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CONSENSUS

Review of once-monthly oral ibandronate and the use thereof

Attendees:

Dr. T de Villiers - Chairman, Dr. M Davey, Dr. B Cassim, Dr. W de Lange (for the Ibandronate Oral Advisory Group)

Endorsements:

The Ibandronate Oral Advisory Consensus Document has been endorsed by Dr. Stanley Lipschitz.

An advisory board meeting of key opinion leaders was held in 2015 to discuss the clinical data on oral ibandronate in the treatment of postmenopausal osteoporosis.

Boniva 150 mg (ibandronate) oral once-monthly is indicated for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures.[1]

BONE and VIBE data summary

Registration of a new bisphosphonate for the treatment of osteoporosis requires fracture data from a randomised, placebo-controlled, clinical trial which has fracture reduction as its primary outcome. The primary fracture prevention trials for the currently available bisphosphonates include:

- Alendronate (10 mg daily) – The Fracture Intervention Trials (FIT 1 & 2) which provided vertebral and non-vertebral efficacy data.[2,3]
- Risedronate (5 mg daily) – The Vertebral Efficacy with Risedronate Therapy (VERT-NA and VERT-International) studies which demonstrated vertebral fracture efficacy. The Hip Intervention Program (HIP) study demonstrated hip fracture reduction with risedronate.[4,5]
- Ibandronate (2.5 mg daily) – The Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) which demonstrated vertebral fracture efficacy. In a post-hoc analysis of non-vertebral fractures, efficacy was demonstrated in high-risk patients.[6]
- Zoledronate (5 mg IV yearly) – The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) trial which demonstrated both vertebral and hip fracture reduction.[7]

Ibandronate – The primary fracture prevention trial (BONE)

The BONE study is the primary fracture prevention trial for oral ibandronate 2.5 mg daily in postmenopausal women with osteoporosis and showed a significant (62%) reduction in the risk of new vertebral fractures with ibandronate 2.5 mg daily over the 3-year study duration.[6]

The BONE trial was, however, relatively small and did not show non-vertebral fracture reduction.

However, a posthoc analysis in a higher risk subgroup of patients (T-score < - 3.0) did show a 69% relative risk reduction in non-vertebral fractures.[6]

Ibandronate – The non-inferiority studies for the longer dosing regimens

The European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) suggest that to register a different dosing regimen (e.g. weekly or monthly) of a bisphosphonate that has previously demonstrated efficacy in primary fracture prevention trials, 'bridging studies' using surrogate endpoints for fracture such as changes in BMD have been used.[8] In other words, it is not necessary to re-evaluate fracture prevention in order to obtain registration for a longer dosing regimen. It is accepted that if BMD gains of the comparator are non-inferior to the originator (within a pre-determined range), then fracture efficacy can be expected to be similar.

The Monthly Oral Ibandronate in Ladies (MOBILE) Trial was a non-inferiority BMD study that compared the efficacy and safety of three once-monthly oral ibandronate regimens with the ibandronate 2.5 mg daily regimen.[9]

Oral ibandronate 150 mg once-monthly provides an approximately two-fold increase in the annual cumulative exposure to ibandronate compared to the 2.5 mg daily formulation.[10] The efficacy of this increased dose was examined in the pivotal registration study (MOBILE), in which BMD gains were significantly greater with 150 mg monthly oral ibandronate than with daily ibandronate.[10] (See section on MOBILE and MOBILE LTE).

Similarly, the Monthly Oral Therapy with Ibandronate for Osteoporosis Intervention (MOTION) study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis

showed that the two regimens were comparable at increasing BMD after 12 months at both the lumbar spine and total hip.[11]

Ibandronate – The VIBE database study

No prospective head-to-head trials comparing the antifracture efficacy of the currently marketed weekly and monthly bisphosphonates have been done, due to the large sample size these studies would require to reliably detect differences in fracture risk, and the associated high costs.[12] For this reason, observational database studies are increasingly being used as such studies can provide sufficient sample sizes and permit the comparison of marketed doses.[12] Furthermore, it is unlikely that future fracture efficacy trials of bisphosphonate versus placebo will be conducted as it would be unethical to randomise patients to placebo.

