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Mini Review

Complications of Bisphosphonate Therapy in Multiple Myeloma: A Review

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Abstract

Background: Patients affected by Multiple Myeloma (MM), osteoporosis and oncologic diseases characterized by bone damage are successfully treated with Bisphosphonates (BPs), a very powerful inhibitors of bone resorption able to correct tumoral hypercalcaemia and to prevent pathological fractures. Among the adverse effects of the pharmacologic treatment, Osteonecrosis of the Jaw (ONJ) is known as the most typical and the worst. Recently, ocular involvement associated with BPs therapy has been suggested: uveitis and scleritis are the most commonly reported events.

Methods: We reviewed scientific literature to determine possible adverse ocular side effects associated with the use of BPs. Clinical studies were collected by using key-words (BPs, zoledronic acid, ocular effects, uveitis, eye and BPs). The World Health Organization's Causality Assessment Guide was used to categorize an adverse ocular drug reaction.

Conclusion: Although the present review was inconclusive in determining the real incidence of the ocular related events, patients that need a treatment with BPs, should be informed on the possibility to develop ocular side effects, which are probably sustained by an inflammatory mechanism which involves IL-6, TNFα, and other similar cytokines. Uveitis and scleritis are the most frequent, but they can be successfully managed with corticosteroid treatment.

Keywords: Bisphosphonates; Zoledronic acid; Ocular effects; Uveitis; Eye and bisphosphonates

Abbreviations

MM: Multiple Myeloma; BPs: Bisphosphonates; ONJ: Osteonecrosis of the Jaw; SRE: Skeletal-Related Events; PPi: Inorganic Pyrophosphate; RANKL: Receptor Activator of Nf-κb Ligand; OPG: Osteoprotegerin; ETI: Etidronate; CLO: Clodronate; PAM: Pamidronate; ZOL: Zoledronate

Introduction

Bisphosphonates represent an effective class of drugs used for patients affected by osteoporosis, hypercalcaemia, oncologic diseases with bone involvement (breast, lung, prostate cancer and Multiple Myeloma), and Paget disease. They can be also used to manage other conditions, such as osteogenesis imperfecta and fibrous dysplasia, resulting in the reduction of bone damage.

In particular, nearly 50% of the patients affected by Multiple Myeloma (MM) may develop complications known as Skeletal-Related Events (SRE) (i.e. bone pain, hypercalcemia, pathological and fragility fractures, spinal cord compression, radiotherapy requirement and surgery for pathological fracture) [1,2].

For these patients the use of bisphosphonates has become the standard of care, and represents an important strategy to reduce about 30-40% of SRE [2-5].

BPs decrease resorptive effects of the metastatic disease process and correct tumoral hypercalcemia; they prevent the occurrence of pathological fractures and, as a consequence, they increase quality of life. The use of BPs reduces bone pain, analgesic consumption and delays skeletal complications. MM patients treated with chemotherapy associated with BP therapy have better clinical outcomes, compared to patients treated with chemotherapy alone [6].

Bisphosphonates activity

Bisphosphonates are potent inhibitors of bone resorption and are widely used in the treatment of many diseases that cause bone mass loss.

BPs are synthetic, stable analogues of Inorganic Pyrophosphate (PPi) and bind quickly and specifically to hydroxyapatite, especially in regions where resorption is occurring. When osteoclasts break down bone, BPs accumulate in the resorption space under these cells, exposing them to high BP concentrations [7].

BPs can down-regulate "Receptor Activator of NF-κB Ligand" (RANKL) and M-CSF expression: this is one mechanism by which BPs—indirectly—affect resorption by the inhibition of osteoclast recruitment, differentiation and maturation.

They also up-regulate Osteoprotegerin (OPG) in osteoblasts; as a consequence they might therefore inhibit osteoclastogenesis preventing the development of monocytes into osteoclasts, inducing osteoclasts apoptosis, interrupting their attachment to the bone and resorptive activity [8-10].

