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Advances in the prevention and management of bisphosphonate-related osteonecrosis of the jaw: A literature review

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SUMMARY

Background. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) emerges as a serious side effect of bisphosphonate treatment worldwide, significantly impairing patients‘ oral health and overall quality of life. Ongoing research shows emerging treatment modalities such as a combination of pentoxifylline and tocopherol, teriparatide, and platelet concentrates that enhances the prospects of BRONJ treatment. However, the need for more accurate and predictable treatment options still remains. The aim of this review is to summarize and ascertain the current prevention and treatment strategies of BRONJ.

Materials and methods. A narrative literature review was conducted using the PubMed, Wiley Online Library, ScienceDirect, and Springer databases using the Medical Subject Headings (MeSH) terms including “Osteonecrosis of the Jaw,” “Disphosphonates,” “Teriparatide,” “Platelet-Rich Plasma,” and “Pentoxifylline“. Inclusion criteria comprised clinical studies involving human subjects that evaluated prevention or treatment strategies for bisphosphonate-related osteonecrosis of the jaw. Randomized controlled trials, prospective and retrospective cohort studies, and clinical comparative studies published in English between 2015 and 2025. The literature search was conducted in January 2025.

Results. Emerging prevention and treatment strategies, including teriparatide and the combination of pentoxifylline and tocopherol, show potential in improving clinical outcomes and reducing disease progression.

Conclusions. Although emerging treatment methods show promising results, BRONJ continues to pose significant clinical challenges.

Keywords: Bisphosphonate-related osteonecrosis of the jaw; BRONJ; bisphosphonates; osteonecrosis; treatment; prevention.

INTRODUCTION

Bisphosphonates (BPs) are antiresorptive drugs that directly inhibit osteoclast activity and thereby suppress bone resorption (1). Bisphosphonates are widely used to treat and prevent osteoporosis, Paget‘s disease of bones (osteitis deformans), bone cancer metastasis, metastatic lung cancer, metastatic breast cancer, metastatic prostate cancer, multiple myeloma and malignant hypercalcemia (2). One of the most serious adverse effects of BPs is bisphosphonate-related osteonecrosis of the jaw (BRONJ) (3). BRONJ is defined as a diffuse bone disease characterized by the presence of bone exposed to the oral cavity that does not heal within 8 weeks of observation and conventional treatment, in patients under or who have taken BP therapy, with no history of radiation therapy in the head and neck region (4).

Although the broader term medication-related osteonecrosis of the jaw (MRONJ) is currently used, this review focuses specifically on cases associated with bisphosphonate therapy.

Management of BRONJ remains a controversial topic in the oral surgery field, as the current consensus on treating BRONJ patients is based on the conservative approach, mainly focusing on symptomatic treatment. To understand it better, the staging

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and treatment of BRONJ are brought out in (Table 1), provided in the systematic review by Gelazius *et al.* (5). The most important predisposing factor for BRONJ is the type and total dosage of BP or other medications. Overall, the risk for BRONJ increases by high dosage, therapy duration more than 3 years, and intravascular administration instead of oral intake (6, 7). Risk factors enhancing BRONJ are periodontal surgery, implant placement, tooth extractions, poor condition of dental prosthesis or chronic mechanical trauma of the jaw bone. Moreover, systemic diseases, consumption of other medications, smoking and alcohol consumption have had a great influence on BP-related osteonecrosis (8).

The treatment strategies of BRONJ may vary and may be chosen individually, treatment may include a combination of pentoxifylline and tocopherol (10). Conservative treatment approaches with antibiotics therapy and other additional methods like 0.12% chlorhexidine mouthwash rinse (15). For more advanced stages of BRONJ, surgical treatment like surgical debridement, sequestration, antrostomy, tooth extractions might be indicated (2). The usage of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) has also been shown to reduce the time of healing of soft and hard tissues after surgical treatment (30-32). Osteoanabolic medication like teriparatide (TPTD) has also been reported as a successful method for BRONJ treatment (35-38). Before starting surgical treatment, drug holiday was thought to be beneficial for some of the patients. During the drug holiday, patient discontinues using bisphosphonates for a prescribed time to minimize the risk of developing BRONJ after surgical treatment (41). However, Aboalela *et al.* (2022) (41) published a meta-analysis and concluded that a drug holiday does not make a significant difference in the development of BRONJ in patients after tooth extraction procedures. The most important aims in BRONJ patients are to minimize progression of the lesion, to promote tissue healing and to control infection (9). In this article, we aim to discuss the latest treatment and prevention strategies for patients suffering from BRONJ.

