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# Adverse Effects of Bisphosphonates: Current Issues

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**Abstract** Four bisphosphonates are used for the treatment of metastatic bone disease: clodronate, which is available outside the United States in both intravenous and oral formulations; intravenous pamidronate; intravenous zoledronic acid; and ibandronate, which is also available in intravenous and oral forms. Since the use of bisphosphonates in patients with cancer is palliative, their impact on patients' quality of life and their adverse-effect profiles are essential considerations for effective patient management. The most common adverse effects associated with bisphosphonates are renal toxicity, acute-phase reactions, gastrointestinal (GI) toxicity, and osteonecrosis of the jaw (ONJ). The incidence of these adverse events varies significantly between bisphosphonates. Renal toxicity is a potentially life-threatening event reported in studies of zoledronic acid and, to a lesser extent, pamidronate. In contrast, the renal safety profile of intravenous ibandronate and oral bisphosphonates is similar to that of placebo. Acute-phase reactions occur only with intravenous aminobisphosphonates and may be more common with zoledronic acid. Gastrointestinal effects occur only with oral agents (clodronate and ibandronate) and may be avoided by adhering to dosing instructions. More recently, ONJ has recently emerged as a complication of bisphosphonate use. However, its true incidence is not yet known. The potential adverse effects of bisphosphonates should be considered in the context of the individual patient's characteristics and preferences when selecting a bisphosphonate for metastatic bone disease.

Bisphosphonates play an important role in the treatment of bone metastases in patients with cancer. Four bisphosphonates are used to treat bone metastases: clodronate (Bonefos; worldwide except US), pamidronate (US and Europe), zoledronic acid (Zometa; US and Europe), and ibandronate (Bondronat worldwide outside the US). All four drugs effectively prevent skeletal complications in patients with metastatic bone disease.[1–6] Because advanced cancers that have metastasized to bone are usually incurable, bisphosphonate therapy is generally used in the palliative setting. Therefore, it is important that such treatment is well tolerated with minimal adverse effects.

Bisphosphonate-related adverse effects are listed in Table 1. The adverse-effect profile of a particular bisphosphonate may depend on a number of factors, such as whether or not it is an aminobisphosphonate, as well as its route and frequency of administration and dose. Various rare adverse effects of bisphosphonates targeting the eyes, skin, central nervous system, and other organs have been reported in individual patients However, three types of adverse effects are more commonly seen with some or all bisphosphonates, namely, renal toxicity, acute-phase reactions, and gastrointestinal (GI) disorders. These adverse events, along with the more recently described osteonecrosis of the jaw (ONJ), are most relevant to clinical practice and are described in detail in this review.

## Mechanisms of Action and Adverse Effects

A full understanding of the adverse effects of bisphosphonates requires knowledge of their mechanisms of action. Bisphosphonates, however administered, localize strongly to the bone surface, with uptake particularly high at sites of increased bone turnover (the principle behind the use of bisphosphonates in bone scanning). Osteoclasts take up bisphosphonates from resorption lacunae in the bone matrix, and the bisphosphonates then trigger the osteoclasts to undergo apoptosis.[7] Ami-

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**Table 1**

Adverse Effects of Bisphosphonates

| |
|---|
| **Common** |
| Renal toxicity |
| Acute-phase reactions |
| Gastrointestinal toxicity |
| **Rare** |
| Hypocalcemia (symptomatic) |
| Ocular complications (retinitis, uveitis, scleritis) |
| Asthma (aspirin-sensitive) |
| Erythema |
| Phlebitis |
| Altered taste |
| Central nervous system side effects |
| **Emerging** |
| Osteonecrosis of the jaw |

nobisphosphonates, such as pamidronate, zoledronic acid, and ibandronate, interfere with the metabolism of mevalonate, which, among other actions, is essential for the biosynthesis of cholesterol and its derivatives. Aminobisphosphonates competitively inhibit the geranylation and function of guanosine triphosphate–binding proteins (eg, Rab, Rac, and Rho). Clodronate, an aliphatic nonaminobisphosphonate, promotes the intracellular conversion of adenosine triphosphate to toxic analogues. Both processes—inhibition of guanosine triphosphate–binding proteins and intracellular conversion of adenosine triphosphate—lead to apoptosis of osteoclasts but may also induce apoptosis in gut mucosa and renal tubules if bisphosphonates accumulate in these tissues.[8,9]

