

BMJ Open Efficacy of bisphosphonates in specific knee osteoarthritis subpopulations: protocol for an OA Trial Bank systematic review and individual patient data meta-analysis

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ABSTRACT

Introduction Randomised clinical trials to date investigating the efficacy of bisphosphonates in knee osteoarthritis (OA) have found divergent results, with a recent meta-analysis finding no superiority of these drugs over placebo. Whether particular patient subgroups are more likely to benefit from this therapy than others is still unclear. We aim to investigate the effects of bisphosphonates compared with a control group (placebo, no treatment, another active treatment) on clinical and structural outcomes in specific knee OA subpopulations with possible distinct rates of subchondral bone turnover.

Methods and analysis Medline, Embase, Scopus, Web of Sciences and Cochrane Central Register of Controlled Trials will be searched from inception to February 2018. Randomised clinical trials will be eligible if they reported at least one potential treatment effect modifier at baseline: gender, menopausal status, age, body mass index, radiographic stage, knee pain severity, presence of bone marrow lesions, levels of biochemical markers of bone turnover (serum and/or urinary) and systemic bone mineral density status. Authors of original trials will be contacted to obtain individual patient data from each study. Risk of bias will be assessed using the Cochrane Collaboration's tool. The primary outcomes will include pain and radiographic joint space width loss. Studies using other MRI-based assessment of disease progression will also be eligible. Outcomes will be grouped into short-term (≤ 3 months), intermediate-term (> 3 months; ≤ 12 months) and long-term (> 12 months). Regression models will be used, adding an interaction term for each subgroup of interest to determine possible subgroup effects. There was no source of funding for this study.

Ethics and dissemination Dissemination of our findings is planned to occur through conference presentations, publication in peer-reviewed journals and social media. No formal ethics approval is generally required as no new data collection will be undertaken.

Strengths and limitations of this study

- Particular subgroups of patients with knee osteoarthritis (OA) may be more likely to benefit from bisphosphonate therapy than others. Previous clinical studies, including conventional meta-analyses, were unable to address this important issue.
- We will use individual patient data meta-analysis, which allows for more consistent identification and extraction of common individual-level characteristics, standardised outcome measures and greater statistical power to conduct subgroup analyses.
- The OA Trial Bank is an international initiative aimed to foster research on the identification of OA patient subgroups for targeted treatment. A steering committee has assessed and approved this study initiative and will provide support for all procedures related to data collection, transfer and management.
- The analyses planned will depend on availability of data provided for this study.
- The variables that will be tested as potential treatment effect modifiers are possibly associated with but are not direct measures of distinct rates of subchondral bone turnover.

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INTRODUCTION

Osteoarthritis (OA) affects more people than any other type of arthritis.¹ The overall lifetime risk of suffering from knee OA is estimated to range from 14% to 44% for the general population.^{2 3} However, specific subpopulations are at higher risk: around 20% to 60% of obese individuals and 34% to 56% of individuals with significant knee injury will develop knee OA.^{2 4} OA was ranked the 12th major cause of global disability in 2016 among all other medical conditions and showed one of

the greatest rises in years lived with disability over the last decade.⁵ This high and growing burden of OA threatens healthcare systems and desperately demands more efficacious treatments to prevent the structural and clinical deterioration associated with this condition.

Subchondral bone is a potential target in OA as there is extensive literature showing the important role of subchondral bone remodelling in OA pathogenesis.⁶⁻⁹ Microstructural subchondral bone changes start early in the OA process, promoting neovascularisation and growth of sensory nerves to the deepest cartilage layers, which facilitate the exchange of local factors between these tissues.⁶ Preclinical studies have demonstrated that bone and cartilage interact through biochemical, cellular and mechanical mechanisms, which contribute to joint pain, changes in cartilage homeostasis and subsequent joint damage.⁹⁻¹⁰ The subchondral bone in OA knees has been characterised as having a high turnover state, resulting in relative hypomineralisation and bone weakness; however, increased subchondral bone thickness and volume have also been observed, which might result in an overall increase in subchondral bone stiffness.¹⁰ A preclinical study suggested an increase in bone resorption in the onset of OA development while increased bone formation prevails in later stages.¹¹ Nevertheless, early subchondral bone changes in human OA joints are still less understood.