The Evaluation of Ibandronate Efficacy (VIBE) head-to-head database fracture study compared fracture rates (hip, non-vertebral, vertebral and any clinical fracture) adjusted for confounding factors, over one year, between patients treated with monthly ibandronate 150 mg orally and weekly oral bisphosphonates (alendronate, risedronate or a combined alendronate/risedronate group).[12]

The results showed that fracture risk was not significantly different between patients receiving monthly ibandronate or weekly bisphosphonates for hip, non-vertebral or any clinical fracture.[12] However, monthly ibandronate-treated patients had a significantly lower risk of vertebral fracture than weekly bisphosphonate patients.[12]

In summary, with respect to fracture data:

- Oral daily ibandronate has demonstrated a 62% relative risk reduction in new vertebral fractures versus placebo in a primary study (i.e. the BONE study).[6]
- Monthly ibandronate 150 mg orally has demonstrated a significantly lower rate of vertebral fractures versus weekly oral bisphosphonates (VIBE study).[12]
- Monthly ibandronate 150 mg orally has demonstrated comparable rates of non-vertebral and hip fractures versus weekly bisphosphonates (VIBE study).[12] Non-vertebral and hip fracture IBN = ALN = RIS.
- Monthly oral ibandronate may be considered non-inferior with respect to hip fracture compared to the other weekly oral bisphosphonates.[12]

IBN – Ibandronate; ALN – Alendronate; RIS - Risedronate

MOBILE and MOBILE LTE data summary (BMD non-inferiority studies)

The MOBILE study was a prospective, randomised, phase III, non-inferiority study that compared the efficacy and safety of three once-monthly oral ibandronate doses (50+50 mg monthly, given on 2 consecutive days; 100 mg monthly; 150 mg monthly) with 2.5 mg daily ibandronate, which has previously been shown to reduce vertebral fracture risk versus placebo. The study was conducted in 1609 women aged 55 to 80 years, who were at least 5 years postmenopausal and had T-scores between < - 2.5 and > - 5.0.[9]

The primary endpoint of the MOBILE study was the percentage change from baseline lumbar spine bone density at one year. Reginster et al. (2006) discussed the 2-year MOBILE data to confirm the one-year results and to provide more extensive safety data. Secondary endpoints included the percentage change from baseline in lumbar spine and proximal femur BMDs over 2 years and the percentage change in serum concentrations of the biochemical marker of bone resorption, C-telopeptide of the α-chain of type I collagen (sCTX), from baseline over 2 years.[9]

Substantial increases in lumbar spine BMD were seen in all treatment arms. It was confirmed that all once-monthly oral ibandronate regimens were at least as effective as daily treatment and, in addition, 150 mg once-monthly was proven to be better at the lumbar spine in terms of BMD gains ($p < 0.001$).[9]

Substantial increases in proximal femur (total hip, femoral neck, trochanter) BMD were also seen, with 150 mg once-monthly producing the most pronounced effect ($p < 0.05$ versus daily treatment). Pronounced decreases in sCTX were maintained throughout the study.[9] Although this study did not assess fracture efficacy, the incidence of osteoporotic fractures was similar in all treatment groups.

