Pamidronate for pain in adult chronic nonbacterial osteitis (PAM-CNO): a randomized, double-blind, placebo-controlled trial

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This study has been transitioned to CTIS with ID 2023-510309-16-00 check the CTIS register for the current data. The primary objective to demonstrate that in CNOpatients with pain 3-monthly treatment with pamidronate will result in significant...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON52471

Source
ToetsingOnline

Brief title
PAM-CNO trial

Condition

- Bone disorders (excl congenital and fractures)

Synonym
SAPHO-syndrome, sterile bone inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: ReumaNederland beurs

Intervention

Keyword: Bisphosphonate, Chronic nonbacterial Osteitis, Chronic nonbacterial osteomyelitis, Musculoskeletal Pain, Quality of life, SAPHO, Sternocostoclavicular hyperostosis

Outcome measures

Primary outcome

Change in score of maximal pain on BPI (VAS 0-10) from baseline to 6 months .

Secondary outcome

• Change in range of motion

• Number of patients with mild pain (maximal pain as measured with NRS score in

BPI 4 or below)

• Number of patients with 50% reduction in maximal pain (NRS score in BPI)

• Change in shoulder rating questionnaire11 and facets of SFA score12 (among

which are ability to dress)

• Change in general health, quality of life, fatigue, work activity score,

physical activity, and partner burden

• Change in standard dose of analgesics (including NSAIDs) possible during

course of the study as evidence for efficacy of treatment.

• Evaluation of confounding factors for outcome of treatment such as delay in

diagnosis and the amount of baseline tracer uptake, pain and range of motion

• Evaluation of a possible neuropathic component of the reported pain

• Number of SCCH patients exhibiting signs of central sensitization

• Association between central sensitization and therapeutic response

• Change in biochemical markers of inflammation

• Amount of tracer uptake of CNO lesions on Na18F-PET/CT

• Cost-effectiveness

• Spinal involvement

Study description

Background summary

Chronic nonbacterial osteitis (CNO) is a rare inflammatory disorder of the axial skeleton, mainly affecting sternum, clavicles and upper ribs. Patients present with swelling and pain in the affected areas and impaired movement of the shoulder girdle. Disease burden is high, and impaired quality of life common. Radiological features include sclerosis and hyperostosis, with increased radioactive isotope uptake on skeletal scintigraphy. Awareness for SCCH is low and diagnosis often delayed, associated with progressive pain, increasingly impaired quality of life, and difficulties in remaining in the workforce.

There is no approved therapy for CNO. The precise trigger for the underlying inflammation associated with local increases in bone turnover is not known. NSAIDs are mostly effective in controlling symptoms in early stages of the disorder (own observations). Literature data on the use of intravenous bisphosphonates or TNF a inhibitors, are scarce and none available from randomised placebo-controlled trials (RCTs).
The rationale for using bisphosphonates in SCCH, is based on the likelihood of pain to be due to the local increase in bone turnover, which should respond to treatment with these agents, although a potential direct anti-inflammatory effect of bisphosphonates is also possible. In our Center, we have been effectively and safely treating patients with SCCH with intravenous bisphosphonates for over two decades, with an observed favourable outcome of reduction in pain, improvement in shoulder mobility, and prevention of disease progression in a majority of patients (unpublished observations). However, there is a need to confirm these promising observations by means of RCTs, using validated tools for evaluation of changes in pain, shoulder girdle function and quality of life in response to treatment, which is the reason for this study.

Study objective

This study has been transitioned to CTIS with ID 2023-510309-16-00 check the CTIS register for the current data.

The primary objective to demonstrate that in CNOpatients with pain 3-monthly treatment with pamidronate will result in significant decrease in maximum pain score (as measured with BPI) as compared to placebo.

