Clinical research program of Union Hospital Affiliated to Tongji Medical College of Huazhong University of science and technology

Study Protocol

entry name	Clinical study of denosumab in the treatment of knee osteoarthritis
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Table of contents

Program summary	
Study name	Clinical study of denosumab in the treatment of knee osteoarthritis
Research Introduction	As an activator of inhibiting nuclear factor kB receptor, denosumab affects osteoclast differentiation and development by inhibiting OPG/RANKL/RANK bone regulatory axis pathway. Therefore, denosumab is widely used in the treatment of bone diseases such as osteoporosis. Osteoporosis is closely related to knee osteoarthritis. RANKL-RANK pathway also plays a key role in the pathogenesis of knee osteoarthritis. Therefore, we propose the hypothesis that denosumab can effectively treat knee osteoarthritis.
research objective	To explore the clinical efficacy of denosumab in the treatment of knee osteoarthritis.
research design	Prospective research
Total number of enrolled patients	30 cases
Number of study groups Number of control groups	15 cases /15 cases
diagnosis	Knee osteoarthritis

Inclusion Criteria	• patients with knee osteoarthritis whose inclusion criteria meet the diagnostic criteria for arthritis • no drug contraindications • aged between 45 and 75 • promised to follow the research procedures and cooperate with the implementation of the whole process of the study • patients understand the relevant treatment process patients have the ability of informed consent patients have not taken drugs that affect observation recently • subjects must meet all the inclusion criteria to be eligible to participate in the study

Exclusion criteria	• mental illness • patients with malignant tumors; • patients with other infectious diseases patients with metabolic bone disease, diabetes, hyperthyroidism • unable to actively cooperate with the treatment of patients • hypocalcemia
Research intervention	Denosumab, 60mg single injection, has been listed. Basis of super indications: denosumab reduces bone resorption by inhibiting OPG/RANK/RANKL pathway, which is widely used in the treatment of osteoporosis. Osteoporosis is closely related to knee arthritis. RANKL-RANK pathway also plays an important role in the pathogenesis of knee osteoarthritis.

Evaluation criteria: primary endpoint: secondary endpoint: safety evaluation:	● Primary end point / outcome: VAS pain score, OKS function of knee joint at 1,3 and 6 months. ● secondary end point / outcome: WOMAC score, incidence of adverse reactions, EQ-5D quality of life score. ● For patients' benefit, some participants opted to withdraw from the trial post-denosumab injection and proceed with knee replacement, with intraoperative synovial tissue obtained for H&E, IHC staining, and WB analysis. ● safety evaluation: incidence of adverse reactions; physical examination; Important signs (such as body temperature, pulse, blood pressure); Radiological or other imaging evaluation; Laboratory evaluation
Statistical method: sample size: analysis set: primary efficacy endpoint: safety endpoint:	The required sample size is calculated by using the non-inferiority design scheme. The alpha value is set to be 5%, the efficacy power is set to be 80%, and the effective rates of both drugs are 90%. Under the condition of non-inferiority limit value of 10%, the number of patients required in each group is calculated to be 15, and the total number of patients planned to be enrolled is 30; Among them, there were 15 people in the denosumab group and 15 people in the placebo group (the same amount of normal saline); Primary end point / outcome: OKS function of knee joint at 1,3 and 6 months, VAS pain score; Secondary end point / outcome: WOMAC score, incidence of adverse reactions, EQ-5D quality of life score; H&E, IHC staining and WB analysis of synovium from patients after knee replacement; Safety end point: incidence of adverse reactions, radiological or other imaging evaluation, laboratory evaluation;
Study duration	2021.08-2025.12
Participants' participation time	6 months
Research unit / location	Domestic single center Union Hospital Affiliated to Tongji Medical College of Huazhong University of science and technology

Information of main researchers
Name, qualification and contact information of main researchers Hongtao,Tian, chief physician, practicing physician certificate, physician qualification certificate, GCP certificate 13955875563 (see the qualification documents of main researchers for details)

List of abbreviations	
abbreviation	Chinese full text
VAS	Pain score
OKS	Oxford hip score
WOMAC	Quality of life score
EQ-5D	Survival treatment score
H&E	Hematoxylin and eosin
IHC	Immunohistochemical
WB	Western blot