## Renal Toxicity

Animal studies and clinical observations have shown that all bisphosphonates (including alendronate sodium [Fosamax] and risedronate sodium [Actonel]) have the potential to cause acute tubular necrosis.[10–12] The renal histopathology associated with individual bisphosphonates can vary greatly, however, depending on the degree to which the drugs accumulate in the renal parenchyma, which, in turn, depends on the drugs' pharmacokinetics and pharmacodynamics.

Orally or parenterally administered bisphosphonates that are not taken up by the bones are excreted unmetabolized via the kidneys; nevertheless, the exact mechanism of renal excretion is still unknown. In rats and mice, the influx of these drugs into tubular cells is passive and is dependent only on the drugs' serum concentration and protein binding. Excretion into the lumen involves an active, limited transport mechanism, as has been shown in animal studies with pamidronate and alendronate.[13–17] Increasing the bisphosphonate dose leads to an increase in the amount of drug measured in the urine only up to a certain point, after which further dose escalation leads to a relative decrease. In contrast, tissue drug levels show a concomitant linear increase as bisphosphonate dose increases. However, since the high doses required for saturation of the renal transport mechanism are not used clinically, the different rates of passive influx and active excretion of bisphosphonates are probably more relevant for the development of renal toxicity.

**Table 2**

Selected Pharmacokinetic Properties of Intravenous Bisphosphonates[7–9]

| | DOSE/INFUSION DURATION (mg/h) | PROTEIN BINDING (%) | $t_{½}$ (h) | $C_{max}$ (ng/mL) |
|---|---|---|---|---|
| Ibandronate | 6/1.0 | 87 | 12.0–16.0 | 384 |
| Zoledronic acid | 4/0.15 | 56 | 1.4–1.9 | 468 |
| Pamidronate | 90/1.0 | 54 | 0.8–2.5 | 2,790 |
| Clodronate | 1,500/2.0 | 36 | 2.0–2.3 | 12,000 |

Adapted from Russell et al,[7] Luckman et al,[8] and Rogers et al[9]

Abbreviations: $t_{½}$ = serum half-life; $C_{max}$ = maximum serum concentration

For intravenous bisphosphonates, the dose, frequency, and speed of infusion are all important determinants of renal toxicity. Reducing the dose and slowing the infusion rate decrease acute toxicity, whereas prolonging the interval between infusions reduces chronic toxicity. To date, there is no evidence that renal complications occur with therapeutic doses of oral bisphosphonates. The degree of protein binding (which determines serum half-life) and renal tissue half-life of bisphosphonates are also important, as they determine drug accumulation in the kidneys. Table 2 compares selected pharmacokinetic properties of the intravenous bisphosphonates.

Although intravenous clodronate is rarely used in clinical practice because of the need for long infusion times (up to 4 hours),[18] renal toxicity can occur with its use. Nephrotoxicity has been reported with intravenous pamidronate. Although nephrotoxicity has occurred primarily when high doses of pamidronate have been used,[12,19,20] it may also develop with the standard dose of 90 mg.[21] Histologic findings include collapsing glomerulonephritis.[21]

Zoledronic acid, the most frequently used intravenous bisphosphonate worldwide, has also been associated with acute tubular necrosis in several reports.[22–24] Renal damage and creatinine level elevation were even observed in the phase III trial of this drug, especially at the 8-mg dose tested initially.[4] On the recommendation of a renal safety committee, the 8-mg dose of zoledronic acid was abandoned, and the infusion time was extended from 5 to 15 minutes. Although prolonging the infusion duration reduced the incidence of nephrotoxicity, patients still experienced renal impairment. For example, in the phase III trial in patients with breast cancer and multiple myeloma, 9% of patients treated with zoledronic acid (4 mg infused over 15 minutes) experienced deterioration in renal function. This rate compared with 8% of patients receiving pamidronate (90 mg infused over 2 hours).[4]

