Efficacy and safety of monthly 150 mg oral ibandronate in women with postmenopausal osteoporosis: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that monthly ibandronate was comparable in efficacy and safety and was preferred to weekly alendronate. Monthly 150mg ibandronate was superior to daily ibandronate and as well tolerated. Potential for error and bias, clinical differences between studies and the small number of studies available (acknowledged by the authors) mean that the conclusions should be treated with caution.

Authors' objectives
To compare the safety and efficacy of monthly oral 150mg ibandronate to daily or monthly bisphosphonate or placebo in women with postmenopausal osteoporosis.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to June 2010. Search terms were reported. Bibliographies of selected articles were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared monthly oral 150mg ibandronate with daily or monthly bisphosphonate or placebo in women with postmenopausal osteoporosis were eligible for inclusion. Outcomes that measured safety or efficacy were eligible for inclusion.

Randomised controlled or randomised crossover trials were included. The trials compared monthly 150mg ibandronate to weekly 70mg alendronate, daily 2.5mg ibandronate or placebo in women with a diagnosis of postmenopausal osteoporosis with a bone mineral density T-score of 2.0 or less. In at least one study pharmaceutical treatment was accompanied by a patient support programme. Outcomes reported were lumbar spine and hip bone mineral density, side effects, gastrointestinal adverse events, withdrawals, withdrawals due to adverse events, compliance, patient preference for treatment and patient perception of treatment convenience. Follow-up ranged from six months to 24 months.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The quality of included studies was assessed using the Jadad scale of randomisation, blinding and withdrawals/drop-outs to give a maximum possible score of 5.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
The mean and standard deviation of change in bone mineral density from baseline was extracted for different skeletal sites. Change in bone mineral density was presented as a percentage change. This was used to calculate mean differences. For dichotomous outcomes, the number of patients in each group for each outcome was extracted and used to calculate relative risk (RR) with corresponding 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks with 95% CIs were calculated for dichotomous outcomes. Weighted mean differences (WMD) with 95% CIs were calculated for change in bone mineral density. Random-effects models were used where significant statistical heterogeneity was detected. Fixed-effect models were used where there was no significant statistical heterogeneity. Statistical heterogeneity was assessed using Cochran's Q and I². A narrative synthesis was used for some outcomes.
Results of the review

Eight studies of seven original populations were included for review (4,885 participants): five double blind RCTs (2,789 participants) included two of the same population; one open label RCT (1,076 participants); and two open label randomised crossover studies (1,020 participants). One study scored 2 on the Jadad, five scored 3 and two (of the same population) scored 5.

Monthly 150mg ibandronate versus weekly 70mg alendronate (three RCTs): Two RCTs of the same sample (1,733 participants) found no significant differences between monthly 150mg ibandronate versus weekly 70mg alendronate for change in bone mineral density at lumbar spine and total hip after 12 months. One RCT (1,076 participants) found significantly greater compliance (56.6% versus 38.6%, p<0.0001) and fewer drop-outs (19.6% versus 25.3%, p<0.023) with monthly ibandronate plus patient support programme compared to weekly alendronate. Meta-analyses of these studies found no significant differences between monthly 150mg ibandronate and weekly 70mg alendronate for incidence of side effects, gastrointestinal adverse events, withdrawals and withdrawals due to adverse events (two studies, 2,809 participants). There was evidence of significant statistical heterogeneity for adverse events ($\Pi^2$=64.2%) and withdrawals ($\Pi^2$=74.9%). Two randomised crossover trials (1,020 participants) reported that significantly more patients preferred monthly ibandronate to weekly alendronate (RR 2.42, 95% CI 2.11 to 2.82, p<1x10^-8) and that significantly more patients found monthly 150mg ibandronate convenient compared to weekly 70mg alendronate (RR 3.09, 95% CI 2.62 to 3.62, p<1x10^-8).

Monthly 150mg ibandronate versus 7.5mg daily ibandronate (one RCT): Monthly 150mg ibandronate resulted in significantly greater increases in femoral neck, total hip and trochanter bone mineral density compared to daily 7.5mg ibandronate at two-year follow-up (one RCT, 803 participants; p<0.05). There were no significant differences between groups for withdrawals and adverse events.

Monthly 150mg ibandronate versus placebo (two RCTs): Monthly ibandronate significantly increased lumbar spine bone mineral density compared to placebo at 12 months (WMD 0.479, 95% CI 0.299 to 1.729; two RCTS, 253 participants).

Authors' conclusions

Monthly 150mg ibandronate was comparable to weekly 70mg alendronate. Women with postmenopausal osteoporosis preferred monthly ibandronate and found it more convenient than weekly regimes. Monthly 150mg ibandronate was superior to daily ibandronate and as well tolerated.

CRD commentary

The review question was clearly stated. Inclusion criteria for study design, participants and intervention were well defined. Inclusion criteria for outcomes were broad so a wide range of outcomes were reported. In one study a patient support programme was included as part of the monthly ibandronate treatment, which made it impossible to separate out the effects of the medication from the patient support component. Only two databases were searched so important data may have been missed. It was unclear whether language restrictions were imposed on the search. Too few studies were included to allow an assessment of publication bias. Language and publication biases could not be ruled out. It was unclear whether appropriate steps were taken during the review process to minimise reviewer error and bias. Study quality was assessed and most were of moderate to high quality.

The number of studies included for review was small. Only one or two studies reported each outcome in each comparator condition. This made it difficult to draw overarching conclusions about the impact of monthly ibandronate. Given the small number of studies and differences between them, the decision to use a narrative synthesis for some outcomes was appropriate. Given that only two studies were included for each meta-analyses, the conclusions that can be drawn from these were limited. It was unclear whether appropriate methods were used for combining crossover studies in the meta-analysis.

Potential for error and bias in the review process, clinical differences between studies and the small number of studies available for each comparator and outcome (acknowledged by the authors), the conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that the efficacy and safety of a monthly ibandronate regime meant that patients can choose a dosing regime according to a frequency that fits their lifestyle, thus improving treatment satisfaction and adherence.

Research: The authors did not state any implications for practice.

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