



This is a repository copy of *Pharmacodynamics of bisphosphonates in arthritis.*

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/98184/>

Version: Submitted Version

Article:

Le Goff, B. and Heymann, D. orcid.org/0000-0001-7777-0669 (2011) Pharmacodynamics of bisphosphonates in arthritis. *Expert Review of Clinical Pharmacology*, 4 (5). pp. 633-641. ISSN 1751-2433

<https://doi.org/10.1586/ecp.11.40>

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Pharmacodynamics of bisphosphonates in arthritis

Benoit Le Goff, Dominique Heymann.

INSERM U957, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Nantes, France.

Keywords: Rheumatoid arthritis; Osteoclasts; Bisphosphonates; Inflammation; Angiogenesis; Osteoporosis; bone erosions.

Word count: 4043

Address correspondence and reprint requests to: Dr Benoit Le Goff, MD, INSERM UMR-S957, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, 1 rue Gaston Veil, 44035 Nantes cedex 1, France.

E-mail: benlegoff@gmail.com

Phone : 33-272-641-143

Fax: 33-240-412-860

Summary

Inflammatory arthritis are a group of auto-immune diseases characterized by a chronic inflammation of the joints. Rheumatoid arthritis, the most common form of arthritis, is associated with local joint destruction and systemic bone loss. Osteoclasts, the only cells of the body able to resorb bone, are key players in these two types of bone loss. Bisphosphonates are analogues of pyrophosphate, inhibiting osteoclasts action and bone resorption. They are indicated in pathology associated with an excess of resorption. Besides their effect on bone they also exhibit extraosseous properties, acting on tumor cells, inflammation or angiogenesis. Thus, they have been trialed in the context of arthritis. It is now clear that they do not have any significant direct effect on disease activity or pain. If their indication in the systemic bone loss is clear, any beneficial effects on bone erosions are still controversial but interesting preliminary results warrant further investigations.

Introduction

Bisphosphonates (BPs) are structural analogues of inorganic pyrophosphate widely used in clinical practice for the treatment of osteoporosis, bone metastasis, hypercalcemia or Paget's disease [1]. Their main effect is to prevent bone resorption by interfering with several metabolic processes needed for osteoclasts survival and function. In normal condition, a balance exists between bone resorption and construction. Osteoclasts, arising from the monocyte/macrophage lineage, remove mineralised bone, action which is followed by the formation and mineralisation of new bone matrix by the osteoblasts. In pathological conditions, such as osteoporosis or bone metastasis, an excess of osteoclast activity exists, leading to a net bone loss. BPs, inhibiting this excessive osteoclast activity, are then a logical strategy to treat those situations. Despite major advances in the understanding of the coupling mechanisms between osteoclasts and osteoblasts, for example with the discovery of the Receptor Activator of Nuclear factor Kappa-B (RANK) / RANK-ligand (RANKL) / Osteoprotegerin (OPG) system, the exact mechanisms underlying the crosstalk between these 2 cells still need to be clarified and could lead to the discovery of new therapeutic targets.

Besides their effect on bone, BPs have also extraskelatal actions, interfering with tumoral cells proliferation, angiogenesis or inflammation [2-4]. The antitumoral effect is partly indirect, via the inhibition of bone resorption and subsequently the release of bone-derived growth factors. A direct effect of BPs on tumor cells has also been shown in vitro when they are administered with cytotoxic agents although small volume of in vivo evidence for direct anti-tumour effects of BPS have been demonstrated. These preclinical results have permitted phase III clinical studies, in breast cancer for example where Zoledronate (ZA), a third generation BPs, has been shown to significantly decrease the risk of recurrence in all sites [5] Besides this anti-tumoral effect, BPs have also been shown to act on inflammation,

angiogenesis and pain. Although these additional effects remain more controversial with mainly in vitro data, they open the range of BPs indications for other pathologic conditions like inflammatory arthritis, hip osteonecrosis or neuroarthropathy [4].

