Three-monthly ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis

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Objective. Corticosteroids are widely prescribed, although treatment-related side-effects are common. Of these adverse events (AEs), osteoporosis is considered the most serious. Currently, oral bisphosphonates are the standard treatment for corticosteroid-induced osteoporosis (CIO). However, intermittent intravenous (i.v.) therapy may have advantages, including lack of gastrointestinal AEs, improved bioavailability and increased compliance. This study investigated the efficacy and safety of 3-monthly i.v. ibandronate bolus injections in patients with established CIO. The results from a planned 2-yr interim analysis are reported.

Method. In this controlled, prospective, open-label, parallel-group study, 104 patients (49 men and 55 women) with established CIO (mean T-score < -2.5 S.D. at the lumbar spine (L2–L4) received daily calcium (500 mg) plus either 3-monthly i.v. ibandronate (2 mg) bolus injections or oral daily alfacalcidol (1 μg). The primary end-point was bone mineral density (BMD) change at the lumbar spine, femoral neck and calcaneus after 24 months.

Results. Compared with oral daily alfacalcidol, i.v. ibandronate produced significantly superior gains in mean (± S.D.) BMD at the lumbar spine (2.2 ± 3.1 vs 11.9 ± 7.4%; P < 0.001), femoral neck (1.3 ± 1.8 vs 4.7 ± 4.0%; P < 0.001) and calcaneus (7.6 ± 3.8 vs 15.5 ± 10.7%; P < 0.0001) after 2 yr. Consistent with these BMD gains and, although the study was not powered for fractures, a trend towards a reduction in vertebral fractures and greater back pain relief was seen in the ibandronate group. The overall incidence of AEs was similar in the two treatment arms.

Conclusions. Three-monthly i.v. ibandronate bolus injections are significantly superior to alfacalcidol in the treatment of CIO. These data confirm the potential of ibandronate for the treatment of osteoporosis associated with corticosteroid use. The ease of administration, lack of AEs and good compliance associated with intermittent i.v. ibandronate make it a potentially valuable alternative to oral bisphosphonate therapy for the treatment of CIO.

Key words: Ibandronate, Bisphosphonate, Alfacalcidol, Corticosteroid-induced osteoporosis, Bone density, Fracture reduction.
Ibandronate 2 mg i.v. provided the most significant finding in 125 postmenopausal women with osteoporosis. Three-monthly intravenous (i.v.) ibandronate bolus injections were well tolerated, with a similar incidence of adverse events (AEs) to placebo.

The primary end-point of the study was the change in bone mineral density (BMD) and the greatest reduction in bone turnover relative to placebo. Patients who received 2 mg i.v. ibandronate every 3 months achieved a 5.2% increase in lumbar spine BMD after 1 yr of therapy, relative to baseline. Furthermore, 3-monthly i.v. bolus injections of ibandronate were well tolerated, with a similar incidence of AEs to placebo.

Three-monthly i.v. ibandronate has now been studied in over 3500 patients with PMO [43; Juttmann JR, Felsenberg D, Halse J et al., unpublished data]. It has been shown that intermittent i.v. ibandronate offers physicians a convenient, effective and well-tolerated alternative to conventional oral bisphosphonate therapy [43; Juttmann JR, Felsenberg D, Halse J et al., unpublished data]. However, thus far, no studies have investigated ibandronate in patients with secondary osteoporosis. Consequently, the aim of the present 3-yr study was to determine the therapeutic efficacy and safety of 3-monthly bolus i.v. injections of ibandronate in patients with established CIO. A planned 2-yr interim analysis of the study data was conducted, the results of which are reported here.

Patients and methods

Study population

Between January 1997 and March 1999, a total of 105 men and women were enrolled in this study, which took place at a single centre in Leverkusen, Germany. All patients were confirmed as having established osteoporosis induced by the long-term administration of high-dose corticosteroids for the treatment of an underlying chronic illness (chronic obstructive lung disease, rheumatoid arthritis or polymyalgia rheumatica). Osteoporosis was defined as a low BMD, of at least 2.5 S.D. below mean young normal values at the lumbar spine (L2-L4). Patients enrolled in the study had been receiving chronic uninterrupted corticosteroid therapy for at least 2 yr or had received a corticosteroid dose of at least 7.5 mg/day.