1. Introduction

1.1 Research background

1.1.1 Basic overview

At present, about 60% of the elderly over 60 years old in China suffer from knee osteoarthritis, and there are more than 100 million patients with knee osteoarthritis in China. It is estimated that the world's elderly population will reach 2.02 billion in 2050, and China will reach 480 million, accounting for almost 5% of the global elderly population, making it the country with the largest elderly population in the world[1]. At present, the treatment of knee osteoarthritis is only analgesic drugs to alleviate symptoms, and there is no effective treatment to reverse the progress of knee osteoarthritis. Therefore, many patients with knee osteoarthritis eventually face knee replacement surgery. In 2019, there were nearly 400000 knee replacement operations in China, and the number will increase by 30% next year, which is undoubtedly a huge economic expenditure for patients. Denosumab is widely used in the treatment of osteoporosis by inhibiting nuclear factor kB activating factor (RANK). RANK and RANKL are important molecular systems that regulate bone remodeling and the dynamic balance of bone metabolism. In osteoporosis, the combination of rank and RANKL will directly promote the differentiation and maturation of osteoblasts, enhance their bone resorption activity and prevent their apoptosis. The relative transcription of RANK in osteoclasts and their precursor cells is significantly increased, which promotes bone loss and leads to osteoporosis. RANKL-RANK pathway also plays a key role in the pathogenesis of osteoarthritis[2]. The chondrocytes and synovial cells of patients with knee osteoarthritis will produce interleukin-1 (IL-1β), TNF- α and prostaglandin E2 (PGE2) and other inflammatory factors after being stimulated by trauma, wear and tear, promoting osteoclasts to secrete metalloproteinases (MMPs) and matrix protease tissue inhibitors (TIMPs), and these inflammatory factors can directly stimulate RANKL to

induce the production of osteoclasts, resulting in the destruction of cartilage matrix, the impairment of bone regeneration ability, the irreversible degradation of cartilage tissue, and even apoptosis[3]. At the same time, it has been reported in the literature that osteoporosis and knee osteoarthritis are closely related, and the two promote each other, forming a vicious circle[4,5]. The symptoms of knee osteoarthritis can be relieved by treating osteoporosis. However, there is no report about denosumab in the treatment of knee osteoarthritis. Therefore, this project plans to use a prospective, single center randomized controlled trial to study the clinical efficacy of denosumab in the treatment of patients with knee osteoarthritis and osteoporosis.

1.1.2 The previous research basis of this study

Xiaona, Li elaborated on the OPG/RANK/RANKL signaling pathway, which exists in the pathogenesis of osteoporosis and knee osteoarthritis at the same time. It has been reported that osteoporosis is closely related to knee osteoarthritis[6]. Bellido et al. showed that when patients with knee osteoarthritis were complicated with osteoporosis, the subchondral bone absorption caused by periosteal degeneration caused by osteoporosis in the early stage would aggravate the degeneration of articular cartilage and promote the development of osteoarthritis[7]. Shen Sheng and other researchers have shown that early anti-osteoporosis treatment can reduce the level of inflammatory factors in the joint, significantly delay the occurrence of knee osteoarthritis, and play an important role in the early prevention of knee osteoarthritis[8]. Ghodasra and others believe that active vitamin D3, as an important carrier for human bone absorption and promoting calcium absorption, is of great significance for maintaining and improving bone mass. Increasing the intake of active vitamin D3 in the early stage of osteoporosis can reduce bone loss and reduce the formation of inflammatory factors[9]. Osteoporosis can aggravate the development of knee osteoarthritis. Treating osteoporosis while treating knee osteoarthritis can make the treatment effect of knee osteoarthritis better. In the early stage, we established a rat model of knee osteoarthritis. The rats in the experimental group were subcutaneously injected with 60 mg denosumab, and the rats

in the control group were subcutaneously injected with placebo (the same amount of normal saline). During the pain test, the rats in the experimental group could tolerate greater force stimulation.