MATERIALS AND METHODS

A narrative literature review was conducted to identify relevant studies addressing the prevention and management of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Electronic searches were performed using the PubMed, Wiley Online Library, ScienceDirect, and Springer databases.

Medical Subject Headings (MeSH) terms and related keywords were used in various combinations, including “Osteonecrosis of the Jaw,” “Diphosphonates,” “Bisphosphonates,” “Teriparatide,” “Platelet-Rich Plasma,” “Platelet-Rich Fibrin,” and “Pentoxifylline.” Boolean operators (AND, OR) were applied to refine the search strategy.

Inclusion criteria comprised original clinical studies involving human subjects that evaluated prevention or treatment strategies for BRONJ. Randomized controlled trials, prospective and retrospective cohort studies, and clinical comparative studies published in English between 2015 and 2025 were included. Case reports, animal studies, systematic reviews, meta-analyses, and articles not available in full text were excluded.

Titles and abstracts were screened for relevance. Full-text articles meeting the eligibility criteria were reviewed, and relevant data regarding study design, patient characteristics, treatment modalities, and clinical outcomes were extracted and analyzed narratively.

TREATMENT OPTIONS

There is currently no 'gold standard' of treatment for BRONJ. Interventions used to treat this complication are diverse, controversial and largely

Table 1. The focus question development according to the PICOS study design

Risk category	No clinical radiological evidence of exposed bone or infection inflammation.
Treatment plan	No surgical treatment is needed. Patient has to be informed about following risks. Good oral hygiene with re-examinations at least once every 6 months should be done.
Stage I	Clinical evidence of exposed bone for more than 8 weeks. This stage is usually asymptomatic. No signs infection is normally seen.
Treatment plan	No surgical treatment is needed. Antibacterial mouth rinses, professional oral hygiene with no injury of exposed bone can be considered, common follow-ups for exposed bone re-evaluation. Antibiotic treatment cai be prescribed if patients condtionis difficult.
Stage II	Exposed necrotic bone with signs of infection, drainage of inflammatory matter can appear.
Treatment plan	Management of pain, broad-spectrum antibiotics, antibacterial mouthrinses, debridement of necrotic bone surface area, common follow-ups with professional oral hygiene and re-evaluation of necrotic bone. Drug holidays maybe considered as an option.
Stage III	Exposed necrotic bone with sings of infection. Extraoral fistula, pathological fra cures can appear.

empirical. Three broad categories of interventions have been described: classical 'wound-healing' conservative treatment, diverse surgical techniques and different "add-on" treatments. These three approaches are often used in combination, either at the same time or in succession (2, 6).

Conservative approaches are recommended for early-stage BRONJ (stage 1). This includes patients who are asymptomatic and show no signs of infection (2). Marx *et al.* recommend that treatment should eliminate and control pain, as well as preventing progression of bone exposure through antibiotics therapy and mouthwash with 0.12% chlorhexidine (15). When treating BRONJ patients, it is crucial to consider the duration of antibiotic therapy, which can range from several months to more than a year. If lesions do not respond to oral treatment, intravenous antibiotics are a viable option (2, 16). It is worth noting that most microorganisms isolated from BRONJ lesions are sensitive to penicillin, making oral amoxicillin (1.5–3 g daily) and amoxicillin with a beta-lactamase inhibitor such as clavulanic acid common treatment options (17). For patients allergic to penicillin, or in cases of antibiotic resistance, alternatives such as fluoroquinolones, metronidazole, clindamycin, doxycycline, and erythromycin can be used (16).

Previously, surgical treatment was reserved for the more advanced stages, but recent data supports that it is also adequate as early intervention (18). The surgical method implies: surgical debridement, sequestration, antrostomy (surgical removal of pathological content from sinuses), extraction of the tooth with the bone affected by osteonecrosis, bone resection, reconstructive surgery. The therapy protocol of bisphosphonate-induced osteonecrosis of the jaws (BION) is recommended by The American Association of Oral and Maxillofacial Surgeons (AAOMS) (2). With surgery, a full-thickness mucoperiosteal flap should be elevated and extended to reveal the entire area of exposed bone and beyond to disease-free margins. Resection of the affected bone should be extended horizontally and inferiorly to reach healthy-appearing, bleeding bone. Sharp edges should be smoothed and primary soft tissue closure achieved in a tension-free fashion with sutures that resorb after 1 week (19). Several authors have reported better outcomes with larger resections compared to limited debridement and/or conservative therapy (20, 21).