There are two main types of BPs: nitrogen containing BPs and non-nitrogen containing BPs. The first generation of BPs are

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Table 1: Nitrogen-containing bisphosphonates.

Patient	Primary diagnosis	BP used	Ocular effects	Type of study	Description	Authors
60-year-old woman	Breast cancer	Zoledronate, 4mg/6 months	Unilateral anterior uveitis	Case Report	Patient with intraocular lens	[1]
57-year-old woman	Osteoporosis	Alendronate	Bilateral anterior uveitis	Case Report		[2]
86-year-old woman	Osteoporosis	Alendronate for 6 months, followed by Risedronate for 2 months	Bilateral anterior uveitis	Case Report	Patient with intraocular lens	[2]
65-year-old woman	Osteoporosis	Alendronate, 70mg orally once at week	Chronic conjunctivitis	Case Report	After 20 months patient changes Alendronate with Risedronate and Etidronate with recurrence of symptoms	[3]
62-year-old woman	MGUS	Zoledronate, 4 mg ev	Bilateral acute uveitis and bilateral conjunctivitis	Case Report		Tyy Lai et al.
934˙147 patients	Patients visited by ophtalmologist, which are asked about BP use	Alendronate and Risedronate	Scleritis and uveitis	Cohort Study	10˙827 patients using BP orally for the first time have an higher risk of ocular effects; 923˙320 patients don't use BP	Mahyar et al.
13˙643 patients	Osteoporosis and Paget's disease	Risedronate	Dry eye, conjunctivitis, 2 cases of iritis and 2 cases of episcleritis, 1 case of keratitis	Cohort Study		[4]
57-year-old man	Spontaneous osteonecrosis of the knee	Zoledronateev	Right orbital pain, edema e proptosis, conjunctival chemosis	Case Report	Resolution with corticosteroids	B Barlogie et al.
78-year-old man	Prostate cancer with lumbar pain because of bone metastasis	Zoledronate, 4 mg ev	Anterior unilateral uveitis	Case Report		[5]
57-year-old woman	Osteoporosis	Alendronate, 70 mg/ week	Left keratouveitis followed by anterior bilateral uveitis	Case Report	Resolution with steroids; maybe the ocular effects are the result of cumulative effect of the drug within the bone	[3]
54-year-old woman	Bone metastasis of breast cancer	Zoledronate	Unilateral anterior acute and anterior scleritis	Case Report		[6]
65-year old male	Multiple myeloma	Zoledronate 4mg ev, followed by Pamidronate	Posterior scleritis (following Zoledronate) and conjunctivitis (following Pamidronate)	Case Report	Resolution with homatropine drops and 2-hourly prednisolone acetate/ phenylephrine hydrochloride drops	[7]
58-year-old woman	Osteoporosis	Zoledronate 5mg ev	Acute anterior uveitis	Case Report	Resolution of symptoms within 4 weeks with prednisolone acetate 1% and dexamethasone	[8]
73-year-old woman	Osteoporosis	Risedronate, 35 mg orally/ week (2007) Risedronate, 150mg orally/ month(2009)	Scleritis	Case Report	First exposure to Risedronate in 2007, with recurrence of scleritisupon Risedronate exposure again in 2009 Improvement of symptoms with methylprednisolone 125 mg intravenously (IV) four times daily	IHemmati et al.
48-year-old woman	Breast cancer with bone metastasis	Zoledronate, 4mg ev	Unilateral anterior uveitis	Case Report	Resolution of symptoms within one week with topical prednisolone acetate (1%)	[9]
47-year-old male	?	Zoledronate ev	Acute retinal pigment epitheliitis	Case Report		[10]
woman	Frontal hyperostosis secondary to breast cancer	Zoledronate ev	Unilateral anterior uveitis	Case Report	Complete resolution of symptoms after one month with topical prednisone and cycloplegic eye drops	[11]
67-year-old woman	Osteoporosis	Alendronate, 70 mg orally once/week	Panuveitisin right eye and anterior uveitis in the left	Case Report	Resolution with steroids and recurrence of symptoms with new administration of Alendronate	Sanchez et al.
86-year-old woman	Osteoporosis	Alendronate	Scleritis in right eye	Case Report	Resolution with Prednisone	[12]
54-year-old male	?	Alendronate sodium 70 mg orally once per week	Inferonasal nodular scleritis	Case Report	Resolution with 4 mg of subtenon's triamcinolone acetate; recurrence of symptoms after rechallenge	[13]
57-year-old woman	History of esophageal, breast, and lung cancers, and postmenopausal osteoporosis	Intravenous Ibandronate for 6 infusions, later changed to Zoledronate infusion	Orbital inflammatory disease: painfully swollen left eye with photophobia and edema of the left upper lid	Case Report	Swelling and erythema disappeared completely in 2 weeks after she started on 2 methylprednisolone dose packs	[14]
2 Men	Paget's disease	Pamidronate 65 mg in three divided infusions on alternate days	Uveitis	Case Report	Next day after infusion worsened; improved on oral steroids	[15]