1.2 research type

- drug intervention research
- exploratory research
- listed
- in line with the recommendations of the "norms for the diagnosis and treatment of knee osteoarthritis"
- super indications
- a large number of literatures report that osteoporosis can aggravate the development of knee osteoarthritis, anti-osteoporosis treatment, and improve the effectiveness of the treatment of knee osteoarthritis. The incidence of adverse reactions such as constipation and muscle pain of denosumab is less than 10%, and the incidence of jaw necrosis, infection and atypical femoral fracture is less than 1%
- randomized controlled study

1.3 research basis

According to Xiaona, Li, the study elaborated the OPG/RANK/RANKL signaling pathway, which exists in the pathogenesis of osteoporosis and knee osteoarthritis at the same time. It has been reported that osteoporosis is closely related to knee osteoarthritis[6]. Bellido et al. showed that when patients with knee osteoarthritis were complicated with osteoporosis, the subchondral bone absorption caused by periosteal degeneration caused by osteoporosis in the early stage would aggravate the degeneration of articular cartilage and promote the development of osteoarthritis[7]. Shen Sheng and other researchers have shown that early anti osteoporosis treatment can reduce the level of inflammatory factors in the joint, significantly delay the occurrence of knee osteoarthritis, and play an important role in the early prevention of knee

osteoarthritis[8]. Osteoporosis can aggravate the development of knee osteoarthritis. Treating osteoporosis while treating knee osteoarthritis can make the treatment effect of knee osteoarthritis better.

1.4 risk / benefit assessment

1.4.1 known potential risks

- hypocalcemia
- limb and muscle pain
- urinary and respiratory system infection
- abdominal discomfort such as constipation
- rash
- jaw necrosis
- atypical femoral fracture
- X-ray low-dose radiation

1.4.2 probability of injury

- rash, constipation, urinary and respiratory infection (>1/100, <1/10), hypocalcemia, jaw necrosis, atypical femoral fracture are rare (<1/10000)

1.4.3 degree of injury

- mild to moderate, generally does not endanger the patient's life

1.4.4 known potential benefits

- patients can receive denosumab drug treatment free of charge
- patients enjoy outpatient registration free of charge, at the same time, you can contact the doctor at any time
- denosumab is injected subcutaneously once every 6 months to avoid the long-term repeated use of analgesic drugs and gastrointestinal irritation.
- exempt the examination and laboratory costs during the follow-up
- after the patient completes the follow-up, if the patient is in the placebo group, the patient can be provided with denosumab treatment for half a year free of charge
- Some patients receiving denosumab injections requested to withdraw from the trial to undergo knee replacement, during which synovial tissue samples were collected for H&E, IHC staining, and Western blot. Knee replacement inherently requires

partial synovectomy to prevent postoperative joint crepitus and alleviate inflammatory pain. The resected pathological tissues during knee replacement—including synovium and cartilage—are routinely sent for pathological examination to exclude neoplasms or infections, confirm diagnoses, and guide postoperative management. Studies suggest that denosumab may effectively reduce periprosthetic fracture risk. Thus, even after trial withdrawal, patients can benefit from its osteoporotic therapeutic effects in preventing post-arthroplasty complications such as prosthetic loosening and periprosthetic fractures. In addition, we could also check whether there are some protective effects by denosumab on molecular level.

1.4.5 potential risk / benefit evaluation

- Denosumab has been widely used in clinic, and its potential risk incidence is low and controllable. Patients with knee osteoarthritis have more benefits than potential risks. In order to reduce potential risks, inclusion and exclusion criteria are strictly set in the study design.

1.4.6 discussion

- This study comprehensively evaluates the risk benefits of patients, so as to maximize the protection of patients' interests, provide protection for patients, and minimize the risk. Patients' benefits outweigh potential risks.

2. Research purpose / end point

- main purpose: To evaluate the effectiveness of denosumab in the treatment of knee osteoarthritis.
- secondary purpose: To explore the safety of denosumab in the treatment of knee osteoarthritis.
- main research end point / outcome: VAS pain score, knee OKS function at 1,3,6 months.
- secondary research end point / outcome: WOMAC score, incidence of adverse reactions, EQ-5D quality of life score.
- H&E, IHC staining and WB analysis of synovium after knee replacement;