Patients were excluded from the study if they had hypocalcaemia, suffered from severe renal impairment, had a history of recent major GI tract disease (e.g. oesophagitis or GI ulceration) or had experienced any previous adverse reaction to bisphosphonate therapy. Patients were also excluded if they were receiving other bone-active drugs, such as hormonal replacement therapy, thiazide and diuretics.

All participants gave their oral informed consent to participation in this study.

Study design

In this open, parallel-group, controlled study, patients were allocated to receive either 3-monthly bolus injections of ibandronate (2 mg) or daily alfacalcidol (1 μg). In addition, all patients were given a daily calcium supplement (500 mg). The method of allocation to therapy was to find pairs of patients with similar baseline characteristics and then to assign one member of the matched pair to each treatment group.

Outcome measurements and methods

The primary end-point of the study was the change in BMD at the lumbar spine and femoral neck after 24 months relative to
baseline. Secondary efficacy end-points were changes in BMD at the calcaneus, change in back pain intensity and changes in body height during the course of the study. The incidence of new vertebral and non-vertebral fractures was also examined.

All efficacy and safety assessments were performed at baseline and every 6 months thereafter. BMD in the lumbar spine, femoral neck and calcaneus was evaluated using dual-energy X-ray absorptiometry (DXA; Lunar Expert, Madison, WI, USA). To ensure standardization and accuracy of BMD results, the same operator, who was unaware of the patients’ identity and treatment, determined all BMD values, using the same machine. To assess for fractures, lateral X-rays of the thoracic and lumbar spine were obtained. X-ray films were evaluated by an experienced radiologist who was blinded to patient treatment. To assess back pain we used a simple score based on four categories of pain: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Height was measured using a stadiometer.

Statistical analysis
The study was analysed using intention-to-treat (ITT) analysis. One patient withdrew prior to treatment on instruction from his physician and so was not included in the analysis. To compare differences between the two treatment groups, data were analysed using the t-test for continuous variables and the χ² test for ordinal or nominal variables. This statistical analysis was performed using the SPSS for Windows® software package (release 10.0.7; SPSS Inc., Chicago, IL, USA). Information entered into the software package was independently checked for errors and inconsistencies by an external institute (Institute for Medical Outcome Research, Loerrach, Germany).

Results

Patient characteristics
Of the 104 patients who received therapy, 52 were assigned to receive 2 mg i.v. ibandronate bolus injections every 3 months and 52 were assigned to receive 1 μg oral alfacalcidol daily. The study population included 49 men and 55 women, with a mean age of 64.7 yr. The major clinical baseline characteristics are illustrated in Table 1. The two treatment groups were comparable in terms of age range, sex distribution, height, weight, percentage of underlying diseases, average BMD values, fracture rates and corticosteroid use.

At baseline, patients from both treatment groups had a mean lumbar spine [L2-L4] BMD T-score of −3.8 (±0.8 and ±0.7 in the ibandronate and alfacalcidol groups respectively). In addition, all patients had experienced a similar number of previous vertebral fractures: 4.0 ± 2.7 (mean ± s.d.) in the ibandronate-treated patients compared with 3.7 ± 2.5 in those treated with active vitamin D.

The mean initial daily corticosteroid (prednisone) dose was 11 ± 6 and 10 ± 4 mg in the ibandronate and alfacalcidol treatment groups respectively. During the course of the study, the mean dose of prednisone decreased by 19% in the ibandronate-treated patients and by 21% in those receiving alfacalcidol. Prior to treatment, patients in the ibandronate group had been receiving corticosteroid therapy for a mean duration of 8 ± 6 yr compared with 7 ± 6 yr in the alfacalcidol group.

Measurements of bone mass
The mean percentage changes in BMD over the 24-month treatment period relative to baseline are reported in Table 2. Compared with alfacalcidol treatment, bolus injections of ibandronate produced significantly superior gains in BMD at the lumbar spine (2.3 ± 3.1 and 11.9 ± 7.4% respectively; P < 0.0001), femoral neck (1.3 ± 1.8 and 4.7 ± 4.0% respectively; P = 0.0005) and calcaneus (7.6 ± 3.8 and 15.5 ± 10.7% respectively; P < 0.0001) after 2 yr of treatment. Notably, the ibandronate-related BMD changes at the lumbar spine (Fig. 1), hip (Fig. 2) and calcaneus (Fig. 3) were maintained throughout the study period. The gains in bone mass were consistently greater in the ibandronate-treated patients than in those receiving alfacalcidol, at all measured time points.