PENTOXIFYLLINE AND TOCOPHEROL

There are some reports that the combination of pentoxifylline (PTX) and tocopherol is effective against bisphosphonate-related osteonecrosis of the jaw (BRONJ) (11, 12). Pentoxifylline is a methylxanthine derivative that improves blood flow and reduces inflammation by increasing red blood cell deformability, reducing blood viscosity, and promoting capillary dilation. Tocopherol, also known as vitamin E, is an antioxidant that protects cell membranes and reduces tissue fibrosis. The immunomodulatory effects of pentoxifylline help to reduce inflammation, while tocopherol's antioxidant properties protect tissues from further damage. In combination, these compounds facilitate bone healing and reduce inflammation in conditions such as chronic osteomyelitis, BRONJ and osteoradionecrosis (ORN).

In the study by Seo *et al.* (11), nine patients were diagnosed with BRONJ who were prescribed PTX and tocopherol for treatment. All patients received a combination of 800 mg of PTX and 800 IU of vitamin E every day. Bony healing was evaluated by two methods: the first method involved measurement of radiographic densities of region of interest (ROI), while the second method calculated the ratio of the densities of ROI to the opposite side. Three and six months after administration, the differences of radiographic densities compared to the contralateral sites exhibited statistically significant reductions ($p < 0.05$). Not only did the degree of densities of the panorama increase, but intraoral bone exposures and inflammation clinically decreased.

Likewise, in a study by Epstein *et al.* (12), six patients referred for management of BRONJ were provided pentoxifylline and α-tocopherol in addition to antimicrobial therapy, and followed for a mean of 10 months. A 74% decrease in area of bony exposure and symptom control was achieved in these cases. PTX has been shown to enhance microvascular blood flow and reduce platelet aggregation to maintain perfusion in radiated tissue. PTX also down-regulates the production of proinflammatory cytokines, particularly TNF-α, in response to noxious stimuli and inhibits granulocyte-mediated cytotoxicity after TNF-α exposure and provides protection against radiation-induced, cytokine mediated cellular damage (13). PTX and tocopherol can be used as an auxiliary to surgery for the treatment of osteoradionecrosis (ORN), BRONJ, and chronic osteomyelitis. Unfortunately, there is no guideline for how long PTX and tocopherol should be taken (14).

PLATELET CONCENTRATES

Another treatment option for BRONJ is platelet concentrates, mostly known by platelet-rich plasma

(PRP) and platelet-rich fibrin (PRF). They are autologous biological blood-derived products, which have high concentrations of protein growth factors (27). These autologous products are reported to decrease the time of the healing period of soft tissues and bone (30-32).

A study carried out by Iram *et al.* (30), aimed to treat BRONJ with PRF as an adjunct to surgical debridement. A total of 37 patients were selected and the inclusion criteria that were followed in the study include diagnosis of BRONJ and need for surgical intervention; patients able to undergo surgical treatment (ASA-1 or ASA-2); patients able to sign an informed consent form. Before the surgical intervention, all patients stopped using anti-resorptive medication three months before surgery. After surgical intervention was done, patients had a follow up until the closure of the soft tissue and until any of the symptoms disappeared, after that the control appointments were scheduled. The study showed that after the treatments with PRF a total of 28 patients showed complete resolution, 7 had delayed resolution and 2 did not resolve. With p value being 0.002, the study showed significant association between response to treatment and the stage of BRONJ.

Another study by Bocanegra-Perez *et al.* (31), also analyzed the effectiveness of leucocyte and platelet-rich plasma (L-PRP) effectiveness. A total of 8 patients were selected, while inclusion criteria being diagnosis of BRONJ. Patients received surgical intervention which consisted of: removal of necrotic bone and curettage of the underlying bone; autologous L-PRP application. After the L-PRP was placed, patients were prescribed amoxicillin-clavulanic acid (875mg every 8 hours for 7-10 days), a mouthwash with chlorhexidine 0.12% and a follow-up visit after 2 weeks for suture removal. Additional visits for the follow-up period were scheduled 4, 6, 10, 14 weeks after surgery. A mean period of patients oral wound improvement was 3 weeks after treatment described as fast soft tissue healing, reduced need for analgesics and resolution of mouth lesions. There was no evidence of exposed bone after the 14 month follow-up time in all patients.