In terms of adverse events, the incidence of upper gastrointestinal (GI) adverse events was similar across the treatment arms (20 to 26%) and events were generally mild to moderate in severity. The incidence of flu-like illness was higher with the 150 mg monthly dosing (3.3%) compared with the other dosing regimens (0.3% to 1.3%). However, none of the patients experiencing flu-like illness during year 1 had a recurrence during year 2 and the 2-year results confirm a low incidence of flu-like illness with ibandronate, similar to that seen with other oral bisphosphonates.[9]

Overall, it was concluded that once-monthly oral ibandronate is at least as effective and well-tolerated as daily oral treatment. In addition, once-monthly administration may be more convenient for patients and improve therapeutic adherence, thereby optimising outcomes.[9]

The long-term efficacy and safety of once-monthly ibandronate was studied in the extension to the 2-year MOBILE study, the MOBILE-LTE.[14] In the long-term extension (LTE), 344 patients from MOBILE monthly ibandronate arms and 698 patients from all arms were reallocated to ibandronate 100 mg monthly or 150 mg monthly for a further 3 years.The primary endpoint was the change in mean lumbar spine BMD from month 24 to month 60. A secondary efficacy endpoint was the change in mean total hip BMD from the end of the 2-year MOBILE study (month 24) to completion of the MOBILE-LTE at month 60. The primary focus of the study, however, was the change in lumbar spine BMD from MOBILE baseline to end of 5 years.[14]

The 344 patients receiving monthly ibandronate showed increases over 5 years in lumbar spine BMD (8.4% with 150 mg once-monthly) from MOBILE baseline. Total hip BMD increased at 12 and 24 months compared to MOBILE baseline in both the 150 mg monthly and the 100 mg monthly treatment groups, but a plateau was reached between 24 and 36 months with no further increases. Only small changes in BMD were seen at the femoral neck and trochanter. Decreases in sCTX and procollagen type 1 amino-terminal propeptide (P1NP) seen in the 2-year MOBILE results were maintained over 5 years.[14]

In terms of adverse events, the incidence of gastrointestinal events in MOBILE LTE was lower than in the MOBILE study (about 7.4% in each treatment group).[14]

Joint pain was reported in 4.0% of patients receiving ibandronate 150 mg. In terms of serious adverse events, there was no evidence of renal compromise and there were no symptoms suggestive of osteonecrosis of the jaw (ONJ).[14]

The conclusion of the MOBILE-LTE study was that 150 mg once-monthly oral ibandronate is an effective and well-tolerated treatment for postmenopausal osteoporosis. The BMD at the proximal femur is maintained, with further small gains in lumbar spine BMD. The efficacy of ibandronate once-monthly is sustained over 5 years and there were no new safety signals.[14]

Harris meta-analysis and Cranney pooled analysis data summary

Harris meta-analysis

In the Harris et al. meta-analysis, individual patient data from four phase lll (BONE, IV fracture prevention, MOBILE and Dosing IntraVenous Administration (DIVA)) studies were grouped into three dose levels based on annual cumulative exposure (ACE), defined as the annual dose (mg) x bioavailability (0.6% oral; 100% IV).[10]

Non-vertebral and all clinical fractures in postmenopausal women over at least 2 years were examined and compared in the high-dose ACE group (≥ 10.8 mg), the mid-dose ACE group (5.5 to 7.2 mg) and the low-dose ACE group (2.0 to 4.0 mg). Both the 150 mg oral once-monthly and the 3 mg IV quarterly fall within the high-dose ACE group.[10]

All four trials had identical procedures for ascertainment of non-vertebral fractures (NVFs), including collection of NVFs as adverse events and mandatory X-ray confirmation.[10]

- The BONE and the IV fracture prevention studies were placebo-controlled 3-year fracture endpoint trials that examined vertebral fractures as the primary endpoint. Inclusion criteria required 1 to 4 prevalent vertebral fractures, lumbar spine BMD and a T-score of -2.0 to -5.0.[10]
- The MOBILE and DIVA studies were active-controlled 2-year BMD studies. Inclusion criteria did not require prevalent vertebral fractures, lumbar spine BMD but did require a T-score of -2.5 to -5.0.[10]

Since high ACE ibandronate has been shown to result in larger increases in BMD, this study assessed whether these doses would also reduce fracture risk relative to placebo.[10]

The primary endpoint was key NVFs (clavicle, humerus, wrist, hip, pelvis, leg). All NVFs and all clinical fractures (a category that includes all NVFs and symptomatic vertebral fractures) were also examined.[10]

