A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover

J.D. Ringe, J.-J. Body

ABSTRACT
Several disorders of increased bone turnover and low bone mineral density (BMD) are associated with severe pain that is refractory to treatment with conventional and even opioid analgesics. Because of their ability to effectively improve the underlying pathogenesis of these disorders (i.e., reduce bone resorption and increase BMD), bisphosphonates are considered part of the palliative care of malignant bone-related pain and also appear to have some analgesic efficacy in other, non-malignant conditions. Ibandronate, a potent, nitrogen-containing bisphosphonate that can be given orally and intravenously, has demonstrated robust effects in relieving the pain associated with several malignant disorders. Unlike other available intravenous (i.v.) bisphosphonates, i.v. ibandronate is not associated with renal side effects, even at high doses such as 6 mg every 3 weeks. In addition, oral ibandronate (50 mg daily) is currently the only oral bisphosphonate proven to reduce and maintain bone pain scores below baseline for 2 years in patients with metastatic bone disease. Lower dose, less intense dosing regimens of ibandronate relieve bone pain in non-malignant conditions: i.v. ibandronate (2 mg every 3 months with or without an initial 4 mg injection) provides pain relief for patients with corticosteroid-induced osteoporosis, localised transient osteoporosis (bone marrow oedema) and sternocostoclavicular hyperostosis. Both oral and i.v. ibandronate are well tolerated. In conclusion, ibandronate offers an effective and convenient choice for the relief of bone pain in a wide variety of underlying bone conditions.

Introduction
Several disorders of pathologically increased bone turnover and low bone mineral density (BMD) are associated with severe bone pain. The mechanisms of bone pain are not fully understood, but may result from a number of causes. For example, pain in patients with metastatic bone disease (MBD) may be the result of mass effects that cause stretching of the periosteum, fracture or tumour growth into adjacent nerves and tissues. Bone pain may also be the result of nerve ending stimulation by factors such as prostaglandins, bradykinin, histamine or substance P. The treatment of bone pain, whether malignant or non-malignant in origin, has been based on the World Health Organization’s three-step analgesic ladder for cancer pain. Primary analgesics such as paracetamol and non-steroidal anti-inflammatory agents are used first line with a concomitant adjuvant agent (e.g. a tricyclic antidepressant or membrane-stabilising agent), as needed. If pain persists, the next step is to add a weak opioid (e.g. codeine) with or without adjuvant agents. For patients with inadequate pain control, a strong opioid is added to replace the weaker one, again with or without adjuvant medication. Nevertheless, intractable bone pain may remain. Refractory bone pain is often associated with disorders such as MBD. Some 70% of patients with MBD will have bone pain, approximately 58% of patients with multiple myeloma have bone pain upon diagnosis and it is estimated that 25-40% of patients with breast carcinoma metastatic to bone will require radiotherapy for bone pain. Bone pain is also associated with other, non-malignant conditions, including Paget’s disease, corticosteroid-induced osteoporosis (CIO) and localised transient osteoporosis. Bisphosphonates may offer an additional therapeutic option. Unlike analgesics, bisphosphonates potently inhibit bone turnover.
resorption (6), thereby addressing the underlying pathogenesis of the condition, with the potential to provide more than just symptomatic relief. Animal studies have suggested that bisphosphonates such as alendronate and ibandronate can also relieve bone pain via other mechanisms (7, 8). A study in a rat model of MBD, showed that alendronate reduced the number of activated osteoclasts and their bone resorbing activity, which the authors suggest should reduce nociceptive stimuli such as acidosis and growth factors (7). Alendronate also attenuated the up-regulation of activating transcription factor 3 (ATF-3), a marker of neuronal injury, which suggests that bisphosphonate therapy can inhibit the destruction of sensory nerve fibres. Furthermore, bisphosphonates may also cause apoptosis in macrophages and myeloma cells, potentially contributing to their pain-relieving properties (1). In addition to analgesic efficacy, bisphosphonates have been proven to reverse bone loss and prevent fractures in both MBD and multiple myeloma (6), and in a wide variety of other bone disorders, including Paget’s disease (9) and osteoporosis (10).

Many published studies support the use of bisphosphonates to relieve pain in these conditions. However, the results of the studies are mixed. In MBD, for example, although there are numerous trials supporting some analgesic effect of the bisphosphonates; etidronate, clodronate, pamidronate and zoledronate (Table I), there is a paucity of evidence to definitively indicate which one offers the best pain relief, and for etidronate, clodronate and pamidronate there is not enough evidence to recommend them as either first-line therapy for alleviating the pain of MBD or to indicate which has the greatest effect on pain relief (34).