55- year-old man	Metastatic renal cell cancer	Zol 4 mg iv Monthly	Orbital inflammatory disease	Case Report	One day 60mg prednisone, tapered during 10 weeks of treatment; no relapse (on steroids)	[16]
62-year-old woman	MGUS with back and leg pain	Zol 4 mg iv	Bilateral acute uveitis and conjunctivitis	Case report	Improved on oral steroids	[17]
Woman	Osteoporosis	Alendronate	Uveitis →corneal graft rejection	Case Report		[18]
64-year-old man and 65-year-old man	Metastatic prostate cancer	Pamidronate ev	Orbital inflammation	Case Report	Improved on oral steroids	[19]
71-year-old man	Paget's disease	Pamidronate 90 mg ev	Right-sided proptosis, conjunctival chemosis and diplopia	Case Report	Next day ''flu like symptoms'' Fifth day: orbital inflammation improved with systemic steroids	[20]
57, 71 and 77-year-old women	Osteoporosis	Alendronate	Posterior scleritis and anterior nodular scleritis with possible contiguous orbital inflammation and myositis	Case Report	Resolution e with steroids	Mbekani et al.
Woman	Osteoporosis	Alendronate	Uveitis	Case Report	Oral steroids	[21]
Man	Paget's disease	Pamidronate	Uveitis	Case Report	1 week topical steroids	[21]
18 patients	?	Pamidronate 30-90 mg ev; rechallenge in 6 cases	heterogeneous ocular effects	Cohort Study	6 hours to 2 days relapse	[22]
Woman	Osteoporosis(?)	Alendronate 10 mg/ die for 1 year, then switched to Alendronate 70 mg weekly	Bilateral acute anterior uveitis	Case Report	Use of local steroids	[23]
60-year-old woman	Osteoporosis	Zoledronate, 5 mg (single dose)	Orbital inflammatory disease	Case Report	Resolution with oral prednisone	[24]
Woman	?	Zoledronate, 4 mg ev	Orbital inflammatory disease	Case Report	Systemic steroids	[25]
77-year-old man	Multiple myeloma	Pamidronateev	Diplopia and chemosis	Case Report	Symptoms 2 days after infusion	[26]
68-year-old male	Metastatic prostate cancer	Zoledronate	Orbital inflammation and anterior ischemic optic neuropathy	Case Report	Resolution with oral prednisone, 100 mg daily, and ibuprofen, 400 mg daily	[27]
75-year-old woman	Osteoporosis	Zoledronate	Unilateral orbital inflammation and bilateral anterior uveitis	Case Report	Intravenous methylprednisolone leads to a complete regression of the inflammatory process within days	[28]
Woman	Osteoporosis	Alendronate	Acute non granulomatous anterior uveitis	Case Report	The symptoms disappeared abruptly after anti-inflammatory therapy and discontinuation of alendronate	[29]
59-year-old man	Metastatic prostate cancer	Pamidronate	Acute retinal pigment epithelial detachment	Case Report		[30]
Post marketing surveillance study conducted on a large cohort of veterans		Oral Alendronate(70 or 35 mg or 70 ml solution) and parenteral Pamidronate (30mg)	Uveitis, scleritis, iridocyclitis, iritis	Cohort study	Most patients had reumathological pathologies (ankylosing spondylitis, rheumatoid arthritis, polychondritis, ecc.); the interval between exposure and symptoms tends to be less with intravenous administrations; inability to confirm whether ocular inflammation improved once bisphosphonate drugs were stopped or whether any rechallenge tests were performed.	[31]
84-year-old woman	Osteoporosis	Zoledronate ev	Giant cell arteritis, complete vision loss of left eye, pain and swelling in left eye, left sided jaw pain and temporal headache	Case Report	Symptoms resolution with methylprednisolone	Metyas et al.
63 year-old man	Multiple myeloma	Zoledronate ev???	Cicatricial ectropion of the lower eyelid, without exposure keratopathy; extensive destruction of bone with an infraorbital fracture surrounded by sclerotic bony changes	Case Report	Resolution with discontinuation of bisphosphonate therapy and topical ocular lubricants	[23]