Chang et al[24] described 72 cases of acute renal failure with zoledronic acid, including some that were fatal. However, most of the patients had multiple myeloma and were therefore at

heightened renal risk from paraprotein formation. Nevertheless, retrospective analyses seem to indicate that the risk of renal impairment may be higher with zoledronic acid than with other bisphosphonates, including pamidronate.[25] Chen et al[26] analyzed data from 3,340 patients with breast cancer treated with zoledronic acid (n = 312), pamidronate (n = 166), or no bisphosphonate therapy (n = 2,862). Although the rate of renal impairment was higher in the two bisphosphonate groups than in the group that did not receive bisphosphonates, significantly more renal events occurred in patients treated with zoledronic acid than with pamidronate ($P = 0.0194$). Multivariate analysis showed that patients who received zoledronic acid had an approximately twofold increased risk of developing renal impairment compared with those who received pamidronate.[26] A similar retrospective analysis of patients with multiple myeloma indicated a 2.6-fold higher risk of renal impairment in patients treated with zoledronic acid than in those treated with pamidronate.[27]

Because of the renal safety issues associated with zoledronic acid, the manufacturer advises that the patient's creatinine clearance be calculated before each infusion. If the creatinine clearance is lower than 60 mL/min, the dose should be reduced according to a prescribed schedule.[28,29]

Results from clinical trials indicate that the renal safety profile of ibandronate is similar to that of placebo. In a phase III study of intravenous ibandronate in 466 patients with breast cancer and bone metastases, 4.0% of patients treated with ibandronate experienced renal adverse events compared with 4.5% of patients treated with placebo.[30] Kaplan-Meier analysis of the time to renal function deterioration showed no clinically relevant increase in serum creatinine levels with intravenous ibandronate.[31] In an extension of this trial, 62 patients received intravenous ibandronate for an additional 2 years (74% of patients received ibandronate for the entire 4-year period).[32] No treatment-related renal events were reported, and serum creatinine levels were similar to those in patients receiving placebo for up to 4 years. Other studies have shown that the renal safety of ibandronate is not affected by the use of shorter infusion durations or higher doses.[33–35]

The renal tolerability of ibandronate may be related to its relatively higher protein binding than zoledronic acid (87%–98% vs 22%–56%) and its relatively short tissue half-life (25 vs 150–200 days).[36,37] Evidence indicates that intrarenal accumulation determines the degree of renal damage.[38]

Based on the available data, the following recommendations can be made to avoid nephrotoxicity: comply strictly with the package leaflet instructions and maintain good hydration. If the serum creatinine level rises (or creatinine clearance decreases) during therapy with one bisphosphonate, reduce the dose or switch to a more renally safe bisphosphonate.

## Acute-Phase Reactions

The term acute-phase reaction encompasses a number of flu-like signs and symptoms, particularly subfebrile temperature (38°C/100.4°F), leukocytosis, exhaustion, and muscle and bone pain. Acute-phase reactions occur only with intravenously administered aminobisphosphonates (zoledronic acid, ibandronate, and pamidronate), typically after the first infusion.[2,5,39] Although not life-threatening, these reactions can be distressing to the patient, sometimes causing treatment withdrawal. Symptoms generally resolve within 48 hours and respond well to nonsteroidal anti-inflammatory drugs and antipyretic measures. The cause of acute-phase reactions is a transient increase in pyrogenic cytokines.[40] In particular, changes in gamma/delta (γ/δ) lymphocytes have been described; after stimulation by dimethylallyl pyrophosphate, these γ/δ lymphocytes increase production of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α; Figure 1).[41–43]

