

# Efficacy and safety of zoledronic acid in the treatment of glucocorticoid-induced osteoporosis

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**Abstract:** Glucocorticoids are essential in treating many disorders and they are widely used in spite of their negative impact on the skeletal system. As bisphosphonates reduce bone resorption through their action on osteoclasts, they play an important role in management of glucocorticoid-induced osteoporosis. Unlike other bisphosphonates, zoledronic acid is given by intravenous infusion and it has a potential advantage of increasing the compliance and adherence of patients when it is given 5 mg once a year. However, this treatment modality seems to be associated with more adverse events than oral administrations, and further studies with longer follow-up periods must be conducted to determine the safety and cost-effectiveness of long-term treatment with zoledronic acid.

**Keywords:** bisphosphonates, glucocorticoids, osteoporosis, zoledronic acid

## Introduction

Glucocorticoids (GCs) are steroidal stress hormones which have many different biological functions.<sup>1,2</sup> Through binding to GC receptors, they exert most of their effects, such as regulating tissue differentiation during development, controlling intermediary metabolism and coordinating the adjustment of physiological processes in response to stress.<sup>3-5</sup> Because of these effects, synthetic GCs have been developed which are widely used in the treatment of allergic, inflammatory, lymphoproliferative disorders, and autoimmune diseases.<sup>6-10</sup> However, such a treatment is not without shortcomings: GCs exert a negative impact on the skeletal system as they result in a rapid, early phase of bone loss which is followed by a more chronic and progressive phase due to excessive bone resorption, in which finally the bone mass declines because of impaired bone formation.<sup>11</sup> The administration of GCs is the most frequent secondary cause of osteoporosis and it has been demonstrated that more than one third of individuals treated with GCs for 5 to 10 years will have an osteoporotic fracture.<sup>12,13</sup>

The purpose of this review is to discuss the pathophysiology of glucocorticoid-induced osteoporosis (GIO) and the efficacy and safety of zoledronic acid in the treatment of this disorder.

## Pathophysiology of glucocorticoid-induced osteoporosis

Although it is estimated that, 30%–50% of patients using long-term GCs experience relevant bone loss, the exact prevalence of GIO is still unknown.<sup>14,15</sup> The pathophysiology of GIO is complicated, as GCs may exert their effects on the skeletal system in many ways. In the beginning GCs cause an increase in bone resorption, however the most important effect of GCs is their action in decreasing bone formation by decreasing

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osteoblast proliferation and inhibiting osteoblasts from producing new bone.<sup>16,17</sup> In addition, osteocyte apoptosis can be detected in GIO, which results in microarchitectural deterioration, as these cells are considered to determine bone strength independent of bone mineral density (BMD).<sup>18</sup> On the other hand, GCs also have systemic effects on bone metabolism as they have a negative effect on calcium homeostasis by decreasing absorption of calcium from the intestine and increasing calcium loss in the urine, as a result of defective vitamin D metabolism. This leads to secondary hyperparathyroidism, which results in increased bone resorption.<sup>15,16</sup> Moreover, GCs affect bone metabolism indirectly by reducing levels of sex hormones as a result of suppressed pituitary gonadotrophin secretion.<sup>16</sup>

## Treatment of glucocorticoid-induced osteoporosis and bisphosphonates

As GIO is an important problem due to the increased risk of fracture, preventive measures are suggested in order to stabilize or increase the BMD in such patients, and consequently reduce the risk of fracture. It has been demonstrated that regular BMD assessment, and management of osteoporosis is sub-optimal in patients using long-term GCs, despite the fact that screening and treatment rates have increased in recent years.<sup>19</sup> In an attempt to increase the rates of screening and treatment of osteoporosis in long-term GC users, Curtis et al employed an online continuing medical education program for physicians who prescribed long-term GC therapy.<sup>20</sup> Although the final results of this study revealed that the education provided did not yield any advantage when compared to the control group, a greater amount of education may be beneficial and the mode of education may affect the outcome.

Calcium and vitamin D supplementation, increasing BMD, and preventing high cortisol levels, are the main strategies in treating GIO. Moreover, numerous clinical trials have now demonstrated that bisphosphonates are highly effective at limiting bone loss in patients with GIO.<sup>21</sup> Furthermore, in GC-treated patients at high risk of fracture, bisphosphonate therapy has proved to be cost-effective.<sup>22</sup> Thus, nowadays bisphosphonates are considered to be the gold standard for the prevention and treatment of GIO, along with sufficient intakes of calcium and vitamin D as they increase BMD, and reduce vertebral fracture risk in patients beginning or continuing GC treatment.<sup>23–28</sup> The nitrogen-containing bisphosphonates act by inhibiting farnesyl diphosphate (FPP) synthase, a key enzyme of the mevalonate pathway, which is critical to the production of cholesterol, other sterols, and isoprenoid lipids. The inhibition of osteoclasts by the nitrogen-containing bisphosphonates

is very likely mediated by their action on the FPP synthase, which leads to protracted apoptosis of these giant cells.<sup>29,30</sup>

