

## Bisphosphonates and Ocular Inflammation

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Osteoporosis, as a musculoskeletal disease, is assigned by low bone mass and degradation of bone microarchitecture, culminating in an escalation in bone weakness and propensity to fracture [1,2]. When the cumulative effect of bone resorption is in excess of bone formation, osteoporosis is induced [1]. Osteoporotic fractures are linked to substantial morbidity, mortality, and high healthcare expenses [1].

Although men tend to show worse results after fractures, the prevalence of osteoporosis and the risk of osteoporosis-induced fracture are higher in women [3,4].

Bisphosphonates, which are applied orally or intravenously, are largely prescribed in the management of osteoporosis and highly effective at limiting the bone loss that occurs in many disorders known by increased osteoclast-mediated bone resorption [1,5]. Bisphosphonates inhibit bone resorption and are widely used to prevent osteoporotic fractures with relatively few side effects [6,7]. However, bisphosphonates have been found to be linked to some rare and severe adverse effects, such as atypical femur fractures, other atypical fractures, osteonecrosis of the jaw (ONJ), an increased risk of aseptic osteonecrosis (AON), atrial fibrillation, esophageal and colon cancer, bone and muscle pain, irregular heartbeat, gastrointestinal intolerance, upper gastrointestinal (GI) adverse effects, acute phase reaction, hypocalcemia, impaired fracture healing, renal complications, electrolyte imbalance, and ocular inflammation [1,2,5-17].

Although the mechanism of adverse ocular reaction is not clear yet [12,13], it has been proposed that bisphosphonates are secreted into the tears by the lacrimal gland and consequently could provoke transitory irritation to the mucous membranes with consequent release of inflammatory mediators [12,18,19]. In addition to the release of cytokines, this irritation may irritate the release of other acute phase proteins in the eye, or induce activation of gamma delta T cells within the orbit [12,14,20,21]. In this context, the resultant rise in the concentration of inflammatory mediators, especially among new users of bisphosphonates, may put them at a higher risk of scleritis or uveitis [8].

Bisphosphonate use has been documented to cause adverse ocular effects, such as uveitis, scleritis, episcleritis, nonspecific conjunctivitis, blepharitis, synechiae, subconjunctival hemorrhage, ocular hypertension, ischemic optic neuropathy, and optic neuritis [6-10,12-14,16,17]. Bisphosphonates can also precipitate orbital inflammation [6,7,9,11,16,17].

However, population-based cohort studies [8,10,22] concluded that the "underlying inflammatory disease" was the most likely determinant of the inflammatory eye reactions in patients taking bisphosphonates [12]. This was concluded due to their findings that the risk of inflammatory eye reactions was found to be at maximum among patients with underlying inflammatory diseases [12].

In most cases, symptoms started within days of initiating bisphosphonate administration and resolved upon stopping the

drug [8]. The technique of bisphosphonate administration affects the timing of the adverse ocular effects so that they usually occur within 48 to 72 hours after intravenous (IV) bisphosphonate administration and 2 to 3 months after oral bisphosphonate administration [17,23]. Others reported that the onset can be from a few hours after exposure up to more than 3 years, with an estimated median of 3 weeks [10,12,24].

In conclusion, although ocular side effects of bisphosphonate therapy are fairly rare, orbital and ocular inflammation are its possible vision-threatening side effects. The important message is to inform clinicians prescribing bisphosphonates and people using them about the risk of ocular inflammation in order to be familiar with the signs and symptoms of these conditions so that they can instantly look for proper treatment.

### Conflict of Interest

The author declares no conflict of interest.

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