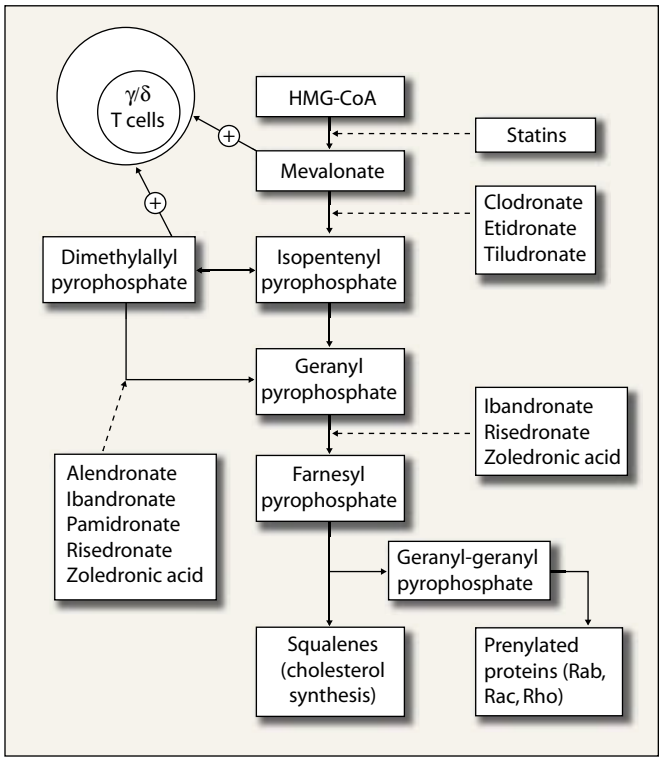


**Figure 1** Presumed Mechanism of the Acute-Phase Reaction Following Activation of γ/δ T Cells by Substrates of Inhibited Mevalonate Metabolism

Abbreviations: HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A[41–43]

The frequency and severity of acute-phase reactions to different bisphosphonates reported in clinical trials appear to vary markedly. However, comparisons between trials are difficult to make because of differences in the definitions and methodologies used for reporting these effects.

Two randomized trials of pamidronate[2,3] in patients with breast cancer reported only that flu-like symptoms were more frequent in the pamidronate group than in the placebo group. In a comparative study of pamidronate and zoledronic acid in patients with breast cancer or multiple myeloma, pyrexia was reported in 38% and 31% of patients in the zoledronic acid and pamidronate groups, respectively.[44] In a placebo-

controlled trial in patients with lung cancer and other solid tumors, pyrexia occurred in 26% of patients in the zoledronic acid group but also in 23% of patients in the placebo group.[45] Other studies have found fever or flu-like symptoms in up to 30% of patients treated with zoledronic acid.[46,47] A phase III, placebo-controlled trial of ibandronate in patients with breast cancer reported only that rates of flu-like symptoms were higher with ibandronate than with placebo.[5]

A phase II, open-label trial compared the safety profiles of ibandronate (6 mg intravenously on day 1 followed by 50 mg/day orally from day 2 onward) and zoledronic acid (4 mg intravenously every 3–4 weeks) in 77 patients with metastatic breast cancer or multiple myeloma.[48] Adverse events occurred less frequently in the ibandronate group than in the zoledronic group. In particular, fewer patients treated with ibandronate than with zoledronic acid experienced acute-phase reactions, such as pyrexia and flu-like symptoms, during days 1–3 (13% vs 26%). A trial comparing oral ibandronate with intravenous zoledronic acid in 274 patients with metastatic breast cancer likewise found a higher incidence of pyrexia and flu-like symptoms in the zoledronic acid group than in the ibandronate group (27% vs 2%; $P < 0.001$).[49] In this trial, patients received either oral ibandronate (50 mg/day; n = 137) or intravenous zoledronic acid (4 mg every 4 weeks; n = 137) for up to 12 weeks.

In vivo examinations comparing the effects of pamidronate, clodronate, and ibandronate demonstrated decreases in peripheral leukocyte and lymphocyte counts and significant increases in plasma IL-6 ($P < 0.006$ versus baseline) and TNF-α levels ($P = 0.0001$ versus baseline) after pamidronate but not after clodronate and ibandronate.[50] In our view, these findings may explain the observation of rare flu-like symptoms after ibandronate infusion.