Although daily oral bisphosphonate therapy with alendronate or risedronate is effective for treatment of GIO, compliance and adherence with daily and weekly therapy has been shown to be suboptimal.<sup>31–35</sup> This finding is important, as an association between poor adherence and increased fracture risk has been demonstrated in women with postmenopausal osteoporosis who were treated with oral bisphosphonate.<sup>36</sup> Therefore, studies were conducted in order to search for an alternative treatment regime which would increase the compliance and adherence of patients with GIO.<sup>37</sup>

## Zoledronic acid in the treatment of glucocorticoid-induced osteoporosis

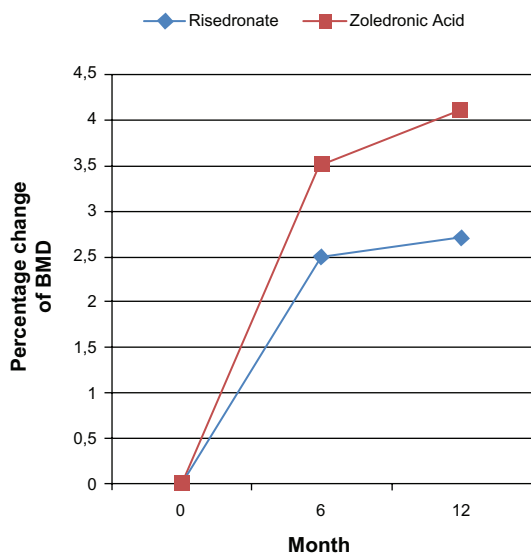
Like other bisphosphonates, zoledronic acid binds to the calcium phosphate bone mineral hydroxyapatite, predominantly localizing at regions of high bone turnover.<sup>38,39</sup> Additionally, the affinity of zoledronic acid for hydroxyapatite was shown to be higher than that of other bisphosphonates in an *in vitro* study.<sup>38</sup> In osteoporosis, zoledronic acid inhibits osteoclast-mediated resorption, therefore reducing bone turnover.

Zoledronic acid, which is available as an intravenous formulation, is approved for the treatment of osteoporosis in postmenopausal women and, more recently, in men at increased risk of fracture, and in patients in Europe with a recent low-trauma hip fracture.<sup>40</sup> Intravenous zoledronic acid 5 mg, administered via infusion, is the first once-yearly treatment approved for these indications.<sup>41–44</sup>

The efficacy of zoledronic acid for preventing and treating GIO was studied by HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once) investigators in a large international study, where patients were randomized to receive either intravenous 5 mg zoledronic acid or oral 5 mg risedronate.<sup>37</sup> This study demonstrated that one 5 mg infusion of zoledronic acid annually increases bone mineral density of the lumbar spine and femoral neck, trochanter, and total hip more than the oral 5 mg risedronate daily, in patients who had recently started GCs (prevention group n:288) and in those who had been already taking them (treatment group n:545).<sup>37</sup> The patients were followed for 12 months and BMD was measured at 6th and 12th months. The primary endpoint of the study was the percentage change from baseline in BMD, while changes in bone turnover biomarker concentrations were measured as secondary end-points. Evaluation of this study indicated that the increase in BMD at 6 months was significantly higher with zoledronic acid than it was with risedronate (Figure 1). It has

also been shown that inhibition of the bone turnover markers was faster and more substantial in patients receiving zoledronic acid. Unfortunately, this study was not able to detect differences in fracture risk.<sup>37</sup> However, various studies have demonstrated that once-yearly administration of zoledronic acid 5 mg is effective in preventing fractures.<sup>45-47</sup> Bearing this in mind, we may speculate that annual administration of 5 mg zoledronic acid will be efficacious in preventing bone fractures. However this speculation requires further studies to verify it.