Furthermore, some bisphosphonates may be inappropriate and/or impractical in some disorders, in certain patients or under particular circumstances. In particular, although rare, i.v. zoledronate has been associated with renal toxicity (35, 36). As such, monitoring of renal function is now mandatory when prescribing zoledronate (37, 38).

Moreover, for some i.v. bisphosphonates (e.g. clodronate and pamidronate), the doses used in clinical studies have been similar whether the pain is due to malignant or non-malignant disease. These doses are relatively high and, consequently, with their various drawbacks and risks (such as renal toxicity), may be more difficult to justify in patients with non-malignant conditions.

With respect to oral bisphosphonate formulations, clodronate poses a particular problem due to the high doses and the large tablets that patients must take (39). Both oral alendronate and risedronate require administration according to the strict pre- and post-dose fasting and posture instructions required for all oral bisphosphonates, which are designed to minimise the risk of post-dose upper gastrointestinal adverse events and to maximise bioavailability (39). However, complying with these instructions on a daily or weekly basis, as required for alendronate and risedronate, may be inconvenient, leading to suboptimal adherence.

Ibandronate is a highly potent, well-tolerated, nitrogen-containing bisphosphate that is effective and has a favourable pharmacological profile (40). In contrast to other oral bisphosphonates, ibandronate uniquely provides convenient i.v. injection and oral schedules, including a simple, once-monthly oral dosing regimen that has been proven to be effective and well tolerated in postmenopausal osteoporosis, even in patients with a history of upper gastrointestinal disorders or taking non-steroidal anti-inflammatory drugs (NSAIDs; 41). Ibandronate therefore enables therapy to be tailored to the individual patient’s needs and circumstances.

The proven efficacy of ibandronate in reducing bone resorption in preclinical (40) and clinical (42-59) studies suggests a potential for pain relief in disorders where these symptoms are ultimately most likely the result of increased bone turnover.

In light of the lack of comparative data favouring one bisphosphonate over another to relieve the bone pain associated with increased bone turnover, the present paper reviews the efficacy of ibandronate in a wide variety of such indications: MBD (42, 60-66]; multiple myeloma (67); CIO (58, 59); localised transient osteoporosis (68); and sternocostoclavicular hyperostosis (69).

Bone pain associated with malignant disorders

A number of studies have assessed the efficacy of both oral and i.v. ibandronate for treating bone pain associated with malignant disease (including, breast cancer, urological cancers and multiple myeloma). The studies of oral ibandronate used standard doses whereas the i.v. studies included standard and non-standard (both low-dose and high-dose) ibandronate regimens. All of these studies consistently demonstrate the ability of ibandronate to provide pain relief, even when opioids are ineffective.

I.v. ibandronate for treating malignancy-related bone pain

Low-dose and standard-dose ibandronate for metastatic bone disease due to breast cancer

One large (n = 466) well-designed, randomised, double-blind clinical study has evaluated the ability of i.v. ibandronate to relieve bone pain in patients with confirmed breast cancer and MBD (42, 63). In this study, patients were allocated to receive either ibandronate 2 mg by i.v. bolus injection (n = 154), ibandronate 6 mg by i.v. infusion over 1-2 hours (n = 154), or an appropriate placebo injection or infusion (n = 158). Patients received the first treatment on day zero and subsequent treatments at 3- or 4-weekly intervals for 60-96 weeks. Bone pain (assessed on a 5-point scale from 0 = none to 4 = intolerable), analgesic consumption and quality of life (QoL) (assessed using a European Organisation for the Research and Treatment of Cancer [EORTC] Quality of Life Scale) were evaluated as secondary endpoints in the study. Patients in the ibandronate 6 mg group showed a significantly improved bone pain score over time compared with the placebo and ibandronate 2 mg groups (Fig. 1).

