ZOledronic acid as DIseAse-modifying drug in Knee osteoarthritis (ZODIAK)

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To study the effectiveness and safety of semi-annual zoledronic acid treatment for reducing articular cartilage and pain loss in knee osteoarthritis.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON50547

Source
ToetsingOnline

Brief title
ZODIAK

Condition

- Joint disorders

Synonym
osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW,ReumaNederland

Intervention

Keyword: Knee, Osteoarthritis, Treatment, Zoledronic acid

Outcome measures

Primary outcome

Change in total mean cartilage thickness in the tibial and load-bearing femoral regions of the most affected compartment of the tibiofemoral joint of the index knee on MRI, 24 months vs. baseline.

Secondary outcome

- Pain on a numeric rating scale at 6, 12, 18, and 24 months vs. baseline.
- KOOS (Knee injury and Osteoarthritis Outcome Score) at 6, 12, 18, and 24 months vs. baseline (pain, symptoms, daily activity, sport, quality of life).
- Pain medication use at 6, 12, 18, and 24 months vs. baseline.
- Bone marrow lesion size at 24 months vs. baseline.
- Change in joint space width on standardized knee radiographs at 24 months vs. baseline.
- Change in total mean cartilage thickness in the tibial and load-bearing femoral regions of the tibiofemoral compartment contralateral to the most affected compartmen of the index knee at 24 months vs. baseline.
- Change in total mean cartilage thickness in the tibial and load-bearing femoral regions of the index knee at 24 months vs. baseline.
- Safety.

Study description

Background summary

There is a great and growing need for disease-modifying treatment for primary

knee osteoarthritis.

Study objective

To study the effectiveness and safety of semi-annual zoledronic acid treatment for reducing articular cartilage and pain loss in knee osteoarthritis.

Study design

A placebo-controlled, double-blinded, randomized clinical trial, with a two-year follow-up.

Intervention

Zoledronic acid, intravenously, 4 mg in 100 cc 0.9% NaCl, semi-anually, four times.
Placebo: 100 cc 0.9% NaCl.

Study burden and risks

The burden and risks of participating in this study are estimated to be moderate.
Zoledronic acid is a registered drug for the prevention of fractures in patients with osteoporosis and Paget disease of bone. Mild side effects such as a flu-like reaction within the first 3 days after infusion are common. Patients will be advised to use paracetamol for alleviating symptoms. The frequency and severity of this adverse effect decrease with sequential infusions.
Potential side effects of concern are kidney dysfunction or hypocalcaemia (symptomatic or asymptomatic). To minimize the occurrence of these side effects, only patients without risk factors for these adverse effects will be included in this study. Daily calcium and vitamin D supplementation will be prescribed. This supplementation has no expected, significant adverse effects in this poulation. Kidney function and serum calcium levels will be checked before each infusion. Because medication is given intravenously there is a small risk for phlebitis or subcutaneous infusion.
All patients receive usual care for osteoarthritis, including lifestyle advices, physical therapy, pain medication. Only intra-articular treatments are not allowed.
The six required hospital visits will each take maximum 3 hours. To assess the effect of the treatment two radiographs and MRI's of the index knee will be made at the start and end of the study and questionnaires will be obtained at every hospital visit. Each MRI will take approx. 30 minutes. The two additional 7T-MRI's of the index knee in a subset of 20 participants will take 45 minutes each. Radiation exposure of the radiographs is considered negligible (0.04 mSv vs. yearly background radiation of 3.0 mSv).
Patients treated with zoledronic acid may benefit if cartilage degradation is

slowed down and/or pain is reduced. Patients receiving placebo have no other risks than those related to intravenous saline treatment.
If zoledronic acid appears to be effective for reducing cartilage loss and/or pain, extended observation of study participants will be pursued. Patients from the placebo group will very likely not yet get access to treatment with zoledronic acid at that stage.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age between 40 and 70 years.
- Primary tibiofemoral (TF) knee OA according to clinical and radiographic ACR criteria. When two knees are eligible, the most painful knee is chosen as index knee. When knees are equally painful the index knee will be selected randomly.

The most affected compartment (MAC) of the index is defined as the TF compartment with the most radiographic joint space loss.
- Pain in the index knee on at least 50% of the days of the previous month (NRS between 4/10 and 8/10).
- At least one bone marrow lesion (BML) in the MAC of the index knee on MRI, as judged by a trained researcher. A BML is defined on T2-weighted MRI sequences as a zone of altered signal intensity in the bone and marrow, located immediately beneath the articular cartilage and visible on at least two consecutive slices.

Exclusion criteria

- Severe structural OA of the MAC of the index knee on plain radiograph: grade 3 radiographic joint space narrowing of the index knee, according to the Osteoarthritis Research Society International atlas.
- Planned or expected surgery of index knee in the next 2 years (physician judgment).
- Intra-articular injection into the index knee: glucocorticoids, hyaluronic acid, or platelet-rich plasma within the last 6 months.
- Knee pain from other causes than knee OA (e.g. fibromyalgia)
- Secondary OA, such as secondary to inflammatory joint disease, significant trauma, metabolic disease, and/or extreme varus or valgus position of the knee (i.e. more than 10º).
- Other self-reported diseases with potential effects on current bone metabolism (e.g. thyroid or parathyroid disease, malignancy, bone fracture within past 6 months).
- Self-reported disease that limits intestinal absorptive capacity (e.g. celiac disease or short bowel syndrome).
- Previous allergic reaction to zoledronic acid, another bisphosphonate, or other substances in the solute.
- Previous and/or current use of bisphosphonates, denosumab, teriparatide, strontium ranelate, calcitonin and/or raloxifene.
- Current use of loop diuretics, glucocorticoids, aminoglycoside antibiotics.
- Uncontrolled or actively treated dental disease and/or otitis.
- Current or previous atrial fibrillation.
- Abnormal blood tests: serum ionized calcium higher than 1.32 mmol/l or lower than 1.15 mmol/l, serum (25OH) vitamin D lower than 50 nmol/l, or estimated creatinine clearance lower than 60 ml/min.
- Contraindications to MRI (e.g. claustrophobia, MRI-incompatible devices/implants/foreign objects).
- Insufficient ability to communicate in Dutch.
- Pregnancy or lactation.
- Other factors that prevent subjects from adhering to the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-08-2018
Enrollment:	86
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zoledronic acid Fresenius Kabi concentrate for infusion 0.8mg/ml in 5ml
Generic name:	zoledronic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-02-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-04-2018
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24160
Source: Nationaal Trial Register

Title:

In other registers

Register	ID
EudraCT	EUCTR2017-001157-14-NL
CCMO	NL61307.041.17
OMON	NL-OMON24160