Bisphosphonates are a class of medication commonly used in the treatment of osteoporosis and other metabolic bone disorders, acting primarily on osteoclasts in active remodelling sites in the skeleton.¹² Through the inhibition of osteoclast-induced bone resorption, bisphosphonates decrease bone remodelling and improve bone mineralisation and trabecular microarchitecture.¹² Numerous preclinical studies have shown a protective effect of bisphosphonates on joint structure, improving subchondral bone quality and protecting the hyaline cartilage from damage,¹³⁻¹⁴ in addition to a possible reduction in synovitis.¹⁴⁻¹⁵ Moreover, observational clinical studies have suggested a potential benefit of bisphosphonates in reducing knee pain,¹⁶ joint space width loss,¹⁶ spinal osteophyte progression¹⁷ and rate of total knee replacement.¹⁸⁻¹⁹ However, a few of these studies were specifically conducted in populations with osteoporosis and it is unclear whether the subchondral bone in these individuals is more prone to beneficially react to the effect of bisphosphonates.¹⁷⁻¹⁹⁻²⁰ Despite these encouraging results, clinical trials to date testing the effectiveness of bisphosphonates on clinical and structural outcomes have found mixed results.²¹ Moreover, a recent systematic review and meta-analysis on bisphosphonates in knee OA including seven randomised, placebo-controlled trials (3013 patients) found no differences in pain, function and the proportion of patients experiencing radiographic progression.²²

There is a growing body of literature describing heterogeneity in the pathogenesis and clinical and structural manifestations of OA.²³ It has been suggested

that increased subchondral bone remodelling may not be universal to all patients or through all stages of the disease process.²⁴⁻²⁷ As a consequence, targeting the OA population as a whole may conceal beneficial effects of bisphosphonates if only specific subgroups of patients experience benefits from the therapy. Other authors have highlighted the need to identify the 'right people at the right time' in whom bisphosphonates may be of benefit.²⁴ Post-menopausal women with decreased subchondral bone density and increased remodelling,²⁵ early OA stages²⁶⁻²⁸ and presence of bone marrow lesions (BMLs)²⁹⁻³⁰ were particularly highlighted as potential subpopulations likely to benefit from bisphosphonates.²⁷ In addition, there is a marked difference in potency across different types of bisphosphonates. This variation is mainly related to the presence of a nitrogen molecule in the structure of the most contemporaneous bisphosphonate drugs, which could also be a factor affecting the magnitude of treatment effect.¹²

The OA Trial Bank is an initiative aimed to foster research on the identification of OA patient subgroups for targeted treatment through individual patient data (IPD) meta-analysis.³¹⁻³² IPD meta-analysis is the gold standard for reviews aiming to synthesise the evidence of clinical studies and is a useful technique to conduct well-defined subgroup analyses as it enables more consistent identification and extraction of common individual-level characteristics, standardised outcome measures and greater statistical power to conduct subgroup analyses.³³⁻³⁴ Prior conventional meta-analyses on bisphosphonates in OA were unable to address this important issue of identifying subgroups of individuals who may most benefit from bisphosphonate therapy.²¹⁻²²⁻³⁵ The steering committee of the OA Trial Bank ensures the appropriateness of the research question and methodology and a strategy is in place to contact the authors of eligible clinical trials in order to obtain original research data from each study.

The unacceptable lack of disease-modifying agents in OA combined with suggestive evidence of a role for bisphosphonates in selected patient subgroups underlies the need for methodologically sound studies to potentially identify differential effects of bisphosphonates in predefined knee OA subpopulations. Under the expertise of the OA Trial Bank, we aim to conduct a systematic review with IPD meta-analysis to perform subgroup analysis of existing clinical trials on the efficacy of bisphosphonates on clinical and structural outcomes in patients with knee OA.

METHODS

A summary of the study proposal along with the research question has been approved by the steering committee of the OA Trial Bank before the preparation of the full study protocol. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-IPD (PRISMA-IPD) checklist to ensure the quality of reporting of this systematic review and IPD meta-analysis protocol.³⁶

Literature search

Identification of studies

We will search the following databases: Medline, Embase, Scopus, Web of Sciences and Cochrane Central Register of Controlled Trials from inception to February 2018. Reference lists of selected studies and relevant reviews will be hand searched for additional studies and Google Scholar will be searched for additional citations associated with the final included studies. The search strategy will contain a combination of key search terms (and related terms) including three main filters: (1) *population*: OA and knee; (2) *intervention*: bisphosphonate, clodronate, tiludronate, etidronate, alendronate, zoledronic acid (or zoledronate), pamidronate, risedronate, neridronate, ibandronate, olpadronate, incadronate; (3) *study design*: randomised and trial. The full search strategy can be found in online supplementary appendix 1. All titles and abstracts will be imported into EndNote X7 for the screening process.

