



Review Article

Osteonecrosis of the jaw during biyearly treatment with zoledronic acid for aromatase inhibitor associated bone loss in early breast cancer: A literature review



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ABSTRACT

Osteonecrosis of the jaw (ONJ) is one of the most relevant and specific complication of bisphosphonates. ONJ in patients receiving zoledronic acid every 3 to 4 weeks is frequently described, but the ONJ biyearly regimen used to reduce aromatase inhibitor associated bone loss (AIBL), is rarely reported. A literature review, focusing on the important trials using zoledronic acid to reduce AIBL, found that the mean risk of developing ONJ when zoledronic acid is used biyearly varies between 0.12% and 0.7%.

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1. Introduction

Osteonecrosis of the jaw (ONJ) emerged as a well-known devastating side effect of parenteral bisphosphonate therapy since the widespread use of bisphosphonates to reduce skeletal related events (SRE) [1]. Bisphosphonates are commonly used every three to four weeks with around 14–48% reduction of SRE occurrence and ONJ occurrence in 1.2–3.8% despite preventive measures [2–5].

Although the positive results of 4 different trials, the use of biyearly bisphosphonates regimens to reduce AIBL is NOT approved [6–9]. This spaced interval of six months achieved an increase in median bone mineral density of 2.7–4.3% in the lumbar spine and 1.6–1.7% in the hip when used in post-menopausal women receiving adjuvant hormonal aromatase inhibitor [7,8]. However, the risk of developing ONJ with the bi-annually regimen of zoledronic acid is not well recognized.

A review of literature in women having breast cancer receiving zoledronate biannually to prevent AIBL was conducted. Reported cases of ONJ are collected from the selected studies and an estimation of the ONJ risk in this category of patients is reported.

2. Material and methods

2.1. Search strategy for the identification of studies

Electronic searches of the literature published until September 2014 were conducted using PubMed and the Cochrane Collaboration Database to identify articles evaluating the ONJ as a side effect in women receiving zoledronic acid every six months for the prevention of aromatase inhibitor associated bone loss (AIBL) in patients with early stage breast cancer.

Only randomized and non-randomized controlled clinical trials were included. We excluded studies enrolling less than 500 patients. The duration of follow-up was not among the exclusion criteria. Search strategies employed included key words and Boolean operators described as follows: 'zoledronic acid', 'early breast cancer' and 'aromatase inhibitors'. This search was augmented by a hand search of the reference lists of relevant articles included in the literature review. Two different investigators performed the search and the abstracts were independently reviewed for possible inclusion.

2.2. Selection criteria

Types of studies: Randomized controlled trials were included. The language of publication of eligible studies was restricted to English.

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Types of Participants: Included studies were limited to postmenopausal women receiving zoledronic acid every six months with aromatase inhibitors to prevent AIBL. Studies presenting data on premenopausal patients or receiving tamoxifen were excluded.

Selection of Studies: The articles were first selected individually on the basis of their titles by two of the authors. Then, the abstracts of the available articles were examined. Our searches yielded 81 study reports from the PubMed database. All the review articles and case reports were excluded. Finally, four reports were considered illegible for our analysis [6–9]. Some of the other studies were included in the literature review.

3. Results

The upfront biyearly regimen of zoledronic acid significantly increased bone mineral density (BMD) in postmenopausal women receiving aromatase inhibitors for early breast cancer [6–9].

The Z-FAST trial enrolled 602 postmenopausal women with early hormone receptor-positive breast cancer receiving adjuvant letrozole [6]. Patients were randomized equally to receive upfront or delayed zoledronic acid with a 4 mg intravenous regimen every 6 months for 5 years. The investigators reported two cases of ONJ in the upfront group during the 60 months follow-up. However, an ONJ adjudication committee deemed one of the cases inconsistent with ONJ and the other one indeterminate because of insufficient information [6].

The ZO-FAST trial recruited 1065 postmenopausal women receiving adjuvant letrozole that were randomly assigned to immediate zoledronic acid with a regimen of 4 mg every 6 months for 5 years, or delayed administration initiated at fracture occurrence or on-study BMD decrease. A total of nine potential ONJ events from seven patients were reported in this study after 60 months follow up. Each event was independently adjudicated by an external panel that confirmed ONJ occurrence in three cases, deemed possible for insufficient data in two cases, and excluded the remaining cases [7]. Therefore, in the ZO-FAST trial, ONJ occurred in 0.28–0.47%.

In the E-ZO-FAST trial, 527 postmenopausal women receiving aromatase inhibitors were randomized to either immediate or delayed zoledronic acid treatment, at 4 mg every 6 months. Two reported cases of ONJ of the immediate zoledronic acid group were confirmed by the adjudication committee. At diagnosis, patients had received 3 and 6 doses of zoledronic acid. Treatment was discontinued in both patients but ONJ only resolved in one patient [8]. Accordingly, the E-ZO-FAST trial report ONJ in 0.38%.