Rheumatoid arthritis is the most common of inflammatory arthritis. It is an autoimmune disease characterised by a chronic inflammation of the joint and is associated with a clear imbalance between bone resorption and formation. RA is associated with a systemic bone loss leading to osteoporosis and joint destruction secondary to the local chronic inflammation [6]. Osteoclasts have been shown to be the major cell types involved in those two types of bone loss and could be targeted by BPs. Although some studies have also pointed out the potential interest of BPs in osteoarthritis, most of the data were negative or showed radiological but not clinical benefits [7]. The goal of this review is to summarise the current knowledge on the mechanisms of action and indications of BPs in rheumatoid arthritis.

Mode of action of bisphosphonates

BPs are used since four decades in the treatment of diseases associated with a high bone turnover. However, it is only recently that their mechanism of action has been unraveled. BPs are analogues to the inorganic molecule pyrophosphate characterized by a phosphore-carbon-phosphore (P-C-P) structure. Importantly, this molecule is resistant to degradation, accounting for its long half-life when it binds to bone. The carbone molecule is linked to 2 side chains known as R1 and R2. The radical R1 is usually a hydroxyl group and is responsible for the avidity of the molecule to the bone whereas R2 is associated with the anti-resorptive capacity and is different for each type of BPs. According to this last radical, a BP is classified as simple (clodronate and etidronate) or nitrogen-containing (pamidronate, alendronate, ibandronate, risedronate and ZA) BP, the latter being the more potent.

The main cellular targets for BPs are osteoclasts. Indeed, the high and selective affinity of BPs to bone brings them in close contact with these cells during the resorption process. BPs are poorly absorbed from the gastrointestinal tract and about 50% of the absorbed drug is taken up selectively by the skeleton, while the rest is excreted unaltered in urine [7]. As already mentioned, their resistance to degradation enables them to stay in the bone for months or years where they are slowly released with the process of bone turnover. Osteoclasts are the only cells type able to degrade the bone. Originating from the monocyte/macrophage lineage, they undergo several steps of differentiation before being mature osteoclasts. The two main cytokines needed for this differentiation process are RANKL and Macrophage colony-stimulating factor (M-CSF). After being recruited, osteoclasts precursors fuse to form multinucleated cells which attach to bone where they create a resorption lacunae. During this final resorption process, BPs are dissociated from the bone mineral by the acidic environment created by the osteoclasts within the resorption lacunae [9]. Then, the BP is taken up by the osteoclasts and interacts with different metabolism processes which differ depending on the type/presence of nitrogen within the molecule (Figure 1).

The main mechanism of action of simple BPs is to interfere with ATP metabolism and induce cell apoptosis [9]. Their chemical structure, which closely resembles to Ppi, allows a condensation of a BP with an AMP to form an AppCp-type nucleotide instead of an ATP. This ATP analogue resembles to ATP but is resistant to hydrolytic breakdown. The intracellular accumulation of this non-hydrolysable ATP is likely to inhibit numerous intracellular metabolic enzymes, having a detrimental effect on cell function and eventually inducing apoptosis. It had been shown that the mitochondrial ADP/ATP translocase is one of the molecular pathways involved in this effect through activation of caspase-3 [10].

Interestingly, the effect of those simple BPs on osteoclasts can be overcome by using caspase inhibitor. RANKL and TNF can also rescue the osteoclasts from BPs-induced apoptosis [11]. Sutherland et al. have recently shown that RANKL and TNF- α were also able to prevent apoptosis induced by the nitrogen-containing BP alendronate and clodronate by increasing the expression of the anti-apoptotic protein Mcl-1 by the osteoclasts [12]. The importance of those cytokines in the focal and systemic bone loss associated with arthritis could explain the lack of efficacy of BPs in this indication.