Course of back pain
The average back pain score decreased consistently in both groups of patients during the course of the study (Fig. 4). However, a trend towards greater back pain relief was noted in the patients receiving ibandronate. After 24 months of therapy, 84.6% of patients receiving ibandronate experienced a marked improvement in back pain.

| Table 1. Patient baseline characteristics (mean ± s.d.) |
|----------------|-----------------|-----------------|-----------------|
|               | Ibandronate (n = 52) | Alfacalcidol (n = 52) |
| Men           | 25               | 24               |
| Women         | 27               | 28               |
| Age (yr)      | 64 ± 10          | 66 ± 8           |
| Height (cm)   | 164 ± 9          | 165 ± 10         |
| Weight (kg)   | 67 ± 14          | 65 ± 10          |
| Underlying diseases |             |                  |
| Chronic obstructive lung disease | 28         | 26               |
| Rheumatoid arthritis | 15           | 14               |
| Polymyalgia rheumatica | 9            | 12               |
| Duration of corticosteroid therapy (yr) | 8 ± 6         | 7 ± 6            |
| Daily corticosteroid dose (mg) | 11 ± 6     | 10 ± 4           |
| BMD T-score   |                  |                  |
| Lumbar spine  | −3.8 ± 0.8       | −3.8 ± 0.7       |
| Femoral neck  | −3.0 ± 1.0       | 3.1 ± 0.6        |
| Calcaneus (n=47) | −2.9 ± 1.0     | −2.1 ± 0.9       |
| Patients with >1 vertebral fracture | 48         | 47               |
| No. of vertebral fractures/patient | 4.0 ± 2.7   | 3.7 ± 2.5        |

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<th>Table 2. Change in BMD (mean ± s.e.) from baseline after 6, 12, 18 and 24 months in patients receiving ibandronate or alfacalcidol</th>
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pain (pain score improved by 2 or 3 points) compared
with 50.0% of patients receiving alfacalcidol ($P = 0.086$).
The trend towards a greater reduction in average back
pain score in the ibandronate group was observed after
only 6 months of initiating therapy.

**New fractures and height loss**

In this study, which was not powered to compare
reduction in fracture risk, there was a non-significant
trend towards fewer vertebral fractures in the group of
patients receiving ibandronate compared with those
taking alfacalcidol (Table 3; $P = 0.264$). During the
course of the study, new vertebral fractures occurred in
five patients receiving ibandronate (9.6%) vs 10 patients
treated with alfacalcidol (19.2%). The incidence of new
non-vertebral fractures was similar for the two agents
(Table 3): 9 and 11 patients receiving ibandronate and
alfacalcidol respectively experienced new non-vertebral
fractures.

Overall, significantly more patients in the alfacalcidol
treatment group lost body height after 24 months of
therapy compared with patients receiving ibandronate
(78.8 and 51.9% of patients respectively; $P < 0.005$).
After 2 yr of therapy, the mean loss of body height was
$-0.27$ and $-0.98$ cm in patients treated with ibandronate
and alfacalcidol respectively ($P = 0.020$).

**Safety**

The incidence of AEs was similar in the 3-monthly i.v.
ibandronate and daily oral alfacalcidol groups (Table 4).
However, a numerically higher incidence of hypercal-
caemia/hypercalciuria was observed in patients taking
alfacalcidol compared with those receiving ibandronate
(7.6 vs 1.9%). Overall, after 24 months of therapy, 18 and
19 of the ibandronate- and alfacalcidol-treated patients
experienced a total of 20 and 23 AEs respectively.
The 2 mg bolus i.v. injection of ibandronate was well tolerated. Most AEs were mild, temporary and manageable, only one patient withdrawing as a result of a treatment-related side-effect. In total, 19.2% of patients receiving ibandronate and 17.3% of those treated with alfacalcidol discontinued the study early. Reasons for patients discontinuing treatment with i.v. ibandronate bolus injections were non-treatment-related death (3.7%), AEs (1.9%), personal reasons unrelated to treatment (11.5%) and missed dose (1.9%). One patient experienced an acute-phase reaction; this was slight to transient.

