Assessing a 12-month course of oral alendronate for adults with avascular necrosis of the hip: MANTIS RCT with internal pilot

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Disclosure of interests

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Scientific summary

MANTIS RCT with internal pilot

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Scientific summary

Background

The Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS) trial was a randomised placebo-controlled superiority trial designed to investigate a potential drug treatment to attenuate the progression of avascular necrosis (AVN) of the hip in adults aged ≥ 18 years. The primary purpose of the trial was to evaluate the clinical effectiveness and cost-effectiveness of an oral course of alendronate (70 mg, taken weekly for 12 months) compared with a placebo-matched course (one tablet, taken weekly for 12 months). The primary outcome was the Oxford Hip Score (OHS) at 12 months. A further long-term primary outcome was also included in the trial, namely, whether or not a total hip replacement operation was regarded as necessary within 3 years of randomisation.

Objectives

Primary objective

The aim of the MANTIS trial was to determine the clinical effectiveness and cost-effectiveness of a 12-month course of alendronate in the treatment of AVN, with the primary objective of answering the question, 'Does bisphosphonate treatment (alendronate) reduce the progression of AVN of the hip?'.

The efficacy of alendronate in reducing the progression of AVN of the hip was to be measured using both the OHS at 12 months (short-term outcome) and the time to decision that a hip replacement is required at 36 months (long-term outcome).

Secondary objectives

The secondary objectives of the MANTIS trial were to assess:

- pain and function using the OHS at 6, 24 and 36 months
- hip function using the international Hip Outcome Tool-33 (iHOT-33) questionnaire over the course of the trial at baseline and at 6, 12, 24 and 36 months
- anxiety and depression across the trial using the Hospital Anxiety and Depression Scale (HADS) questionnaire at baseline and at 6, 12, 24 and 36 months
- quality of life across the trial using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at baseline and at 6, 12, 24 and 36 months
- radiological progression at 12 and 36 months using assessment of magnetic resonance imaging (MRI) scans and radiographs
- health-care resource use at 6, 12, 24 and 36 months.

Methods

The MANTIS trial was funded to be a definitive, multisite, two-arm, placebo-controlled, double-blind, Phase IV randomised controlled superiority trial commissioned following a commissioning brief set by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. Given the low prevalence of AVN of the hip and difficulty in detecting individuals with the condition at an early stage, the trial had an internal pilot phase with prespecified go/no-go criteria. It aimed to evaluate and compare the effectiveness of oral alendronate for attenuating the progression of AVN of the hip.

The trial was double blind. Active and placebo oral medication were produced and encapsulated identically and packaged into identical packaging. The trial aimed to randomise participants (1 : 1) into either the:

- intervention group – 12-month course of 70 mg of alendronate once per week
- control group – 12-month course of matched placebo once per week.

Results

A total of 108 patients were screened, 86 of whom had completed the screening process at the time the trial was closed. Thirty-eight patients were found to be eligible and approached for consent, 21 of whom consented and were randomised; 22 patients had not competed the screening process when the trial closed and so their eligibility/ineligibility remained undetermined. Forty-eight (56% of those fully screened) were deemed ineligible. The most common reason for ineligibility was that the avascular necrosis was too advanced (Ficat and Arlet stages 3 and 4); the second most common reason was that the patients had already started bisphosphonate therapy. In addition, 17 patients (16%) declined to consent and 22 patients (20%) could not be randomised for other reasons.

A total of 21 patients were recruited and randomised into the MANTIS trial. All participants were recruited from secondary care by MANTIS trial researchers from six hospitals. Ten participants were randomised to the intervention group and 11 participants were randomised to the control group. Most participants (67%) had Ficat and Arlet stage 2 disease.

Of the participants randomised, 4 out of 10 (40%) in the intervention arm and 4 out of 11 (36%) in the control arm completed the full 12-month course.

Of the 21 participants randomised, two participants (both of whom were in the intervention group) withdrew from the trial.

Conclusions for practice and research

The MANTIS trial was terminated at the end of the pilot phase, because it did not meet its go/no-go criteria. The main issues were a low recruitment rate owing to lower than expected disease prevalence, difficulties in identifying the condition at an early enough stage and more widespread use of the drug than expected.

Implications for future research

We would not recommend that a short-term interventional study is conducted on this condition until its prevalence, geographic foci and natural history are better understood.

One means of developing this understanding would be the introduction of a database/registry for AVN of the hip that would include the clinical pathway to diagnosis. By analysing the current NHS pathway to diagnosis in terms of health-care setting by specialty and radiological modalities used, researchers could in turn design recruitment strategies that identify patients at an early stage of disease.

Trial registration

The trial was registered as ISRCTN14015902.

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This report

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