## Gastrointestinal Effects

Bisphosphonate-induced adverse effects in the GI tract are naturally seen only with oral treatment. All levels of the GI tract can be affected, from the lower esophagus to the colon. Although ulceration in the esophagus, stomach, and duodenum can occur, mucositis, flatulence, and diarrhea are more common.[51–53] Since oral bisphosphonates are used much less often than parenteral formulations in patients with cancer, most of the data on the GI toxicity of oral bisphosphonates come from studies of the oral aminobisphosphonates ibandronate, alendronate, and risedronate in patients with osteoporosis.[54,55] However, it is unclear whether these data in osteoporosis can be extrapolated to the oncology setting.

Esophageal inflammation and ulceration have been described as rare but serious adverse effect of alendronate and, less frequently, risedronate. Most of the affected patients were elderly and had concomitant gastroesophageal reflux. Because the patients took their medication before bedtime, the bisphosphonate reached the esophagus while they were supine, resulting in erosion. For this reason, patients treated with these drugs are advised to take their medication in the morning after arising. Since absorption of bisphosphonates is impaired by food and beverages containing twofold positive cations (eg, $Ca^{++}$ and $Mg^{++}$), it is recommended that patients take these drugs on an empty stomach with 6–8 fl oz (130–240 mL) of water and that they wait 30–60 minutes before eating breakfast. Most clinically apparent complaints vary between nonspecific epigastric symptoms and severe flatulence and/or diarrhea. Some studies have shown that the frequency of upper GI inflammation and ulceration with bisphosphonates is similar to that with aspirin.[56–58]

Clodronate (a nonaminobisphosphonate) and ibandronate (an aminobisphosphonate) are the only two oral bisphosphonates approved for treating bone metastases. Neither drug is approved for this indication in the United States, however, and consequently is barely mentioned in the American Society of Clinical Oncology recommendations on the role of bisphophonates in women with breast cancer.[59] The history of oral bisphosphonates in oncology might have taken a different course had oral pamidronate not proved to be so toxic to the GI tract in early studies. Many reports highlighting the high dropout rate due to GI side effects in women with osteoporosis treated with pamidronate were published, despite clear evidence of its efficacy.[60–62]

Clodronate has been used for approximately 15 years in the oncology setting. Although initially tested only in small groups of patients with metastases or multiple myeloma, toxicity data from 2,000–3,000 patients are now available. Studies have reported upper GI adverse-effect rates of 3%–10% with clodronate, which were similar to rates with placebo.[1,63,64] In large studies, only diarrhea was significantly more common in clodronate-treated patients than in untreated groups. Diarrhea, abdominal distension, and, very rarely, epigastric pain are the reasons cited by patients for discontinuation of clodronate treatment in routine clinical practice. However, the large size of clodronate tablets can cause problems for patients. In one study, 11% of patients described difficulty in swallowing tablets as the reason for discontinuing clodronate.[65]

Ibandronate had low rates of GI toxicity (< 7%) in two phase III studies involving patients with breast cancer.[6] Although the rates of dyspepsia, nausea, abdominal pain, and esophagitis were higher in the ibandronate groups than in the placebo groups, the rate of lower GI adverse effects (diarrhea) with ibandronate was not increased compared with placebo. A 2-year extension study in which patients from the original trials were treated for up to 4 years reported no further increases in GI or other toxicities.[66] The smaller pill size of ibandronate tablets makes them easier for patients to take than clodronate. In addition, a minimum of 30 minutes after taking ibandronate is recommended before consuming food (compared with 1 hour after taking clodronate).