3. Research design

3.1 Overall design

- domestic single center research
- this research project is a randomized controlled study, and the subjects are randomized into groups: 1. Denosumab group; 2. Placebo group (equivalent normal saline).
- this study adopts the principles of randomized grouping and double-blind to reduce the selection bias, and the two people make independent statistics to reduce the information bias.
- all patients were followed up in the outpatient department, with a period of 6 months. A total of 3 visits were required, 1,3 and 6 months after injection. The follow-up examination items were blood routine examination, CRP, ESR, electrolyte, X-ray of the knee joint in the anterior and lateral position, magnetic resonance of the knee joint, and bone mineral density measurement.
- calculate the incidence of adverse reactions of patients in the two groups, including the OKs function of knee joint at 1,3 and 6 months, VAS pain score, WOMAC score and EQ-5D quality of life score.
- For patients' benefit, some participants opted to withdraw from the trial post-denosumab injection and proceed with knee replacement, with intraoperative synovial tissue obtained for H&E, IHC staining, and WB analysis.

3.2 sample size

- calculate the required sample size using the non-inferiority design scheme, set the alpha value as 5%, the efficacy power as 80%, and the effective rates of both drugs are 90%. Under the condition of non-inferiority boundary value of 10%, calculate the number of patients required in each group as 15, a total of 30 patients are planned to be enrolled.

3.3 blinding and Unblinding procedures

- no

3.4 definition of start, end and completion of the study

- after the ethical review is passed, the first patient is included as the start of the

study

- the end of the study is the completion of the follow-up of the last patient
- complete the data collation and analysis of all patients, and report to the ethics institution for the completion of the study

4. Study population

4.1 diagnostic criteria

- the diagnosis is based on the "guidelines for the diagnosis and treatment of knee osteoarthritis"
- patients with knee osteoarthritis whose inclusion criteria meet the "diagnostic criteria for arthritis"
- no drug contraindications
- aged between 45 and 75
- committed to follow the research procedures, and cooperate with the implementation of the whole process study
- the patient understands the relevant treatment process
- the patient has the ability to give informed consent
- the patient has not taken drugs that affect the observation recently
- the subjects must meet all the inclusion criteria to be eligible to participate in the study

4.2 exclusion criteria

- mental illness
- patients with malignant tumors
- patients with other infectious diseases
- patients with metabolic bone disease, diabetes and hyperthyroidism
- patients who cannot actively cooperate in the treatment
- hypocalcemia

4.3 grouping method of subjects

- Strictly screen the subjects according to the inclusion criteria and group them

according to computer randomization.

4.4 subject withdrawal criteria

- subjects can withdraw unconditionally at any stage of this study
- the subjects have other diseases that affect life treatment or life-threatening that are not related to the knee joint
- the patients die
- for the non-death withdrawal patients, based on the care of the patients, continue to track the patients and conduct telephone follow-up with the permission of the patients.

4.5 subject recruitment

- the research object comes from outpatient patients
- recruitment advertisement for publicity

5. Research intervention

5.1 research intervention description

- the intervention measures of denosumab group are subcutaneous injection of denosumab preparation 60mg, single injection.

5.2 research drugs such as research drugs or medical devices or diagnostic reagents or questionnaires

- Denosumab, which has been listed. The production unit of denosumab injection is Amgen Manufacturing limited, 60mg (1.0ml) / piece (pre filled syringe), clear, colorless to light yellow solution, subcutaneously injected once every 6 months, stored in a refrigerator at 2-8 ℃ and protected from light. There is no indication for knee osteoarthritis in the drug Manual of denosumab, but it is recommended by the guidelines or expert consensus. Belido et al. showed that when patients with knee osteoarthritis were complicated with osteoporosis, subchondral bone absorption caused by periosteal degeneration caused by osteoporosis in the early stage would aggravate the degeneration of articular cartilage and promote the development of osteoarthritis. Shen Sheng and other researchers have shown that

early anti osteoporosis treatment can reduce the level of inflammatory factors in the joint, significantly delay the occurrence of knee osteoarthritis, and play an important role in the early prevention of knee osteoarthritis.