Screening process

Two independent reviewers (LAD, WMO) will screen all titles and abstracts for potentially eligible studies. In a second step, the full text of the selected studies will be assessed for eligibility by the same independent reviewers and any disagreements will be discussed and resolved with a third reviewer (DJH) if consensus is not achieved. The results of the literature search will be summarised in a flowchart as suggested by the PRISMA guidelines.³⁷

Study selection

All trials that fulfil the following eligibility criteria will be included in the IPD meta-analysis.

Inclusion criteria

Participants

Studies including participants with a diagnosis of symptomatic knee OA according to the American College of Rheumatology classification criteria,³⁸ physician diagnosis or other diagnostic criteria based on clinical manifestations, with or without radiographic data.

Intervention

All bisphosphonates will be considered for the purpose of this study regardless of the route of administration (oral, intravenous or intra-articular), dosage or molecular characteristics (nitrogenous vs non-nitrogenous).

Control

Trials comparing bisphosphonate treatment with a control group (placebo, no treatment or another active treatment) will be eligible.

Outcome

Trials will be eligible if there are individual patient data available for both bisphosphonate and control groups on at least one of the following outcomes: knee pain (primary clinical outcome), irrespective of the scale used, or structural disease progression based on radiographic

joint space width (JSW) (primary structural outcome) or other MRI-based assessment of disease progression, at baseline and any follow-up time points.

Study design

Only studies that are randomised clinical trials will be eligible.

Variables for subgroup analyses: All studies included in the IPD meta-analysis should have at least one of the variables that will be used as potential treatment effect modifiers assessed at baseline (described in the 'Subgroup Analyses' section below).

Exclusion criteria

Studies in which the intervention group received bisphosphonate combined with another active treatment (pharmacological or non-pharmacological) will be excluded. We will also exclude studies exclusively assessing the effect of bisphosphonates in animals or in joints other than the knee, reviews, editorials, conference abstracts with no other source of data available, and non-randomised trials. There will be no language restriction.

Data acquisition, transfer and checks

We will use the same strategy for data acquisition and transfer used in all other studies in the OA Trial Bank.^{31 39} The corresponding author of the eligible trials will be contacted first by email with two subsequent email reminders, followed by telephone if needed. If the corresponding author is unavailable, the other trial authors and/or institutions listed will be contacted. On favourable response and willingness to share the data, data deliverers will be asked to sign the data delivery license agreement, which will contain items on input data, obligations, ownership of data, terms, authorship, subgroup analyses planned and dissemination of the results. All de-identified data will be transferred to a secure database at Erasmus University Medical Center, Rotterdam, the Netherlands. Data sets will be accepted in any format, provided that variables and categories are adequately labelled within the data set or with a separate codebook. To ensure quality, data from all studies will be checked for duplicates and completeness. Outliers or unusual values will be assessed by range checks. Numbers related to participants baseline characteristics and changes over time for the primary outcome measures will be compared with published papers to check for consistency. In case of differences, authors of the original studies will be contacted to clarify any discrepancies.

Methodological quality assessment

Two raters (LAD, WEvS) will independently assess the risk of bias and the quality of evidence of the included studies using the 12 items from the Cochrane Collaboration's tool.⁴⁰ The following areas will be assessed: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective reporting and other sources of bias. Each item will be scored as yes (low risk

Table 1 Potential treatment effect modifiers

Characteristic	Description
Gender	Male vs female
Menopausal status	Premenopausal vs postmenopausal
Age (years)	Continuous variable
Body mass index* (BMI)	BMI ≥ 30 (obese) vs < 30 (non-obese)
Radiographic osteoarthritis (OA) stage	Radiographic minimum joint space width (continuous); Kellgren Lawrence grade
Baseline knee pain severity	Continuous variable
Bone marrow lesion (BML)	Presence of at least one moderate to large BML vs absence of presence of small BML
Baseline levels of systemic markers of bone turnover (eg, CTX-I, CTX-II and NTX-I)	\geq mean value vs $<$ mean value†
Systemic bone density status	Either as continuous variable or presence vs absence of osteopenia/osteoporosis

*Measured in kg m^{-2} .

†Values will be standardised if the distribution is skewed.

of bias), no (high risk of bias) or unclear. A low risk of bias study will be defined as fulfilling six or more of the criteria items, as previously used in other studies in the OA Trial Bank.^{39 41} Any disagreements will be discussed and resolved by consensus or consulting a third reviewer (BTS).