Secondary objectives:
• To study the number of patients with mild pain (maximal pain 4 or below 4) after 3-monthly treatment with pamidronate
• To study the number of patients with 50% reduction in maximal pain (VAS score in BPI)
• To study change in shoulder rating questionnaire (SRQ) and facets of Shoulder function assessment (SFA) score (among which is ability to dress)
• To study change in range of motion
• To study improvement in general health as measured with Short Form Health Survey (Sf-36), work activity score, and physical activity International Physical Activity Questionnaire (IPAQ, short form, previous 7 days)
• To investigate partner burden before and after therapy using Care-related Quality of Life Instrument (CarerQol)
• To study a change in standard dose of analgesics possible during course of the study as evidence for efficacy of treatment
• Evaluation of confounding factors for outcome of treatment such as delay in diagnosis and the amount of baseline tracer uptake, pain and range of motion
• Significant alteration of inflammation and quantifiable decrease in Na18F-PET/CT tracer uptake of SCCH lesions after pamidronate therapy, and its relation to disease symptoms as measured using above mentioned questionnaires and SFA
• Evaluation of a possible neuropathic component of the reported pain (pain detect)
• To estimate the number of CNOpatients exhibiting signs of central pain sensitization by Central Sensitization Inventory (CSI) (18)
• To determine the association between central sensitization symptomatology and patient reported outcomes (pain) after treatment with pamidronate/placebo, amongst which the primary outcome measure (maximal pain)
• To evaluate cost-effectiveness of therapy in an economic evaluation
• To assess spinal involvement of SCCH-lesions

Study design

Adult patients with an established diagnosis of CNO with a reported maximum pain score >= 6/10, signs of disease activity on imaging,
and no treatment with bisphosphonates for the previous 6 months will be included in the study.
Female patients should be warned of the need to use contraceptives during the study because of
absence of data on possible teratogenic effect of bisphosphonates.

The design of the first 6 months of the study is double-blind placebo-controlled. Randomization
(computer based) will be performed for either pamidronate or placebo infusions.

Treatment with
intravenous pamidronate (30 mg/day on 3 consecutive days) or placebo (saline 0.9%) will be given
at time point 0 and after 3 months. The hospital pharmacy will prepare the active
and placebo study medication. Placebo will be similar in appearance as pamidronate and the
research nurse will be blinded to its nature while administering it, as will be patients, doctors and
researchers.

Patients are allowed to use analgesics. NSAIDs may be continued or decreased during the study, but increase is not preferred. If necessary to achieve pain control, patients are instructed to report increase of NSAIDs to the researcher. All analgesics are recorded in the patient diary and thus available for the researcher. Patients are allowed to use analgesics, for which NSAIDs will be fixed to the dosage used before
start of the trial. Patients can continue using their normal own medication after providing a list of
these medications. Study medication (pamidronate or placebo) will only be started if vitamin D level
is adequate, with serum calcium and levels within the normal range. If necessary, calcium
and vitamin D will be started or dosage will be increased. During infusion of study medication
patients will be advised to use paracetamol 1000 mg QD during one to three days depending on
symptoms of acute phase reaction. They are allowed to start or continue physiotherapy.

After the first 6 months, the study will stop being double-blind placebo-controlled and will follow an
open label design. Patients can choose between pamidronate treatment in the same schedules at month 6 and month 9, or only analgesic treatment.

Every 3 months patients will be requested to complete the following questionnaires:
- BPI to assess pain and interference of pain with daily life
- Pain-DETECT to assess neuropathic pain
- S,shoulder rating questionnaire and shoulder function assessment to assess shoulder complaints.
- Work activity (work activity score) to assess work activity
- IPAQ will be used to evaluateto assess physical activity both during work and leisure time (short form, last 7 days)
- sf-36 for general health
- ,MVI-20 for fatigue
- EQ-5D for quality of life

- CarerQol for partner burden
- Patient Global Impression of Change (PGIC, score 0-7) will be used to evaluate changes in well-being.
- Central Sensitization Inventory (CSI) to assess symptoms of pain sensitization (only at baseline, month 6 and month 12)
- For economic evaluation the iMCQ questionnaire, and iPCQ questionnaire will be evaluated every 3 months to measure healthcare use and productivity respectively

Expected results
It is expected that 3-monthly pamidronate courses will decrease the locally increased bone turnover, to be confirmed by a quantifiable decrease in radioisotope uptake on Na18FD-PET/CT scans and that this will be associated with a measurable decrease in pain scores (primary endpoint), improvement in shoulder girdle function, quality of life, and physical and work activity (secondary endpoints) in the active treatment arm compared to placebo.