Table 2: Non nitrogen-containing bisphosphonates.

Patient	Primary diagnosis	BP used	Ocular effects	Type of study	Description	Authors
438 cases of ocular effects reported in the National Registry of drug-induced ocular side effects	Multiple myeloma, bone metastasis of breast cancer, Paget's disease, osteoporosis	Pamidronate, Alendronate and Risedronate (nitroge-containing bisphosphonates), Etidronateand Clodronate (non nitrogen-containing bisphosphonates)	Conjunctivitis, uveitis and episcleritis	Review		[22]
Woman	Paget's disease (pelvis and sacrum)	Started on etidronate 400 mg/d x 6 months (no reaction), Risedronate 30 mg/d x 84 days; Pamidronate 60 mg	Iritis	Case Report	3 days after starting Risedronate responded to steroid e<24 hours after Pamidronate infusion responded to steroid eye drops	[32]
68-year-old woman	Osteoporosis	CLO 100 mg/week im	Bilateral anterior acute uveitis	Case Report	5 months recover on topical steroids	Fiettaet al.
28 patients	?	BPs	Eterogeneous ocular effects	Cohort study	Onset and response to treatment:2 days to more than 3 years	[33]
		Pamidronate, Alendronate,Zoledronate and Risedronate (nitroge-containing bisphosphonates),Etidronate (non nitrogen-containing bisphosphonates)	Bilateral uveitis and/or unilateral scleritis and episcleritis	Review		[34]
Literature up to mid-2014	Osteoporosis	Nitrogen and non nitrogen-containing BPs, selective estrogen receptor modulators, strontium, denosumab, teriparatide	Conjunctivitis, uveitis, scleritis, episcleritis, keratitis	Review (case reports, case series, cohort studies)	The drug is secreted into the tears by the lacrimal gland and could cause irritation to the mucous membranes with subsequent release of inflammatory mediators, similar to the systemic response typically seen after infusion of bisphosphonates	Clark E. et Durup D.

non-nitrogen-containing compounds such as Etidronate (ETI) and Clodronate (CLO), which are metabolized to cytotoxic ATP analogues, which induce osteoclast cell death [11].

Among intravenous N-BPs, the most commonly used in MM are zoledronic acid and pamidronate [12].

With regards to potency, Pamidronate (PAM) is less effective than Alendronate which is less effective than Risedronate. Risedronate is less effective than Zoledronate (ZOL). Pamidronate appears to be much less effective than other BPS while Zoledronate is the most effective drug. Nevertheless PAM and ZOL have been approved for use in MM patients in Europe [6,13].