Subgroup analyses

The characteristics that will be assessed as potential treatment effect modifiers if sufficient data are available are (table 1): (1) gender: male vs female; (2) menopausal status: premenopausal vs post-menopausal; (3) age (as continuous variable); (4) body mass index (BMI): obese (BMI $\geq 30 \text{ kg m}^{-2}$) vs non-obese; (5) radiographic disease stage, assessed by baseline radiographic minimum JSW or Kellgren Lawrence grade,⁴² depending on data availability; (6) knee pain severity at baseline (as continuous variable); (7) BMLs: presence of at least one moderate or large BML on MRI vs absence or presence of small BML; (8) baseline levels of serum or urinary biochemical markers of bone turnover (eg, CTX-I, CTX-II and NTX-I): \geq or $<$ mean value (values will be transformed if the distribution is skewed); and (9) systemic bone mineral density status (either as continuous variable or presence vs absence of osteopenia/osteoporosis).

Data analysis and reporting

A descriptive synthesis of each study and participants' demographic characteristics will be conducted. Publication bias will be investigated using funnel plot analysis.⁴³ Assessment of heterogeneity across trials for the primary

outcomes will be based on the I^2 . A complete case analysis will be carried out preferably over imputation of missing data. If a high proportion of missing data is encountered, multiple imputation will be used for potential treatment effect modifiers and covariates within each trial due to missing at random assumption before the results are pooled⁴⁴ and a sensitivity analysis will be carried out to assess any difference in results compared with the non-imputed data set.

For the analysis of the magnitude of treatment effect in the whole population, including all studies, and in each specific subgroup of interest described above, a one-step approach meta-analysis will be carried out as the primary analysis.⁴⁵ This is done by appending the data from all studies after appropriate standardisation of variables and outcomes has taken place and performing the analyses in this new dataset. To assess for possible subgroup effects, interaction effects will be determined using random-effects regression models, adding an interaction term for each subgroup of interest and adjusting for a variable representing the study to account for residual confounding by study differences. As a secondary analysis, a two-stage meta-analysis approach will be used. According to this approach, subgroup analysis will be performed within each trial for all standardised outcomes. In a second step, interaction terms will be pooled for each potential predictor using random-effects models in the same way as conventional meta-analysis with aggregated data. The main comparison will be made between bisphosphonate and placebo and other comparisons will be planned according to the availability of trials and data.

Risk ratios and 95% CI will be the preferred measure of effect to be presented for dichotomous outcomes (radiographic progression, other MRI-based assessment of disease progression and progression to total knee replacement). Mean differences and 95% CI will be presented for continuous outcomes (knee pain and physical function) if the same scale was used for outcome assessment across trials or standardised mean differences and 95% CI if different scales were used. Primary outcomes (pain and radiographic JSW) will be grouped into three main time-points of assessment: short term (≤ 3 months), intermediate term (> 3 months; ≤ 12 months) and long term (> 12 months). Radiographic assessment of progression based on JSW will be dichotomised into progression if JSW loss $\geq 0.7 \text{ mm}$ or non-progression if JSW loss $< 0.7 \text{ mm}$ if JSW measurements are available, which is the smallest detectable difference of this method.⁴⁶ Secondary outcomes will include physical function, progression to total knee replacement and structural progression based on other OA-related features on MRI and radiograph such as Kellgren Lawrence grade (KLG)⁴² and size or volume of BMLs, if available. The incidence of adverse events and serious adverse events will be compared between the intervention and control groups using IPD from all studies. We will use intention-to-treat analysis preferably over per-protocol or as-treated analysis. The results will be interpreted taking into account the number of trials

and participants included in the analyses and the methodological quality of the trials.

To determine the influence of bisphosphonate type on pooled treatment effects, analyses for the primary outcomes will be stratified by route of administration (ie, intravenous vs oral vs. intra-articular) and molecular characteristics (nitrogenous vs non-nitrogenous) using data from all trials included in the meta-analysis.

Patient and public involvement

There are two members of the Arthritis Research UK OA Research Users Group who are representatives of patient and public involvement in the Steering Committee of the OA Trial Bank. The Steering Committee assesses all study proposals before the preparation of the protocol and approves and agrees on the study's design and methods, subgroups proposed and statistical analysis.

ETHICS AND DISSEMINATION

No formal ethics approval is generally required as no new data collection will be undertaken. If ethics approval is required in order to perform new analyses in any individual eligible study, approval will be requested and obtained before conducting any additional analysis. A data delivery license agreement will be provided and signed by one of the authors of each of the original trials providing data for this study. Dissemination of our findings is planned to occur through presentations at international conferences, publication in peer-reviewed journals and social media such as Twitter.

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