In summary, oral bisphosphonates have good to very good GI tolerability, with ibandronate showing some advantages over clodronate. According to current data, life-

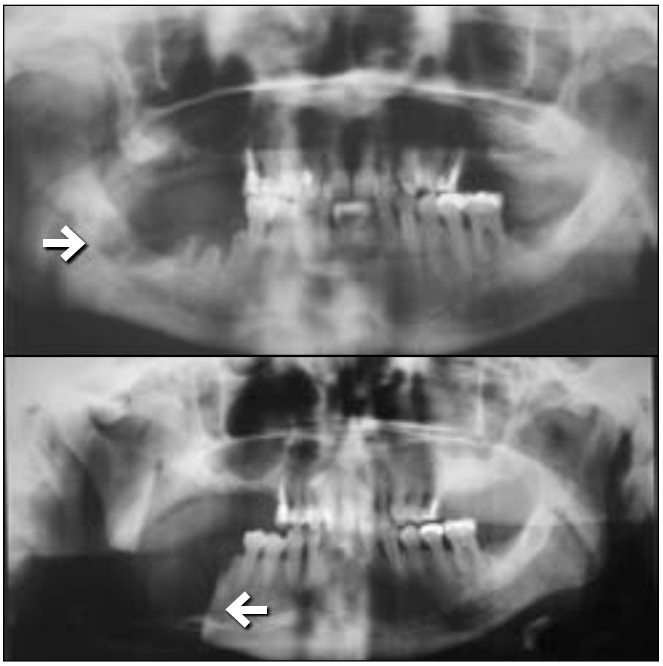

**Figure 2** Osteonecrosis of the Jaw

Top: Panoramic jaw views showing advanced right mandibular osteolysis (arrow). Bottom: Partial right mandibular resection after multiple failed debridement (arrow).[76]

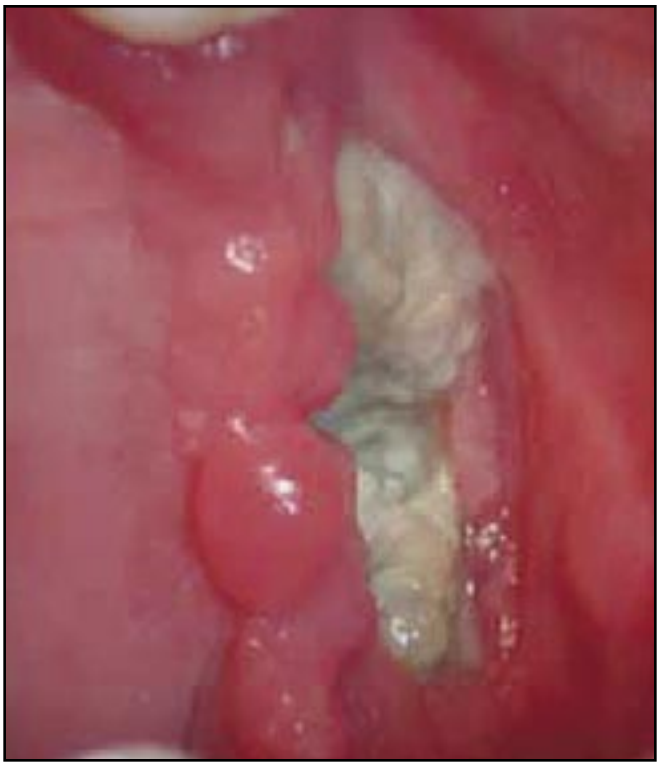

**Figure 3** Exposed Jawbone

Typical clinical appearance of exposed jawbone (left maxillary buccal region) in a patient with a history of spontaneous loss of severely loosened teeth (chronic deep marginal periodontitis).[76]

threatening complications are extremely rare. If adverse GI effects persist, administration should be switched to the intravenous route.

## Osteonecrosis of the Jaw: An Emerging Problem

ONJ was first described in association with bisphosphonate treatment in 2003,[67,68] although these reports referred to earlier observations. Initially, ONJ was perceived to be a puzzling adverse effect because bisphosphonates were assumed to have exclusively positive effects on bone turnover that would be expected to prevent rather than trigger necrosis.