Zoledronate can normalize cytokines pattern, through the inhibition of IL-6, the most potent survival factor for the MM clone, from the diseased bone-marrow stroma [14,15].

Superiority of any N-bisphosphonate (zoledronate or pamidronate) versus non-ammino bisphosphonates has not been demonstrated yet.

However zoledronate seems to be superior to placebo and non-nitrogen BPs and seems to give a major advantage on overall survival [16].

Adverse effects of BPs

It is well known that BPs are generally well tolerated, but they are also associated with potential adverse effects. The most common are gastrointestinal complications, like diarrhea, nausea and esophagitis, inflammatory reactions at the injection site, acute phase reactions following i.v. use, hyperthermia, hypocalcemia and hypophosphatemia and renal impairment [17]. The major complication is ONJ that seems to be correlated with BP treatment duration and has been shown to be 5%-15% at 4 years [18,19]. In the last years an increase in the incidence of subtrochanteric stress fractures (atypical fractures) has been reported [20].

Adverse ocular effects with bisphosphonate therapy

Among the adverse effects, scientific literature has recently reported some forms of ocular inflammation secondary to both intravenous and oral use of BPs: conjunctivitis, scleritis, episcleritis, iritis, keratitis and uveitis as major side effects, and eye dryness and red eye, edema and ptosis as minor side effects. Overall, the incidence of ocular adverse events after bisphosphonate exposure is difficult to be estimated because of the absence of reviews about this problem. In fact most reports in literature are simple case reports and data from voluntary drug-reporting system. Usually the onset of ocular symptoms, that are tipically unilateral, occurs in about 72 hours from administration of the bisphosphonate, and symptoms generally improve after cessation of drug use. The pathogenesis is not clear, but with high doses of topic/oral corticosteroids pain symptoms and inflammatory damage resolve, probably because inflammatory factors (TNF, IL-1, IL-6, IL-2, IFNα) may play a role in inducing eye inflammation [21-25]. Also Pazianas et al. seem to confirm this inflammatory ipothesis, as they found that uveitis onset is frequently associated with inflammatory bowel disease, rheumatic disorders (especially seronegative rheumatoid arthritis), sarcoidosis, rheumatoid arthritis and Sjogren syndrome [26]. These ocular complications have been initially associated with N-bisphosphonates;

alendronate, pamidronate, risedronate and zoledronate, and non-ammino bisphosphonates as well, seem to have therefore a certain role in the pathogenesis of ocular problems. However, the clinical trials do not explain if inflammation is the result of direct effect of drugs, or the expression of patient's background disease. It is also possible that ocular structure is temporary involved by more inflammatory processes (for example episcleritis associated with uveitis), a situation to be treated with therapy interruption and expert ophthalmologist's advice.27 The popularity of single drugs among the population probably explains the variance in the number of ocular inflammations reported for each type of bisphosphonate (Tables 1 & 2) [28].

Different ocular effects associated with Bps use can be classified as follows (World Health Organization Classification of Bisphosphonates and Ocular Side Effects) (Table 3):

Side effects as conjunctivitis or episcleritis generally have a complete resolution of symptoms [21] whereas uveitis, scleritis or orbital inflammation can cause serious complications like synechiae or ipopion, determining ocular lasting damages. Scleritis is the most frequently BPs-associated ocular side effect; it occurs within 48 hours from the infusion, and a new administration can cause recurrence in the same eye in the majority of cases. With each infusion patients can develop tolerance, so the inflammatory reaction can decrease in intensity [23,29]. According to several clinical studies, a causal relation between BPs administration and suspension can be hypothesized on the onset and disappearance of symptoms [21].