All year data showed statistically significant reductions in the risk of key non-vertebral fractures, all NVFs and all clinical fractures for the high-dose ACE group compared with placebo. Reductions in fracture risk for the low- and mid-ACE groups compared with placebo did not reach statistical significance for most of the fracture types examined. The high-dose group (ACE ≥ 10.8 mg) also showed a significantly longer time to fracture versus placebo for key NVFs, all NVFs and all clinical fractures at 2 years.[10]

Cranney pooled analysis

The Cranney pooled analysis of ibandronate assessed the efficacy of high versus low doses of ibandronate on non-vertebral fractures (humerus, clavicle, wrist, pelvis, hip and leg). Eight randomised treatment trials were considered for inclusion. Treatment trials were defined as those trials in which baseline lumbar spine T-score was ≤ -2.5, or the baseline prevalent vertebral fracture rate was > 20%, or the mean age of participants was over 60 years. Only two trials were selected for inclusion as they provided data on prevalent vertebral fractures and data on both higher and lower doses of ibandronate.[15]

Several doses in addition to the ones used in clinical practice were included in the analysis. As in the Harris meta-analysis, the annual cumulative exposure (ACE) was used to categorise doses as high (≥ 10.8 mg) and low (≤ 7.2 mg).[15]

The results showed that combining higher ACE doses of ≥ 10.8 mg versus ACE doses of 5.5 mg resulted in a hazard ratio of 0.62 or a 38% reduction in the incidence of non-vertebral fractures (95% CI 0.396-0.974, p=0.038). There was also a dose-response effect seen with increasing ACE doses (7.2 to 12 mg) compared with ACE of 5.5 mg, with unadjusted hazard ratios ranging from 0.746 to 0.573.[15]

- An ACE of 12 mg resulted in a 43% reduction in NVF risk (95% CI 0.037-1.004)[15]
- An ACE ≥ 10.8 mg resulted in a 38% reduction in NVF risk (95% CI 0.396-0.974)[15]
- An ACE ≥ 7.2 mg resulted in a non-significant NVF reduction of 25% (95% CI 0.505-1.103)[15]

The Kaplan-Meier plot of time to non-vertebral fracture for higher versus lower ACE ibandronate doses shows that higher doses prolong the time to non-vertebral fractures compared with lower doses.[15]

In summary, higher doses of ibandronate significantly reduced the risk of NVFs in this pooled analysis. However, data on prevalent vertebral fracture is not available for all studies, and the pooled analysis does not provide enough data in order to comment on effect on hip fractures because NVF rate does not correlate with hip fracture rate.[15]

Ibandronate – Long-term data

Ibandronate is a nitrogen-containing bisphosphonate. It has an increased potency compared to alendronate and risedronate and a higher bone affinity compared to clodronate and risedronate.[16] Ibandronate offers greater ease of use compared weekly with other bisphosphonates. It is suitable for both oral and IV administration.[16]

The long-term safety and efficacy data for the currently available bisphosphonates are as follows:

- Alendronate – 10 years, based on the Fracture Intervention Trial Extension[17]
- Risedronate – 7 years, based on the Vertebral Efficacy with Risedronate (VERT) trial extension[18]
- Zoledronate – 9 years, based on the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) trial extension[19]
- Ibandronate – 5 years, based on the MOBILE-LTE study[14]

Efficacy and safety of ibandronate has been demonstrated over 5 years[14]

Observational data over 12 months suggest that ibandronate had a significantly lower risk of vertebral fracture than weekly bisphosphonate patients (adjusted RR 0.36, 95% CI 0.18-0.75, p=0.006)[12]

Observational data over 12 months suggest that ibandronate fracture risk was not significantly different between patients receiving monthly ibandronate or weekly bisphosphonates for hip, non-vertebral or any clinical fracture (adjusted RR: hip 1.06, p=0.84; non-vertebral =0.88, p=0.255; any clinical fracture =0.82; p=0.052).[12]

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