Since these first descriptions, more than 1,000 cases of ONJ have been reported in the United States and over 300 in Germany (as of the summer of 2006).[69,70] Most of the reports to date have originated from the United States and therefore are confined to patients treated with pamidronate, zoledronic acid, alendronate, and risedronate. In Germany, there have been isolated reports of necrosis in patients treated with intravenous ibandronate, although most of them occurred after previous treatment with other bisphosphonates.[69,70] The concern is that all aminobisphosphonates may cause ONJ with long-term use.[71] To date, no case of ONJ has been described with clodronate, and there have been too few reports associated with ibandronate treatment to determine frequency.

The incidence of ONJ associated with bisphosphonate treatment in patients with cancer (eg, multiple myeloma, breast cancer, and prostate cancer) varies between 1% and 10%.[69–72] Durie et al[72] reported ONJ in 10% of patients with multiple myeloma who received zoledronic acid and 4% of patients who received pamidronate. Other studies with these two bisphosphonates have suggested ONJ rates of 3%–8%,[73–75] but as yet the true incidence of ONJ is unknown. Accumulated case reports may currently be distorting the actual level of risk because many patients contact several clinics to get a second opinion before starting treatment. This possibility notwithstanding, ONJ has a major clinical impact on the individual patient, since chewing, speaking, and swallowing can all be substantially and lastingly impaired (Figure 2). Severity is comparable to that of osteonecrosis after radiotherapy to the head and neck.[76]

A study by Ruggiero et al has provided some of the most valuable insights into ONJ.[75] Analysis of records from an oral surgery department identified 63 patients with ONJ. Of them, 56 patients with cancer had received intravenous bisphosphonates and 7 patients had received oral bisphosphonates exclusively for osteoporosis. The patients with cancer had been treated with pamidronate, zoledronic acid, or both drugs sequentially. Most, but not all, patients had preexisting dental, gingival, or jawbone disease, which had provided portals for pathogen entry or had led to inflammatory foci.

Usually jaw necrosis is characterized clinically by chronically exposed jawbone (Figure 3), up to and including suppu-

**Table 3**

Most Common Adverse Effects of Bisphosphonates

| COMPOUND | ROUTE OF ADMINISTRATION | RENAL TOXICITY | ACUTE-PHASE REACTIONS | UPPER GI SIDE EFFECTS | DIARRHEA | ONJ |
|---|---|---|---|---|---|---|
| **Nonaminobisphosphonate** | | | | | | |
| Clodronate 1,500 mg | Intravenous | + | 0 | 0 | 0 | 0 |
| Clodronate 800 mg (× 2) | Oral | 0 | 0 | + | ++ | 0 |
| Clodronate 520 mg (× 2) | Oral | 0 | 0 | + | ++ | 0 |
| **Aminobisphosphonates** | | | | | | |
| Ibandronate 6 mg | Intravenous | 0 | + | 0 | 0 | + |
| Ibandronate 50 mg | Oral | 0 | 0 | + | 0 | 0 |
| Zoledronic acid 4 mg | Intravenous | ++ | ++ | 0 | 0 | ++ |
| Pamidronate 90 mg | Intravenous | ++ | ++ | 0 | 0 | ++ |

Abbreviations: GI = gastrointestinal; ONJ = osteonecrosis of the jaw

ration and sequestration. The lesions are markedly refractory to treatment, including intensive antibiotic therapy and repeated jaw surgery. These features are also reminiscent of osteoradionecrosis.[76] ONJ may develop due to dentogenic portals of pathogen entry (eg, periodontal disease and periapical granuloma) or to prosthetic pressure points, leading to endosteal infiltration of the jawbone. Bisphosphonates promote the processes of inflammation and destruction by decreasing bone remodeling and exerting antiangiogenic and apoptotic effects.[77] An important radiographic sign in the jaw, therefore, is the presence of so-called persisting alveolar sockets after teeth extractions.[78]

Guidelines and/or recommendations for the prophylaxis and treatment of ONJ have appeared in both the United States and Germany.[79] Close cooperation among dentists, oral maxillofacial surgeons, and oncologists will prove crucial for accurate diagnosis and effective management in the future. Oncologists should discuss this potential complication with patients being offered bisphosphonate therapy. Recommendations for prevention include mandatory examination of the teeth and all potential oral foci of inflammation before starting bisphosphonate treatment. This recommendation is particularly important if radiotherapy to a jaw metastasis is planned in a patient who has been receiving long-term bisphosphonate therapy.[76] If in doubt, the oral cavity should be inspected as part of routine cancer follow-up.