Our experience

As reported in 2012, we followed-up for at least one year 50 MM patients: those who were treated with zoledronate had a better clinical outcome and quality of life versus patients not treated with BPs [30]. In this group of patients we evaluated too, if zoledronic acid could be the cause of any major or minor ocular effects (unpublished data). The data are reported in Table 4.

Among our series of patients, we found a 77-year old man (#1) affected by left eye Best maculopathy, treated with zoledronate (1 fl/month) for 1 year; the ophthalmologist's advice was vit. E, lutein and vit. B administration. However the not inflammatory nature and the long latency between appearance of symptoms and the start of the therapy disavow a possible correlation between zoledronate and maculopathy.

Two patients were diagnosed with cataracts (#2, #4), supposedly of senile nature, and one patient (#3) had a visus reduction caused by phisiologic presbyopia, and not because of BPs.

A 60-year old woman (#5) developed right eye uveitis after fourteen administrations. The patient complained eye dryness and red eye, photophobia and sting, treated with sodium ialuronate and liposomial spray, with complete resolution of clinical symptoms. Although the temporal relationship between ocular event and BP therapy, we think that this ocular involvement is not strongly related to BPs, because of the long latency of symptoms and the history of sclerodermia by which the patient was affected. It's well known, in clinical practice, the relationship between sclerodermia and xeroftalmia.

Conclusion

Adverse effects strongly correlated with BPs therapy, including ONJ (which is considered to be the most dangerous), have long been known. Recently several cases of ocular events have been reported in literature in patients who are having drug treatment. At the moment the real incidence of the complication and the existence of a real relationship between drug administration and adverse effect is not strongly proved.

The aim of the present paper was that to review the literature with the specific topic to update the knowledge's on the pathogenesis of the complication and to estimate, if possible, the real incidence of the complication.

The inflammatory origin of the complication seems to be the most suitable explanation of the disease at the moment. In fact, the interruption of BPs therapy and the administration of corticosteroids are generally followed by a prompt recovery of the symptoms with the avoidance of the worsening of the complications.

At the moment, the real incidence of the complications is impossible to establish due to the lack of sufficient data in literature. For the future, it is advisable a more careful attention focused on the possible relationship between BPs and adverse ocular events through a strict survey of patients belonging to large case series such as those who are followed in oncology centers. We also evaluated our own data belonging to an omogeneous group of patients affected by multiple myeloma and treated with zoledronate. Zoledronic acid is

Table 3: Side effects.

Certain	Possible
Blurred vision	Retrobulbar neuritis
Ocular irritation	Yellow vision
Nonspecific conjunctivitis	Diplopia
Pain	Cranial nerve palsy
Epiphoria	Ptosis
Photophobia	Visual hallucinations
Conjunctivitis	
Uveitis	
Scleritis	
Episcleritis	
Periocular lid and/or orbital edema	

Table 4: Cases.

#	Sex	Age	BP	Dosage	Duration	Ocular effects	Ophthalmologist's assessment
1	Male	77	Zoledronate	1 fl	1 year	Left eye Best maculopathy	Vit E, Vit B, lutein 1/die
2	Male	81	Zoledronate	1 fl	3 years	Blurredvision (senile cataracts)	Assessment for cataracts
3	Male	60	Zoledronate	1fl/month	24 months		Visus reduction (diagnosis: presbyopia)
4	Male	70	Zoledronate	1fl/month	23 months	Visus reduction	Assessment for cataracts
5	Female	60	Zoledronate	1fl/month	14 months	Right uveitis, eye dryness, photophobia and red eye	Therapy with ophthalmic solution and liposomial spray

the most effective and powerful bisphosphonate widely used in MMs patients for its proved capacity to reduce skeletal related events. In our case series we do not recognize major ocular complication. Only five patient's complaint minor events not clearly related to the drug therapy.

In conclusion we think that, even in the absence of a clear pathogenic relationship between BPs and side ocular events, patients should be always advised about the possibility, even rare, to develop ocular disease during the therapy.

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