5.3 research intervention discussion

- summarize the relevant evidence of the safety, effectiveness and feasibility of research intervention or research drugs
- the basis for the setting of research drugs, doses and administration methods
- other intervention methods can improve the relevant contents of safety, effectiveness, feasibility and implementation details according to the characteristics of the intervention, Provide scientific evidence for the implementation of this intervention
- the full text of the product manual should be provided for the marketed products

5.4 study the relevant matters of the intervention

- subcutaneous injection of 60 mg / 6 months
- clear, colorless to light yellow solution
- store in a refrigerator at 2-8 ℃ away from light

6. Relevant regulations on combined medication, drugs allowed to be used, drugs used with caution, forbidden drugs and concomitant treatment

- None

7. Items and times of clinical and laboratory examinations to be carried out

- blood routine examination 4 times
- CRP 4 times
- X-ray of knee joint 4 times
- magnetic resonance of knee joint 4 times
- bone mineral density measurement 4 times

8. Evaluation

8.1 primary and secondary endpoint / outcome evaluation

- primary endpoint evaluation: VAS pain score, OKs function of knee joint at 1,3,6 months
- Secondary endpoint evaluation of: WOMAC score, incidence of adverse reactions, EQ-5D quality of life score
- Some participants opted to withdraw from the trial post-denosumab injection and proceed with knee replacement, with intraoperative synovial tissue obtained for H&E, IHC staining, and WB analysis.

8.2 safety evaluation

- incidence of adverse reactions
- physical examination
- important signs (such as body temperature, pulse, blood pressure)
- radiation or other imaging evaluation
- laboratory evaluation

9. Adverse events and serious adverse events

- events that do not endanger the patient's life and can return to normal after active treatment, such as limb pain, constipation, etc., are adverse times, The doctor in charge shall report to the attending physician within 6 hours, and the attending physician shall report to the chief physician within 12 hours.
- patients with irreversible and life-threatening events, such as jaw necrosis and atypical femoral fracture, are serious adverse events. The competent doctor shall report to the attending physician within 2 hours, and the attending physician shall report to the chief physician within 6 hours. The investigator will immediately report any SAE to the sponsor, whether or not related to the study intervention.

10. Statistical analysis and statistical methods

- for descriptive statistics, percentage is used to describe classified data, and mean ± standard layer is used to describe continuous data
- for inferential statistics, P value and confidence interval are calculated, and it is pointed out that one-sided or two-sided test

- there is no need to preset covariates
- hypothetical tests (such as normal test) are required, and no transformation or nonparametric test is required
- the main observation variable is the incidence of adverse reactions of patients, independent sample t-test and chi square test were used to describe and analyze
- the primary end points / secondary end points of the study were VAS pain score, knee OKs function score, WOMAC score, EQ-5D quality of life score. Independent sample t-test was used to describe and analyze
- mean, non-compliance and loss of follow-up patient data, ± standard deviation, percentage and 95% confidence interval were used to describe the statistical analysis results
- missing values were not included in the analysis

11. Medical treatment and protection of subjects

11.1 risk assessment of subjects in the study, risk disposal measures and plans

11.1.1 risk assessment

- natural risks are mainly two aspects. One is the adverse reactions of drugs used by patients for treatment, including gastrointestinal reactions, systemic reactions (alopecia, fever, rash, etc.), effects on various organs (cardiotoxicity, hepatotoxicity, pulmonary toxicity, neurotoxicity, urinary tract toxicity, etc.), infection, etc.
- There are two main aspects of human risk. One is researchers' compliance. Due to the tension of clinical work, many researchers are involved in clinical trials at the same time, so they are not familiar with the procedures or steps in the scheme, which increases the risk of scheme deviation and scheme violation during the implementation of the trial. For example, the subjects met the withdrawal criteria during the test but continued the test, failed to follow up or check the safety indicators according to the protocol requirements, and failed to record the adverse events during the study in time. The other is subject compliance. Different subjects have different purposes of participating in the clinical trial. The degree of cooperation of subjects also determines the success of the clinical trial. In some

clinical studies, subjects' expectations of research intervention are too high. If the psychological treatment effect of patients is not achieved within a period of time, it may also cause poor compliance of subjects, who do not take drugs according to the plan or do not continue to follow-up.