Treatment recommendations for established ONJ are more controversial. Whether ongoing bisphosphonate therapy should be suspended or discontinued in patients who develop ONJ is unclear, as no improvement has been observed when such measures have been taken, no doubt in part because of the long half-lives of bisphosphonates (ie, several months to years). One option may be to switch treatment to oral clodronate.

Isolated ONJ is a now almost forgotten occupational entity. First described in the mid-19th century, ONJ was particularly common in workers in match and munitions factories who came into contact with white phosphorus.[80,81] After white phosphorus was replaced by the far less reactive red phosphorus and ventilation was improved, cases of "phossy jaw" largely disappeared and have since been reported only in Chinese firework factory workers. Whether this disease from the history of medicine merely provides an interesting analogy to bisphosphonate-related ONJ or offers a clue to its pathophysiology is still unclear. To better understand and prevent this adverse effect of bisphosphonates, physicians urgently need results from basic research.

## Conclusion

Since the use of bisphosphonates in oncology is palliative, tolerability and maintenance of quality of life are extremely important considerations. The incidence of adverse effects varies greatly between bisphosphonates (Table 3). Among the intravenously administered aminobisphosphonates, renal toxicity is a major concern for zoledronic acid and, to a lesser extent, pamidronate. This is reflected in the product labeling for zoledronic acid, which carries a warning about this potential adverse reaction and mandates renal function testing in patients treated with the drug, as well as dose reductions in those with mild to moderate renal impairment. In contrast, clinically significant renal toxicity has not been observed with ibandronate.

Acute-phase reactions are a less life-threatening, but distressing, adverse effect of intravenous bisphosphonates. The frequency of these reactions varies widely between trials and is dependent on methods of measurement and reporting. Acute-phase reactions have been reported with all intravenous bisphosphonates, although a comparative study indicated that their incidence was lower with ibandronate than zoledronic acid.[48]

For oral bisphosphonates, GI toxicity is the most common adverse effect, and its frequency varies greatly between bisphosphonates. Gastrointestinal toxicity can usually be avoided by adhering to dosing instructions, remaining upright, taking the medication with 6 to 8 fl oz of water, and waiting an appropriate interval before consuming food. The relatively small dose of 50 mg required for ibandronate allows for a shorter interval before food can be consumed, which may minimize GI toxicity.

The other major adverse effect that physicians should consider when prescribing a bisphosphonate is ONJ. At present,

it is unclear exactly how many patients are at risk of ONJ. It is also impossible to state definitively whether ONJ is more or less common with any particular bisphosphonate; however, it does appear to occur only with aminobisphosphonates. To prevent this adverse effect, clinicians should perform dental checks prior to initiating bisphosphonate therapy and should include such examinations as part of routine follow-up in all patients, particularly those who have undergone previous jaw surgery.

The choice of a bisphosphonate for the treatment of a patient with metastatic bone disease therefore depends on a number of factors. Choosing between oral or intravenous therapy may rest primarily on patient preference—a single monthly infusion versus a daily tablet. Patients who experience acute-phase reactions may be better suited to oral therapy, whereas intravenous treatment may be more appropriate for those who develop GI toxicity. For patients at risk of renal impairment, either an oral agent or intravenous ibandronate, which has not shown evidence of renal toxicity, should be considered. Selecting the most appropriate bisphosphonate based on these factors and switching between bisphosphonates if necessary will help to ensure that patients being treated for metastatic bone disease maintain quality of life with minimal adverse effects of treatment.

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