This 6 mg ibandronate dose rapidly and significantly reduced and maintained bone pain scores below baseline for the entire study period of 2 years (-0.28 ± -1.11, p < 0.001). Analgesic use was markedly lower with ibandronate than...
Table I. Efficacy of various bisphosphonates in relieving pain due to metastatic bone disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>I.v.</th>
<th>Oral</th>
<th>Control</th>
<th>no.</th>
<th>Dosage schedule</th>
<th>Analgesic efficacy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>x</td>
<td>None</td>
<td>30</td>
<td></td>
<td>400 mg/day for 2 weeks</td>
<td>“Transient”</td>
<td>Iwamoto et al. 2002 (11)</td>
</tr>
<tr>
<td>Clodronate</td>
<td>x</td>
<td>None</td>
<td>85</td>
<td></td>
<td>300 mg i.v. for 8 days followed by oral maintenance 1600 mg daily</td>
<td>Significant decrease in pain scores in 75%; 22% pain free without analgesics and 45% significantly decreased daily consumption. Effect lasted for a mean of 9 weeks</td>
<td>Heidenreich et al. 2001(12)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>800 or 1600 mg daily for 3 months</td>
<td>Significant decrease in pain score in treated vs. untreated groups but pain scores increased in 29%, 19% and 18% of 800 mg/day, 1600 mg/day and control groups, respectively</td>
<td>Arican et al. 1999 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1600 mg daily</td>
<td>Modest improvement</td>
<td>Robertson et al. 1995 (14)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57</td>
<td>300 mg daily i.v. followed by oral 1.6 g/day for 12 months</td>
<td>Pain relief only 10% better in clodronate than placebo group</td>
<td>Kymala et al. 1997 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>300 mg daily for 10 days</td>
<td>Relieved pain in 10 patients but benefit short lived</td>
<td>Creswell et al. 1995 (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>55</td>
<td></td>
<td>300 mg i.v. for 3 weeks followed by oral 3200 mg for 4 weeks</td>
<td>No significant differences between treatment arm and controls</td>
<td>Strang et al. 1997 (17)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>600 mg or 1500 mg daily crossed over after 2 weeks to the other dose</td>
<td>Significant analgesic effect but optimal dose and duration of effect need further evaluation</td>
<td>Ernst et al. 1997 (18)</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>x</td>
<td>Placebo</td>
<td>382</td>
<td></td>
<td>90 mg every 3-4 weeks</td>
<td>Pain scores decreased over time but significantly more in the placebo group</td>
<td>Hortobagyi et al. 1998 (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>372</td>
<td>90 mg every 4 weeks for 24 cycles</td>
<td>At final measurement, pain scores had increased significantly more in the placebo group</td>
<td>Therault et al. 1999 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>180 mg monthly</td>
<td>‘Excellent’ pain relief</td>
<td>Pistevou-Gombaki et al. 2002 (21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200</td>
<td>60 mg for 6 infusions over 7 weeks + one infusion every 3 weeks for a total of 24 infusions</td>
<td>Pain intensity decreased</td>
<td>Groff et al. 2001 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>Active</td>
<td>55</td>
<td>1600 mg orally daily vs. 1500 mg i.v. followed by 1600 mg orally vs 90 mg i.v. pamidronate</td>
<td>Significant improvement in pain scores with pamidronate vs. clodronate but no significant difference in pain scores between the two pamidronate-treated groups</td>
<td>Jagdev et al. 2001 (23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>90 mg monthly for 12 cycles</td>
<td>Significant decrease in bone pain</td>
<td>Vitale et al. 2001 (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>Active</td>
<td>70</td>
<td>60 mg or 90 mg every 3 weeks for maximum six cycles</td>
<td>Significant reduction in pain</td>
<td>Gessner et al. 2000 (25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>751</td>
<td>90 mg every 3-4 weeks</td>
<td>Pain and analgesic scores significantly worse in placebo group</td>
<td>Lipton et al. 2000 (26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>60 mg or 90 mg every 3 weeks for maximum six cycles</td>
<td>60% and 63%, respectively, of patients had sustained reduction in pain intensity; median response duration was 15 vs. 12 weeks, respectively</td>
<td>Koeberle et al. 1999 (27)</td>
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<tr>
<td></td>
<td></td>
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<td>86</td>
<td>Single 120 mg infusion</td>
<td>Reduction in pain symptom score and analgesic consumption</td>
<td>Coleman et al. 1997 (28)</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>x</td>
<td>Placebo</td>
<td>643</td>
<td></td>
<td>4 mg every 4 weeks placebo</td>
<td>Less increase in pain scores than with placebo</td>
<td>Saad et al. 2002 (29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>638</td>
<td>4 mg every 3-4 weeks</td>
<td>Pain scores decreased from baseline</td>
<td>Vogel et al. 2004 (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>101</td>
<td>4 mg every 3 weeks</td>
<td>Significant reductions in worse pain</td>
<td>Wardley et al. 2005 (31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>Active</td>
<td>1648</td>
<td>4 mg or 8 mg every 3-4 weeks vs. pamidronate 90 mg every 3-4 weeks for 12 months.</td>
<td>Pain scores decreased in all treatment groups, i.e. zolendronate and pamidronate similarly effective.</td>
<td>Rosen 2001 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>228</td>
<td>4 mg every 4 weeks</td>
<td>Fewer patients reported bone pain with Zoledronate vs. placebo, especially grade 3 or 4 bone pain</td>
<td>Kohno et al. 2005 (33)</td>
</tr>
</tbody>
</table>
Bone pain relief with ibandronate / J.D. Ringe & J.J. Body