11.1.2 disposal measures and plans

- Improve the researchers' organization and management system and quality control system, and improve the system construction, including system, technical specifications, standard operating procedures (SOP), and strengthen the allocation and training of research echelons. In particular, we should improve the SOP and plan for emergency and critical treatment, establish a green channel for the transportation of emergency and intensive care units, and improve the plan for the transportation of patients in the hospital. First aid equipment and drugs should be managed in a normal and standardized way, special first aid drugs should be prepared according to different tests, and multi-specialty communication mechanism should be strengthened. Researchers participating in the trial should participate in the scientific and reasonable scheme design, establish targeted emergency plans and carry out training, strictly abide by the screening criteria of clinical trials, and be familiar with the clinical research scheme.
- Set up a medical protection and treatment team to be responsible for the prevention and treatment of medical risks in clinical research, regularly evaluate the risks, and put forward rectification measures to prevent risks.

During the study, once a medical risk occurs, the risk disposal plan should be launched immediately, and the clinical researcher should immediately report to the main investigator and the medical protection treatment team. And immediately take measures to protect patients. In dealing with overweight, it should be carried out quickly, orderly and effectively.

11.2 medical treatment and protection of subjects during the study

- subjects can withdraw unconditionally and voluntarily during any process of this study
- during the study, patients can consult doctors at any time if they have any questions or discomfort

- patients with drugs involved in this study do not need to pay their own expenses, and the research topic provides

11.3 medical treatment and protection of subjects after the study

- for patients who have discomfort after the study, there are effective routine treatment measures, Targeted treatment based on pain relief, detumescence, etc.
- after informing the patients of the research process in detail, they can consult medical services through the orthopedic clinic of Wuhan Union Medical College Hospital
- this study does not require the subjects to give up the right to receive free treatment and compensation for the damage related to the study

12. Supporting documents and precautions

12.1 informed consent process prior to the start of the study

- the informed consent form obtained the consent of the ethics committee. For patients who meet the admission criteria, we will discuss matters related to informed consent with patients and sign the informed consent. In the process of informed consent, we will inform patients of the research process, the purpose of the research, possible risks and their rights, answer the questions raised by the research objects, and tell the research objects that they are willing to participate in the research, and can withdraw from the research at any time. After withdrawing from the research, the medical health quality of patients will not be affected.

12.2 privacy protection

- this researcher actively informed patients that the protection of personal information involved in the research process mainly includes the following two aspects: 1. Information related to personal identity, such as name, gender, age, date of birth, work, education, home address, etc.; 2. Information related to personal health, such as medical records, family history and genetic history.
- when communicating with patients, choose a relatively private space to avoid the harm to patients caused by privacy leakage. When collecting patient data, the researcher conducted it under the condition of good confidentiality, trying to avoid

the existence of a third party

- all inspection reports and imaging reports in this study are specially kept by Xiaoguang, Zhang

12.3 collection and use of samples and data

- synovial samples obtained after knee arthroplasty for H&E, IHC staining, and WB analysis.
- this study does not involve third-party testing institutions or foreign-funded background research institutions. The collection of data is completed by Xiaoguang, Zhang and Yangyang, Shi, which is limited to the use of this research group.

12.4 quality control and quality assurance

- data are independently collected by Xiaoguang, Zhang and Yangyang, Shi, and the subjective data are taken as the average value
- the original documents are saved in detail and summarized and reported weekly, Jie Jia is the person in charge of quality control
- participants receive relevant training before carrying out clinical trials

12.5 data processing and record keeping

12.5.1 data collection and management

- the source data to be collected includes the following parts, CRF, medical records, AE, OKS knee score, EQ-5D score, WOMAC score, laboratory results and H&E, IHC staining and WB analysis of synovium from patients after knee replacement. Xiaoguang, Zhang and Yangyang, Shi are responsible for this part of data collection.
- data collection is carried out by clinical researchers under the supervision of the person in charge, who will be responsible for the accuracy, integrity and timeliness of the reported data. All data shall be clear to ensure traceability.
- a database will be established for safekeeping. The database is password protected, and a logic proofreading program will be set up when the database is established.

12.5.2 research data retention

- all research data and original documents shall be retained for a minimum of 2 years,

and permission shall be obtained before destruction.

12.6 issue agreement with data sharing

- participate in data sharing of all personnel

12.7 declaration of conflict of interest

- declaration of consistency of all participating members that there is no conflict of interest

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