Discussion

Patients who receive long-term corticosteroid therapy are chronically ill. As a result of their underlying disease, these patients are required to take a number of daily medications and may, therefore, find it a burden to take further tablets. Unfortunately, however, bone loss associated with long-term corticosteroid use often necessitates the administration of additional supportive drug therapy.

At present, oral bisphosphonates are considered to be the standard treatment for patients with CIO. However, an effective therapy that can be administered as a bolus injection and that needs to be given only a few times a year may have several advantages over conventional oral bisphosphonates. Potential benefits include increased patient compliance, lack of GI AEs and eliminated risk of reduced enteral absorption due to incorrect intake of beverages.

Three-monthly i.v. ibandronate bolus injections have been specifically designed to provide an effective therapy for the management of osteoporosis that enhances patient concordance. Studies have demonstrated the potential of ibandronate in PMO [39, 40, 43]. However, the present parallel-group study is the first to investigate the efficacy and safety of intermittent i.v. ibandronate in patients with established CIO.

BMD is the most important predictor of the risk of fracture, regardless of which skeletal site is measured [44, 45]. Therefore, it is universally used as an end-point in studies investigating novel and conventional agents for the treatment of osteoporosis. In this study, 3-monthly administration of 2 mg i.v. ibandronate significantly and consistently increased lumbar spine, hip and calcaneal BMD relative to active vitamin D. Other bisphosphonates, including cyclical oral etidronate, intermittent i.v. pamidronate, oral daily alendronate and oral daily risedronate, have been investigated for the treatment of established CIO (BMD T-score < −2.5) [14, 16, 46, 47]. Although direct comparisons are not possible, the percentage BMD increases in lumbar spine in the patients receiving 3-monthly i.v. ibandronate (8.7 and 11.9% at 1 and 2 yr respectively) compare very favourably with those observed with other bisphosphonates (oral etidronate, 5.4% after 2 yr [46]; i.v. infusions of pamidronate, 3.4% increase after 1 yr [47]).

In addition to statistically significant increases in bone mass, patients receiving 3-monthly bolus injections of ibandronate showed a trend towards greater back pain relief than those taking active vitamin D, and also lost significantly less body height (P=0.020). Furthermore, the significant increases in BMD observed with 3-monthly ibandronate i.v. bolus injections correlated with a non-significant trend towards a reduction in the risk of new vertebral fractures. The incidence of non-vertebral fractures was similar in the two treatment groups.

The value of biochemical markers of bone turnover is becoming progressively more evident in the management of patients with osteoporosis, with consistent associations being reported between bone marker concentrations and bone loss, as well as fracture risk [48–55]. Continuous (oral and weekly) dosing with bisphosphonates is associated with a sustained decrease in the levels of bone markers [56, 57]. Although it is not fully characterized, less frequent dosing schedules produce a more complex time course of bone marker suppression relative to continuous dosing schedules. Levels of biochemical markers of bone turnover, which were not assessed during this study, could have provided further insights into the patterns of bone marker suppression during intermittent i.v. bisphosphonate therapy.

Three-monthly i.v. ibandronate was found to be well tolerated in this corticosteroid-treated population, with a similar incidence of AEs compared with daily oral alfacalcidol. Of particular note, i.v. ibandronate was not associated with the GI AEs that have been associated with some orally administered bisphosphonates. Furthermore, compliance with treatment was very high, only one patient discontinuing therapy because of an AE (1.9%) and only one patient missing an injection of ibandronate (1%).

Conclusions

For patients with established CIO, 3-monthly administration of i.v. ibandronate bolus injections significantly increases BMD at the lumbar spine, femoral neck and calcaneus, relative to oral daily alfacalcidol. These 2-yr interim results confirm the findings from studies conducted in patients with PMO. For the treatment of both PMO and CIO, 3-monthly i.v. ibandronate produces significant, meaningful increases in BMD. Furthermore,
in all studies to date, intermittent i.v. ibandronate has been well tolerated.

The ease of administration, scarcity of AEs and good compliance associated with intermittent i.v. ibandronate bolus injections makes this novel treatment approach an interesting and feasible alternative to current oral bisphosphonate therapy for the treatment of patients with CIO.

References

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