in the placebo group, indicating that the better pain relief was not due to the increased use of analgesics (63). The 6 mg ibandronate infusion also increased mean QoL scores compared with placebo over the course of the study; differences were significant for global functioning ($p = 0.004$) and global health status ($p < 0.05$) and with significantly better scores on the domains of physical, emotional, and social functioning ($p < 0.05$).

High-dose ibandronate for metastatic bone disease due to urological cancers

A publication search revealed two open-label, prospective studies that have assessed the ability of high-dose i.v. ibandronate to provide pain relief in patients with MBD resulting from urological cancers (prostate cancer, renal cancer or bladder cancer). In the first of these studies, 45 men with prostate cancer and MBD received i.v. ibandronate (6 mg) in a 1-hour infusion on 3 consecutive days (as a loading dose) followed by a single infusion of i.v. ibandronate 6 mg every 4 weeks for a mean duration of 9 months (45, 65). Forty patients (89%) experienced a rapid and significant ($p < 0.001$) improvement in bone pain score (evaluated using a 10-point visual analogue scale [VAS] from baseline). Of these, 11 (25%) were completely pain free following ibandronate treatment. As pain decreased, daily analgesic use and patient mobility and functioning (assessed by the Karnofsky index and the Eastern Cooperative Oncology Group [ECOG] performance status) improved.

In the second study, 53 patients with prostate, renal or bladder cancer and MBD received a loading dose of i.v. ibandronate (6 mg in a 1-hour infusion on 3 consecutive days), followed by 6 mg i.v. ibandronate every 4 weeks for 20 weeks (66). Consistent with the study in men with prostate cancer, i.v. ibandronate rapidly and significantly relieved pain (3-point reduction in VAS and 50% reduction in analgesic use) in 44 patients (83%) and completely relieved pain in 25% of participants. Mean bone pain scores (10-point VAS) fell progressively from 6.8 at baseline to 2.5 on day 3 ($p < 0.001$). The bone-pain scores remained below baseline for 20 weeks, and were accompanied by improved patient mobility and functioning, as measured by Karnofsky Index and ECOG performance status (Fig. 2). Indeed, some previously bedridden patients became mobile and independent within a few days of starting ibandronate treatment (66).

High-dose ibandronate for opioid-resistant metastatic bone disease

One open-label, pilot study has assessed the analgesic effect of high-dose i.v. ibandronate in 18 patients with various advanced cancers, MBD and opioid-resistant bone pain (64). At baseline, participants had bone pain, despite receiving the equivalent of 400 mg/day oral morphine. Patients received a high-dose schedule of 4 mg ibandronate by i.v. infusion over 2 hours for 4 consecutive days, and were then assessed for 6 weeks or until death. I.v. ibandronate significantly reduced pain scores within 7 days compared with baseline; pain scores were then maintained at this lower level throughout the study period ($p < 0.05$). It is important to note that this improved pain relief was not due to increased analgesic use. Significant and maintained improvements in QoL,
Bone pain relief with ibandronate

**Multiple myeloma**

A randomised, double-blind, placebo-controlled, parallel-group study has evaluated a non-standard dose of ibandronate (2 mg administered as a monthly i.v. injection) vs. placebo in 198 patients with stage II/III multiple myeloma (67). Secondary variables of this study included bone pain score (scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = intolerable) and analgesic score (scale: 0 = none, 1 = mild analgesic or non-steroidal anti-inflammatory drug [NSAID], 2 = mild analgesic + NSAID, 3 = moderate analgesic, 4 = opiates morphine <40 mg daily, 5 = opiates morphine 40-100 mg daily, 6 = opiates morphine >100 mg daily). At final evaluation, patients with confirmed osteolytic lesions had significantly decreased bone pain scores compared with baseline (Wilcoxon rank sum test; \( p < 0.047 \)). However, overall there were no significant differences versus placebo in bone pain or analgesic drug use. This lack of a significant analgesic effect in the overall patient population is likely due to the use of an inadequate ibandronate dose in this study, i.e. 2 mg. There was an effect on the reduction of skeletal-related events in patients with an ‘adequate’ inhibition of bone resorption (evaluated by bone markers) confirming that the dose was too low for most patients. This explanation is consistent with the inadequate effect of this 2 mg i.v. dose in patients with MBD due to breast cancer (70). Higher doses (i.e. 6 mg) in MBD associated with breast cancer were, however, associated with significant and sustained pain relief. **Summary:** i.v. ibandronate for managing bone pain in patients with malignant disease.