Finally, the ABCSG-12 trial is the largest study recruiting 1803 patients with early breast cancer receiving zoledronic acid 4 mg intravenously every 6 months. There were no confirmed cases of ONJ during a follow up of 84 months [9]. All these studies are summarized in the Table 1.

Keeping in mind the limitation of these studies by the absence of long-term follow-up, the mean risk of developing ONJ varies

between 0.23–0.41% in patients receiving immediate or late zoledronic acid. This risk increases up to 0.7% in patients receiving immediate zoledronic acid.

4. Discussion

Zoledronic acid has been approved for prevention and treatment of osteoporosis and glucocorticoids-induced osteoporosis, treatment of Paget's disease, hypercalcemia, multiple myeloma and bone metastasis. In the particular case of breast cancer, it is recommended as a monthly administration in breast cancer patients with bone metastasis and as a biyearly administration in early breast cancer patients receiving adjuvant aromatase inhibitors for AIBL prevention [10].

Zoledronic acid is a high potency aminobiphosphonate with an osteoclastic inhibiting activity. It is incorporated into the skeleton without being degraded and consequently decreases bone turnover and inhibits of the bone's reparative ability [11,12]. Prolonged use of zoledronic acid suppresses bone turnover disabling repair of microdamage [13].

Reports of the side effects of zoledronic acid most commonly describe bone pain, nausea, fever, fatigue and constipation. ONJ is an uncommon, but severe, adverse event that has been reported with prolonged zoledronic acid therapy.

In women with advanced breast cancer and bone metastases, the use of bisphosphonates in adjunction to hormone therapy or chemotherapy reduces the SRE occurrence and the SRE rate, as well as increases the time to skeletal event occurrence [2]. Their major adverse event remains the ONJ. Effectively, breast cancer patients receiving bisphosphonates represent more than 20% of patients developing ONJ [14].

Metastatic breast cancer patients treated by zoledronic acid monthly develop ONJ in 1.2–3.8% with the long-term treatment [3,4]. On the other hand, biyearly zoledronic acid for AIBL prevention in early breast cancer is complicated with ONJ in less than 0.7% according to our literature review. Unfortunately, these trials did not report the time of occurrence of the ONJ [6–8]. However, the AZURE trial used a regimen that consisted of monthly zoledronic acid for six doses then every three to six months to compete the 5 years treatment and reported a comparable prevalence of ONJ [15]. This comparison allows a safe administration of the “loading dose” of zoledronic acid. Effectively, the pharmacology of the zoledronic acid characterized by a long half-life correlates well with this finding. A recently published abstract, SWOG 0307 compared three different bisphosphonates clodronate, ibandronate and zoledronic acid administered in a specific schedules in the adjuvant setting of early breast cancer. No evidence of differences in efficacy by type of bisphosphonate either in the intent to treat analysis or based on age and menopausal status was detected between the three arms. At 5 years follow-up, the rate of ONJ was 1.2% in zoledronic acid arm administered monthly for six months then every 3 months for 2.5 years [16].

Table 1
The number and percentage of ONJ described in Z-FAST, ZO-FAST and E-ZO-FAST trials.

	Patients included in the study/follow-up duration	Patients receiving upfront Zoledronic acid	Number of ONJ	Percentage of ONJ in all included patients	Percentage of ONJ in patients receiving upfront Zoledronic acid	Annual risk of ONJ in patients receiving up front zoledronic acid
Z-FAST	602/60 months	301	0 ONJ confirmed, 2 ONJ possible	0–0.33%	0–0.66%	0–0.13%
ZO-FAST	1065/60 months	532	3 ONJ confirmed, 2 ONJ possible	0.28–0.48%	N/A	N/A
E-ZO-FAST	527/12 months	263	2 ONJ confirmed	0.38%	0.76%	0.76%
ABCSG-12	1803/84 months	–	0 ONJ confirmed	0%	–	N/A

Denosumab, a fully monoclonal antibody RANKL inhibitor, was also evaluated at 60 mg every six months instead of zoledronic acid in patients presenting aromatase inhibitor associated bone loss in early breast cancer. In ABCSG 18 trial comparing denosumab 60 mg every six months to placebo, 3425 patients were included; overall lower number of fractures was demonstrated in the denosumab arm versus the placebo arm. 35 dental problems were identified by proactive monitoring of ONJ during the trial, 31 suspected cases of ONJ were detected but no case was eventually judged to meet the diagnosis criteria of ONJ [17]. Denosumab seems to be safer concerning ONJ in the indication compared to zoledronic acid; a randomized trial comparing these two agents can only confirm this hypothesis.

5. Conclusions

Osteonecrosis of the jaw is a major complication of monthly bisphosphonate regimens that seems to be encountered also in biyearly administration. But its occurrence remains lower in the later setting. The literature review on zoledronic acid given every six months to prevent AIBL, showed a relatively low risk for ONJ not exceeding 0.7%. Despite this low prevalence, avoidance of dental manipulation and recommendations of oral hygiene must be universally respected, regardless of zoledronic acid schedule of administration.

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