A study by Mauceri *et al.* (32), aimed to evaluate the outcome of PRP use in post-extraction sockets in BRONJ patients. Twenty patients were selected for the study, with entry criteria being: patients aged over 18 years, history of BPs treatment, tooth extraction required because of the infection and inflammation, follow-up period of at least 24 months after the extraction. Surgical protocol remained the same for all the patients and PRP was applied in post-extraction sockets for each patient. Treatment was considered successful if there were absence of any clinical or radiological signs of ONJ in the surgical area after 12 months period. A total of 63 teeth were extracted. Out of them, 24 extraction sockets had a complete oral mucosa healing at the suture removal visit, rest of them (39 extraction sockets) had a presence of granulation tissue. During first follow-up visit at 1 month, a stable and healed mucosa was recorded in all of the sockets. The study was held successful, as after 12 months, all of the patients showed no clinical or radiological sign of BRONJ.

The pooled analysis of the three included studies demonstrated favorable clinical outcomes following surgical management of BRONJ with adjunctive platelet concentrates. The majority of patients achieved complete resolution, while only a small proportion showed delayed or no resolution (Table 2).

TERIPARATIDE

Teriparatide has shown promising outcomes in selected clinical studies involving BRONJ patients. It is an osteoanabolic medication, mainly prescribed for the treatment of male, postmenopausal and glucocorticoid-induced osteoporosis. It is made out of 34 amino acids of the human parathyroid hormone (33). It stimulates osteoblasts to develop new bone structure and osteoclasts for bone resorption, in general regulates bone remodeling (34). Harper *et al.* (35) presented the first successful case of BRONJ treatment using TPTD back in 2007. A variety of new studies containing TPTD for the treatment of BRONJ have been released since then and showed its positive outcomes.

In a study by Yoshiga *et al.* (36), 27 BRONJ diagnosed patients were selected to study the complications and patients' response to TPTD treatment. Out of 27 patients, 9 patients made a non TPTD therapy group, rest of the patients were divided equally into weekly or daily TPTD treatments groups. Both groups continued their conservative treatment for BRONJ with the addition of daily or weekly subcutaneous TPTD injection (20 μg or

Table 2. Clinical outcomes of BRONJ patients treated with platelet concentrates

Patients diagnosed with BRONJ treated with platelet concentrates	Full resolution	Delayed resolution	No resolution
65	56 (86.2%)	7 (10.8%)	2 (3%)

56.5 μg, respectively). Three patients out of daily group dropped out because of the adverse effects and did not complete the study. Daily injection group was self-administered with the injections meanwhile weekly injections were administered at the hospital. The conservative treatment consisted of anti-inflammatory treatment, pain medication and penicillin-based antibiotics. Both, daily and weekly injections were administered until the full bone healing and additionally, sequestrectomy was performed in all patients for the separated sequestrum. Patients were clinically followed for two years. Healing period was different in TPTD-treated groups – it was significantly shorter than in a group treated only with conservative treatment. Both TPTD groups reached success rate of 100%, meanwhile the non-TPTD group only 67%, TPTD injections daily or weekly did not have significant difference in healing period. Out of non-TPTD group, two patients died due to non-related reasons and one was still left with the asymptomatic exposed bone area.

Another study by Ohbayashi *et al.* (37), examined the effectiveness and difference outcomes of daily and weekly TPTD treatments. A total of 13 patients were selected. They were randomly assigned to weekly or daily groups. Both groups continued TPTD treatment for 6 months, except that the weekly group received 56.5-μg TPTD injections once a week and daily group 20-μg injections. Besides TPTD injections, patients received conventional BRONJ treatment based on their stage with additional intensive antibiotic therapy if needed. After 6 months of TPTD treatment, additional CT, blood examination and bone scintigraphy procedures were done and measured at 3 and 6 months after the start of the treatment. Partial remission or complete remission was reached in 5 daily-group patients and 3 patients of the weekly group. The change of the BRONJ stage after the treatment was held as a positive index and signified clinical efficacy, meaning all 12 patients attained success.

Study carried out by Morishita *et al.* (38), aimed to prove safety and effectiveness of TPTD use in treatment of BRONJ. A total of 29 patients were selected with diagnosis of BRONJ with inclusion criteria being physical possibility to undergo TPTD therapy. One patient discontinued TPTD therapy because of the adverse effect and did not result in the study. In total, adverse effects occurred in 17.2% of patients (5 out of 29). 24 patients were receiving oral BPs, rest of them (5) had intravenous administration of BPs. TPTD was administered with daily subcutaneous injection of 20 μg. Treatment outcomes were defined as: complete resolution (all symptoms disappeared for at least 3 months); improvement (reclassification to a lower stage of BRONJ for at least 3 months); stable disease (no change during treatment), exacerbation (reclassification to a higher stage of BRONJ). Successful treatment outcomes were recognized in 22 patients (75.9%). Stable disease was observed in 6 patients, exacerbation in 1 patient. A total of 20 out of 24 patients treated with oral BPs achieved success, meanwhile patients treated with the intravenous administration of BPs reached 40% success rate. The use of BPs in oral form was linked to more favorable treatment outcomes with teriparatide (p=0.062).