Severe adverse effects associated with the use of intravenous bisphosphonates are uncommon, however approximately 10% to 30% of patients receiving their first nitrogen-containing bisphosphonate infusion will experience an acute phase reaction within the first 3 days of treatment. This is most commonly characterized by transient pyrexia with associated myalgias, arthralgias, headaches, and influenza-like symptoms.<sup>37</sup> This acute phase response is believed to be the result of proinflammatory cytokine production by peripheral blood T cells.<sup>48</sup> The reactions are typically self-limited and resolve completely within 24 to 48 hours. In addition to the administration of adequate fluid, NSAIDs or acetaminophen may be useful supportive treatments. The frequency of pyrexia within the first days of treatment was 15% in a study where no co-drug was used during the administration of zoledronic acid, however in a study where NSAIDs or paracetamol was administered with zoledronic acid the rate was 8.7% (Figure 1).<sup>37,45</sup> Fortunately, the frequency of these reactions is rare in subsequent infusions of nitrogen-containing bisphosphonates.<sup>37,49</sup>



**Figure 1** Percentage changes in BMD of lumbar spine in GIO patients treated with either daily risedronate or annual zoledronic acid (HORIZON).<sup>37</sup>

**Abbreviations:** BMD, bone mineral density; GIO, glucocorticoid-induced osteoporosis.

Ocular complications, nephrotoxicity, and/or electrolyte abnormalities such as hypocalcemia, hypophosphatemia, and hypomagnesemia are also reported.<sup>31</sup> The most frequent observed ocular complication is nonspecific conjunctivitis, which is usually self-limited.<sup>50</sup> On the other hand uveitis can also be seen after the administration of zoledronic acid and this requires medical treatment.<sup>51</sup> The physician administering intravenous bisphosphonates should be alert for such situations where patients present with ocular pain, itching, or decrease in vision, and in such cases they should promptly direct the patient to be examined by an ophthalmologist.<sup>50</sup>

Previous studies have proved that the effect of riseteronates on renal functions is comparable with placebo even in patients with impaired renal functions.<sup>52</sup> It is well known that all intravenous bisphosphonates have the potential to affect renal functions, especially in patients whose renal function is compromised.<sup>53</sup> However the findings of the HORIZON study did not demonstrate a higher rate of renal impairment in patients receiving zoledronic acid treatment than in patients in the risedronate arm.<sup>37</sup> When we take the previously-mentioned studies' results into consideration it may be further speculated that zoledronic acid may be comparable with placebo with respect to renal complications.

Electrolyte abnormalities can also be a problem in zoledronic acid treatment. In a multicenter review hypocalcemia was reported in 35% of patients after zoledronic acid infusion whereas symptomatic hypocalcemia requiring treatment was observed in 8% of patients despite prophylactic measures.<sup>54</sup>

Bisphosphonates have been linked to osteonecrosis of the jaw which can be prevented with pretherapy dental care.<sup>55</sup> It has been shown that prolongation of bisphosphonate treatment increases the frequency of osteonecrosis of the jaw.<sup>56</sup> The management of this situation is a matter for debate and depends on the stage at which it is diagnosed.

In the HORIZON-PFT (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Pivotal Fracture Trial), where patients were treated annually with intravenous zoledronic acid, a statistically-significant increase in the incidence of serious atrial fibrillation (defined as events resulting in hospitalization, or disability, or judged to be life-threatening) was noted.<sup>42</sup> The etiology of this electrophysiologic abnormality is not clarified yet. Unfortunately, we have limited data regarding other bisphosphonate preparations which may have the potential to produce similar rates of atrial fibrillation. One large population-based case-control study suggested a correlation between alendronate administration and a slightly-increased incidence of atrial

fibrillation, whereas another population-based case-control study showed no evidence of an increased risk of atrial fibrillation or flutter with alendronate use.<sup>57,58</sup> On the other hand, no increase was detected in the rate of atrial fibrillation seen in patients received IV zoledronic acid after a hip fracture (the HORIZON Recurrent Fracture Trial).<sup>45,59</sup> Apparently, more studies examining the potential relationship between bisphosphonate use and atrial fibrillation are required.

## Conclusion

Since GCs are essential in treating many disorders, physicians should consider their negative effects on skeletal health, and they must be aware of GIO prior to administering these drugs. As bisphosphonates reduce bone resorption through their actions on osteoclasts, they play an important role in management of GIO. However awareness rates are much below those expected. Future studies focusing on improving the understanding of GIO and its management should be conducted, as it may be beneficial to increase the awareness of physicians about GIO and its treatment options through rigorous education programs.

Zoledronic acid, which is given by intravenous infusion, has a potential advantage of increasing the compliance and adherence of patients when it is given 5 mg, once a year. Zoledronic acid is effective in preventing and treating GIO, with a overall high safety and tolerability rate, and a low rate of serious adverse events. Future studies concentrating on the long-term effects and cost-effectiveness would be beneficial. In addition, research focusing on new targets such as anabolic drugs which stimulate bone formation by acting on osteoblasts and osteocytes could lead to a more compelling rationale for use than bisphosphonates.

## Disclosures

The authors report no conflicts of interest in this work.

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