of secondary endpoints will be based on the Full Analysis Set (FAS), using mixed-effects models and generalized estimating equations to compare differences in secondary endpoints between different groups.

（3）Sensitivity analysis: Sensitivity analysis will be conducted using the Per Protocol Set (PPS). Additionally, different methods for imputing missing data will be used for sensitivity analysis.

（4）Safety analysis: This will be based on the Safety Analysis Set (SS), with descriptive summaries of exposure to the study drug according to the actual treatment received, adverse events, laboratory tests, and other safety endpoints.

7. Quality control of the study

The enrolled patients were all patients with type 2 diabetes and high fracture risk due to osteoporosis. Stratified block randomization was used, with stratification based on baseline lumbar spine bone density levels and centers. A third-party statistician generated the random number table, and all subjects were randomly assigned to the intervention group and the control group at a 1:1 ratio. This method effectively controlled diagnostic and selection biases. The grouping, treatment, and follow-up were strictly carried out in accordance with the study design requirements. A documented management approach was implemented, with detailed, accurate, and

objective recording of research data in scientific research notebooks to ensure the authenticity, integrity, reliability, and comparability of the data. Strict laboratory quality control and experimental drug management were implemented in the clinical research, along with recording of adverse events and reporting of serious adverse events. The statistical analysis of experimental data was scientific, and the writing of research reports was true and rigorous. Finally, research materials were properly archived and preserved.

8. Follow-up

Follow-up visits will be conducted at 1 week and at 3, 6, 9, and 12 months post-treatment.

- 1-week visit: serum biochemistry, parathyroid hormone (PTH).
- 3-month and 9-month visits: serum biochemistry, glycated haemoglobin (HbA1c), urinary calcium-to-creatinine ratio.
- 6-month visit: complete blood count, serum biochemistry, 25-hydroxyvitamin D, parathyroid hormone, glycated haemoglobin (HbA1c), urinary albumin-to-creatinine ratio, urinalysis, urinary calcium-to-creatinine ratio, muscle-strength test.
- 12-month visit: complete blood count, serum biochemistry, 25-hydroxyvitamin D, parathyroid hormone, glycated haemoglobin (HbA1c), urinary albumin-to-creatinine ratio, urinalysis, urinary calcium-to-creatinine ratio, muscle-strength test, lateral thoraco-lumbar spine radiograph, bone mineral density measurement.