Zoledronaat ter behandeling van pijn en gewrichtsschade ten gevolge van knieartrose

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Semi-annual treatment with zoledronic acid reduces both pain and progression of structural damage in knee osteoarthritis patients with MRI-observed bone marrow lesions

Ethische beoordeling	Goedgekeurd WMO
Status	Werving gestopt
Type aandoening	Gewrichtsaandoeningen
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24160

Bron
Nationaal Trial Register

Verkorte titel
ZODIAK

Aandoening

- Gewrichtsaandoeningen

Aandoening

Knee osteoarthritis

Betreft onderzoek met
Mensen

Ondersteuning

Primaire sponsor: University Medical Center Utrecht
Overige ondersteuning: The Netherlands Organisation for Health Research and Development (ZonMW), Dutch Arthritis Foundation

Onderzoeksproduct en/of interventie

Toelichting

Uitkomstmaten

Primaire uitkomstmaten

Total mean cartilage thickness in the tibial and load-bearing femoral regions of the MAC of the index knee on MRI (mm)

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Osteoarthritis (OA) is the most common joint disease worldwide, causing pain and disability in hundreds of millions of people worldwide. Yet, disease-modifying drugs are not available for OA. Disease-modifying drugs for OA (DMOADs) should, by definition, have the capability of both slowing down joint deterioration and reducing pain. Antiresorptive drugs for osteoporosis may be effective DMOADs. For example, zoledronic acid has been suggested to be an effective DMOAD in several in vitro studies, animal studies, and observational studies in human. It may be hypothesized that antiresorptive treatment is particularly effective in subsets of knee OA patients in whom increased metabolic activity of the bone is part of the pathogenesis of knee OA. We hypothesize that semi-annual treatment with zoledronic acid will reduce both pain and progression of structural damage in knee OA patients with MRI-observed bone marrow lesions (BMLs) suggesting periarticular bone involvement. Objective: To investigate efficacy of zoledronic acid in reducing cartilage loss, pain, and disability in patients with symptomatic knee OA with BMLs. Study design: Single-center, placebo-controlled, double-blind, randomized clinical trial. Study population: 86 Patients, ≥40 years old, with symptomatic tibiofemoral (TF) knee OA and ipsilateral BMLs on MRI. Intervention: Patients will be randomized in a 1:1 ratio to receive either 4 mg zoledronic acid or sodium chloride intravenously, every 6 months during 2 years (4 gifts in total). Main study parameters/endpoints: Study endpoints are MRI-observed cartilage thickness in the most affected TF compartment (MAC) of the index knee (mm, primary outcome parameter), radiographic joint space width in the MAC of the index knee (mm), and BML size in the MAC of the index knee (mm2) at 24 months vs. baseline, and NRS pain, KOOS pain and function, utilisation of pain medication at 6-month intervals between baseline and 24 months, and adverse events throughout the study period (NRS = numeric rating scale, KOOS = Knee disability and Osteoarthritis Outcome Score). Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Zoledronic acid is registered for preventing osteoporotic fractures, complications from osseous metastasized malignancies, and treating Paget’s bone disease and malignancy-induced hypercalcemia. It is generally well-tolerated. A flu-like reaction within the first 3 days after treatment is common, resolves spontaneously in a few days, and usually responds to paracetamol. Potential serious side

effects are renal insufficiency, hypocalcaemia, osteonecrosis of the jaw, and atypical femur fractures. Therefore, only patients with normal kidney function, with normal serum levels of calcium, without dental problems, without malignancies, without previous antiresorptive treatment, and without vitamin D deficiency at baseline will be included. Patients will receive daily calcium and vitamin D supplementation. Kidney function and serum calcium levels will be monitored before each infusion and at the final visit. Zoledronic acid will be administered in a day-care setting, according to local protocols and safety procedures. In total, patients will need to visit the hospital six times over two years (i.e. screening visit, day-care department visits at 0, 6, 12, and 18 months, and final visit at 24 months). Day-care department visits will each take 1-2 hours. They will have to undergo an MRI scan and two radiographs of their index knee (posteroanterior and lateral view) twice. MRI scans will take 30 minutes each. The knee radiographs will expose patients to a summed effective radiation dose of 0.04 mSv, which is considered small as compared to the yearly background radiation of 3.0 mSv. (1) Other outcome parameters will be collected via questionnaires. Venous blood samples will be collected five times, for safety outcomes. All patients will receive usual care for knee OA from their treating physicians. Only intra-articular injections into the index knee are discouraged and will lead to study dropout. Pain medication will not be restricted, but documenting pain medication use will be requested. When zoledronic acid proves effective in reducing pain and structural damage from knee OA, patients in the treated group will benefit from these effects. Patients in the placebo group have no other risks than those related to intravenous saline treatment and oral calcium and vitamin D medication (negligible).

Doel van het onderzoek

Semi-annual treatment with zoledronic acid reduces both pain and progression of structural damage in knee osteoarthritis patients with MRI-observed bone marrow lesions

Onderzoeksopzet

0, 6, 12, 18 and 24 months

Onderzoeksproduct en/of interventie

Zoledronic acid 4 mg or placebo (sodium chloride), four times, at six-month intervals

Contactpersonen

Publiek

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Deelname eisen

Leeftijd
Volwassenen (18-64 jaar)
Volwassenen (18-64 jaar)
65 jaar en ouder
65 jaar en ouder

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Age between 40 and 70 years. - Primary tibiofemoral (TF) knee osteoarthritis (OA) according to clinical and radiographic American Collega of Rheumatology 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 (numeric rating scale 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Severe structural osteoarthritis (OA) of the most affected compartment 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. - 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. >10º). - Knee pain from other causes than OA, such as fibromyalgia or (pseudo)radicular syndrome. - 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 >1.32 mmol/l or <1.15 mmol/l, serum (25OH) vitamin D <50 nmol/l, or estimated creatinine clearance <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.

Onderzoeksopzet

Opzet

Fase onderzoek:	2
Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo
Doel:	Behandeling / therapie

Deelname

Nederland

Status:	Werving gestopt

(Verwachte) startdatum:	17-08-2018
Aantal proefpersonen:	86
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Goedgekeurd WMO

Datum:	24-04-2018
Soort:	Eerste indiening
Toetsingscommissie:	METC NedMec

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 50547
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8009
CCMO	NL61307.041.17
EudraCT	2017-001157-14
OMON	NL-OMON50547

Resultaten