PREVENTION AND BIOMARKERS

While the exact treatment strategies are still being evaluated by the scientists, prevention from BRONJ is vital (22). Bisphosphonates have been used for more than three decades; however, recognition of jaw osteonecrosis as a serious complication has emerged only in recent years. Now, there is growing evidence that bisphosphonates influence and cause osteonecrosis of the jaws (43). To begin with, educating patients receiving bisphosphonate therapy about the risk of BRONJ is necessary. After that, patients should be motivated to improve their overall health alongside oral hygiene in minimizing the risk of BRONJ development. All of the surgical procedures covering oral region such as tooth extractions, grafting, periodontal or apical surgeries should be done before the start of BPs therapy (15). If the therapy is already started, endodontic treatment is preferred and recommended over extractions or other invasive oral surgery procedures. In case endodontic treatment is helpless and tooth extraction is indicated, patient should be informed about the potential risk of BRONJ development and pre and post-operative care (23). In a study by Lodi *et al.* (24), there were 23 patients treated with intravenous bisphosphonates (mainly zoledronate) who received tooth extractions. The extraction protocol included mouth rinsing with 0.2% chlorhexidine, antibiotic therapy, extraction and curettage of the extraction socket, application of 1% chlorhexidine gel. In total, there were 38 extractions, the mean follow-up was 229.5 days and no case of BRONJ was recorded. This implies that, with the correct preventive protocol for the prevention of local and systemic infectious complications, tooth extractions can be carried out with no complications.

Biomarkers also play a significant role in the prevention of BRONJ. Serum C-terminal telopeptide of type-1 collagen (CTX) is a biochemical marker of

bone metabolism that is used to evaluate osteoclast activity and to assess the level of bone resorption (26). Patients receiving oral bisphosphonate for more than 3 years or fewer than 3 years but without the existence of chemotherapy or corticosteroid use, having CTX values greater than 150pg/mL have minimal risk of developing BRONJ after surgical procedures. If the CTX value is lower than 100 pg/mL, patients are considered to be in a high risk group of developing BRONJ. To minimize the risk, patients with CTX values lower than 100 pg/mL are recommended to consider a drug holiday to allow increase of CTX value (26).

DISCUSSION

This literature review was performed to summarise data about the prevention and treatment options for patients suffering from BRONJ.

Treatment strategies depend on the stage of the disease (Table 1). 0.12% chlorhexidine mouth rinsing and antibiotic therapy are recommended as a conservative approach for early stage of BRONJ (15). Stage 2 treatment options include previously mentioned conservative treatment but also involves debridement of necrotic bone (2). More invasive and aggressive surgical modalities are required for further stages of BRONJ when complications involve exposed or necrotic bone. Treatment options for stage 3 BRONJ might be extensive debridement, resection, sequestrectomy, reconstructive surgery (2).

Recent studies suggest new and advanced treatment strategies for patients suffering from BRONJ. These approaches include both surgical and non-surgical modalities (43). Parathyroid hormone, also called teriparatide, showed promising results healing and promoting new bone (33, 35-38). Also, the combination of pentoxifylline and tocopherol shows promising result in patients with BRONJ, yet, the duration of the this treatment is still unknown (11, 12). Combined, they can promote bone healing and reduce inflammation (11). As an adjunct to a surgical treatment, platelet concentrates such as PRP and PRF has also been used. They showed positive results in decreasing the healing time of soft tissues and bone (30-32). Biomarkers such as CTX can also play a significant role in prevention of BRONJ and be very important before the start of surgical treatment (26).

Prevention of BRONJ is as vital as treatment. All patients that are using or are starting bisphosphonate therapy should be educated about oral health requirements, focus on good oral hygiene and perform any oral surgical procedure that is necessary before the start of BPs therapy in order to minimize the risk of BRONJ (15).

CONCLUSION

Effective patient education, early risk assessment, and emerging adjunctive therapies may improve clinical outcomes in BRONJ patients; however, high-quality controlled clinical studies are still required to establish standardized treatment protocols.

STATEMENT OF CONFLICTS OF INTEREST

The authors state there is no conflict of interest.

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