Conclusion
CNO is a rare bone disease of unknown aetiology, with to date no approved treatment. The objectives of our proposed RCT are three-fold: to confirm our long-term experience spanning more than two decades on the favourable outcome of 3-monthly intravenous pamidronate on the clinical manifestations of SCCH; to evaluate the potential contribution of an anti-inflammatory effect of bisphosphonates to the outcome of treatment; and to explore the potential use of quantification of radioisotope uptake on sequential Na18FD-PET/CT scans to monitor disease activity and thus outcome of treatment.

Intervention

Pamidronate infusion 30 mg/day (diluted in 0.9% saline) or placebo (0.9% saline) on 3 consecutive days, at start of the study and after 3 months (double blind randomized phase) and possibly during open label phase pamidronate 30 mg/day (diluted in 0.9% saline) at month 6 and month 9.

Study burden and risks

Burden and risks of participation are minimal, since care is similar to standard care, and pamidronate is used for decades for osteoprosis and metabolic bone diseases. The only differences between this study and Standard Care Path are questionnaires every 3 months (20 minutes for all questionnaires) and keeping a pain/fatigue and analgesic use diary 2x per week. Risks for pamidronate are well known: possible acute phase respons after first application (fever, myalgia and arthralgia up to several days after application), hypocalcemia although this can be prevented if serum calcium/vitamine D and PTH are normal before infusion (which will be checked), and the very rare complication of osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF). ONJ is hardly ever seen in case of this dosage, and mainly if dental hygiene is poor; in case of poor dental hygiene patients will only get pamidronate after maxillary surgeon consultation. Every visit patients will be asked for complaints pointing at AFF.

The radiation exposure does not constitute an additional risk as well. For this study, 2 total body low dose Na18F PET-CT scans will be performed at t=0 and t=12. This is part of the standard care as currently available at the LUMC/Alrijne Ziekenhuis for CNO . Until recently, standard care encompassed 99mTc+SPECT-CT scans. The radiation exposure of a single PET-scan is lower than this conventinal SPECT-CT: 3.4mSv +7.1 mSv (99mTc+SPECT-CT) versus 1.7 + (5.5+1.7) mSV for the newly introduced Na18F PET-CT. At t=6 months not a total body CT will be performed, but a Na18F PET-CT of the sternum solely. The radiation exposure for the scans at T0 and T12 = 1.7 mSv for PET + 5.5mSv for LDCT TB= 7.2 mSv. The scan at T=6 = 1.7 mSv (PET) + 3.5 mSv (CT sternum) = 5.2 mSv. The total radiation exposure for this study is therefore 7,s x 2 + 5,2 = 19.6 mSv. As only the scan at T=6 is additional in comparison to standard care, the extra radiation exposure is 5,2 mSv. The study therefore falls into the risk category of 1-10 mSvdetr.

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

Adult patients (> 18 years of age or older) with an established diagnosis of CNO based on clinical imaging features with a reported maximum pain score of 6/10 or higher and signs of active disease on imaging, and no treatment with bisphosphonates for the previous 6 months, and willing to participate.

Exclusion criteria

Patients who are under 18 years of age will be excluded. Active pregnancy wish, pregnancy or nursing are exclusion criteria. Patients with generalized pain without CNO-related pain are excluded. Bisphosphonate use during previous 6 months before study entry, bisphosphonate allergy, estimated glomerular filtration rate < 30 ml/min, uncontrolled endocrine abnormalities, and active cancer treatment are exclusion criteria. Patients will not be included in the study in case of language barrier, severe co-morbidity, including poor mobility and other causes preventing attendance for control visits, as are mentally disabled patients. In case of poor dental hygiene or inadequate dental care, patients will only be enrolled after oral maxillary surgeon consultation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-12-2020
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pamipro
Generic name:	pamidronate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-11-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	01-12-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	21-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	19-04-2021

Application type: Amendment

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Approved WMO
Date: 12-08-2021

Application type: Amendment

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Approved WMO
Date: 01-12-2021

Application type: Amendment

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Approved WMO
Date: 01-07-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 29-04-2024

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 07-05-2024

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 19-08-2024

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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: 27475
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2023-510309-16-00
EudraCT	EUCTR2020-001068-27-NL
CCMO	NL68020.058.20