**Bone pain with associated non-malignant disorders**

Various bisphosphonates have demonstrated efficacy in providing pain relief in several non-malignant disorders of increased bone turnover, including Paget’s disease (73-81) CIO (82) and localised transient osteoporosis (bone marrow oedema) (83-86). Other published reports document the efficacy of bisphosphonates in a group of ill-defined and poorly understood chronic inflammatory bone metabolic disorders, collectively known as sternocostoclavicular hyperostosis (87-91). The pain of diffuse sclerosing osteomyelitis (92) and of fibrous dysplasia (93-96) is also reported to respond to bisphosphonate therapy. The studies that have evaluated the efficacy of ibandronate for relieving the bone pain associated with these non-malignant disorders of increased bone resorption are discussed below. The majority of these studies have been conducted with the i.v. formulation of ibandronate.
I.v. ibandronate for treating non-malignancy-related bone pain

Corticosteroid-induced osteoporosis

The efficacy of i.v. ibandronate for relieving the pain associated with established osteoporosis due to long-term, high-dose corticosteroid treatment was assessed in an open-label, randomised study (58, 59). In total, 115 patients were randomised to receive daily calcium supplements plus either 3-monthly i.v. injections of 2 mg ibandronate or daily oral alfacalcidol (1 μg) for 3 years. At 3 years ibandronate i.v. injections produced significantly superior increases in mean lumbar spine and femoral neck BMD (p < 0.001 for both analyses) vs daily oral alfacalcidol (primary study endpoint). In addition, patients who received ibandronate injections experienced significantly fewer vertebral fractures after 3 years (8.6%) compared with alfacalcidol (22.8%; relative risk reduction, 62.3%; p = 0.043). Change in back pain intensity (measured on a 4-point Likert scale) was a secondary endpoint of the study. Three-monthly injections of ibandronate provided significant back pain relief over the course of the study. At 3 years, the proportion of patients who achieved a pain score reduction of two or three degrees from baseline was 86.2% for ibandronate and 49.1% for daily alfacalcidol (p < 0.001). In addition, 62% vs. 30% of participants, respectively, reported no pain at the end of 3 years’ treatment (Table II). Thus, i.v. ibandronate appears to provide significant benefit for patients with established CIO with bone pain.

Localised transient osteoporosis

The findings from one published study indicate the potential benefit of ibandronate in relieving the pain associated with localised transient osteoporosis. This 6-month, open-label, prospective, observational study enrolled 12 patients diagnosed with localised transient osteoporosis (by acute onset of pain at the hip, knee or ankle without prior trauma, increased radiolucency on x-ray with increased 99Tc uptake on bone scan, typical bone marrow oedema on MRI and normal routine laboratory values and calcium metabolism) (68). Patients received a single i.v. administration of 4 mg ibandronate with an optional 2 mg injection at 3 months. Local pain on a 10-point VAS were assessed at baseline and 1, 2, 3 and 6 months. After 6 months i.v. ibandronate injections provided rapid and substantial pain relief (Fig. 4). Most patients experienced noticeable pain relief by month 1 and the majority were almost or completely pain free by month 3. By month 6, the mean VAS pain score had decreased considerably from 9.3 at baseline to 0.5 and seven patients were completely pain free. Pain relief was accompanied

**Table II.** Corticosteroid-induced osteoporosis: change in the course of back pain from baseline to study end in patients receiving ibandronate or alfacalcidol (58, 59).

<table>
<thead>
<tr>
<th>Assigned treatment group</th>
<th>Ibandronate</th>
<th>Alfacalcidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Pain at baseline None</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
<td>32.8</td>
</tr>
<tr>
<td>Severe</td>
<td>37</td>
<td>63.8</td>
</tr>
<tr>
<td>Pain at last visit None</td>
<td>36</td>
<td>62.1</td>
</tr>
<tr>
<td>Mild</td>
<td>20</td>
<td>34.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Severe</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Change in pain from baseline to last visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved three degrees</td>
<td>22</td>
<td>37.9</td>
</tr>
<tr>
<td>Improved two degrees</td>
<td>26</td>
<td>44.8</td>
</tr>
<tr>
<td>Improved one degree</td>
<td>9</td>
<td>15.5</td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Worsened</td>
<td>–</td>
<td>–</td>
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**Fig. 4.** Impact of intermittent i.v. ibandronate injections in patients with localised transient osteoporosis: average pain before and after i.v. ibandronate (VAS 1-10) (68). Reprinted from Ringe JD et al.: Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate. Osteoporos Int 2005; 16: 2063-8 with kind permission of Springer Science and Business Media.
by substantial improvements in mobility and QoL.

—Sternocostoclavicular hyperostosis

Detailed case studies of three patients indicate the benefits of i.v. ibandronate in sternocostoclavicular hyperostosis (69). All three patients had failed to respond to previous conventional analgesics and physiotherapy. I.v. ibandronate was administered as a single 4 mg infusion, followed by 2 mg injections every 3 months for 1 year. Pain scores were assessed at baseline and at regular intervals using a 10-point VAS. Rapid and persistent pain relief with ibandronate injections was observed in all patients. The average VAS pain score of the three patients was 9.7 at baseline, falling to 4.7 at 2 weeks, 1.7 at 3 months and 0.3 after 12 months.

Summary: i.v. ibandronate for managing bone pain in patients with non-malignant disease.

I.v. ibandronate demonstrates robust efficacy in relieving the pain associated with non-malignant disorders characterised by increased bone turnover. Notably, this analgesic efficacy was achieved using lower doses and less intensive dosing regimens than used in malignant disease, reflecting the less aggressive underlying pathophysiology of these conditions. This contrasts with findings for other i.v. bisphosphonates in which similar dosages appear to be needed for both malignant and non-malignant bone-related pain.

Discussion

Although some of the studies included within this review have low patient numbers or are not placebo-controlled, the body of evidence as a whole demonstrates that ibandronate significantly and persistently reduces bone pain scores and consequently improves patient functioning and QoL in a wide variety of malignant and non-malignant disorders associated with increased bone turnover.

In MBD, both i.v. and oral ibandronate compare favourably with several other bisphosphonates in terms of both efficacy and tolerability. This is in contrast with previous oral bisphosphonate therapy (e.g. oral clodronate), which has often been seen as less effective than i.v. bisphosphonates (pamidronate and zoledronate), thereby proving no real alternative. Therefore, ibandronate uniquely offers patients and healthcare professionals greater choice and flexibility, with proven efficacy in both formulations.

In several non-malignant disorders of bone turnover, i.v. ibandronate demonstrates promising analgesic efficacy with lower doses and less intensive dosing schedules than needed for pain relief in MBD. These findings are in marked contrast to those with other i.v. bisphosphonates (e.g. clodronate and pamidronate), in which similar high-dose-intensity schedules appear to be needed to relieve pain in both malignant and non-malignant conditions. Additionally, in generally benign disorders with increased bone turnover, safety, tolerability, simplicity and convenience are of high importance when deciding on a therapy to ensure good long-term therapeutic adherence. It is therefore notable that both oral and i.v. ibandronate have demonstrated good safety and tolerability profiles, comparable to placebo (97). In addition, oral ibandronate has been shown to be well tolerated even in patients with a history of upper gastrointestinal disorders or taking NSAIDs, while no clinical complications with renal function have been detected with i.v. ibandronate. Furthermore, ibandronate is the only bisphosphonate to offer both i.v. injection and oral regimens with extended (beyond weekly) between-dose intervals in this therapeutic area. Once-monthly (150mg) oral and 3-monthly (3mg) i.v. injection regimens of ibandronate (both approved for the treatment of postmenopausal osteoporosis) provide prescribers the ability to offer their patients simple and convenient treatment options (97).

In conclusion, ibandronate uniquely offers the flexibility to tailor treatment to the individual patient’s needs and circumstances. Intensive, high-dose oral and i.v. regimens are effective in alleviating malignant, bone-related pain, while lower, less frequent doses are suitable for pain due to non-malignant disorders of bone turnover. Both i.v. and oral formulations are well tolerated over the extended dose range examined in the studies reviewed herein, highlighting the wide therapeutic window of this bisphosphonate. Further randomised, controlled trials are required to fully assess the effects of ibandronate on bone pain, however, ibandronate is an appropriate choice for bone pain relief in patients with a broad spectrum of underlying conditions.

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