Nitrogen containing BPs act mainly by inhibiting farnesyl pyrophosphate (FPP) synthase, a key enzyme in the mevalonate pathway. The mevalonate pathway produces isoprenoids that are vital for diverse cellular functions, ranging from cholesterol synthesis to growth control. FPP synthase catalyses the sequential condensation of dimethylallyl pyrophosphate (DMAPP) with 2 units of 3-isopentenyl pyrophosphate (IPP) to form FPP. This molecule is required for the prenylation (transfer of the isoprenoid group) of several proteins that is essential for their function and attachment to the cell membrane [13]. The main targeted proteins are the small GTPase signalling proteins such as Ras, Rho, Rac, Cdc42 and Rab families which regulate a variety of cell processes within osteoclasts like cytoskeletal arrangements, membrane ruffling, trafficking of intracellular vesicles and apoptosis. N-BPs inhibit another enzyme of the mevalonate pathway, the geranylgeranyl diphosphate synthase (GGPP), also involved in the prenylation of the small GTPase [14]. Finally, the inhibition of FPP synthase leads to the accumulation of IPP that becomes conjugated to AMP to form a novel ATP analogue (ApppI). This ATP analogue inhibits mitochondrial adenine nucleotide translocase leading to apoptosis [15].

Why targeting osteoclasts in arthritis?

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis and is characterized by a chronic inflammation of the joint. Bone loss is common during the progression of the disease and occurs inside the joint where chronic inflammation lead to osteoarticular destructions and related disability. Systemic bone loss favored by the chronic inflammation can also lead to osteoporosis and increase the risk of fracture. Osteoclasts are the principal cell type responsible for both focal and systemic bone loss in RA [16].

Gravallese et al. first described TRAP positive multinucleated cells at the bone-inflammation interface in the joint of patients with inflammatory arthritis [17]. Several lines of evidence have since confirmed the role of osteoclasts in bone destruction during RA. Osteopetrotic mouse models such as RANKL^{-/-} mice develop arthritis but display no bone erosion [18]. Treatment with a chimeric OPG fusion protein (Fc-OPG), which inhibits osteoclast differentiation, efficiently prevents bone erosion but not inflammation in the rat collagen-induced arthritis model [19]. The origins of those osteoclasts remain unclear. They probably differentiate from monocytes/macrophages precursors, abundant in the inflamed synovial tissue in RA. This process is activated by cells present in the synovial tissue which express pro-osteoclastogenic factors. Indeed, synovial fibroblasts, as other inflammatory cells, are source of M-CSF and RANKL. Moreover, pro-inflammatory cytokines like TNF alpha, IL-6 or IL-1 expressed by macrophages also promote osteoclasts differentiation. Finally, chronic inflammation has been shown to increase the number of osteoclast precursors in the systemic circulation and, then, the chance for these cells to be attracted by the chemokines within the joint [20].

Osteoclasts also play a major role in the systemic bone loss associated with inflammation. This complication is not only observed in inflammatory arthritis but is also a feature of all

chronic inflammatory disorders. For instance, patients with chronic inflammatory disease such as Crohn's disease or ulcerative colitis have a decrease of their BMD and an increased level of serum resorption markers [21]. This bone loss is correlated with the activity of the disease and serum markers of inflammation. Increase in the level of systemic pro-inflammatory cytokines is the main mechanism driving to this bone loss. They increase the pool of osteoclast precursors coming from the bone marrow. For example, psoriatic arthritis patients exhibit a marked increase in osteoclast precursors compared with those from healthy controls [22]. Osteoclast precursors found in the blood of RA patients express higher level of Osteoclast Associated Receptor (OSCAR), a co-stimulator of osteoclasts, compared to general population [23]. This may lead to a greater capacity for these cells to differentiate into osteoclasts. Pro-inflammatory cytokines also create a negative environment within the bone by activating local osteoclastogenesis and inhibiting osteoblasts activity [24].

Extraosseous effect of bisphosphonates

One of the interests for evaluating BPs in the context of arthritis was that, apart from their effect on bone, these drugs had demonstrated effects on other pathological processes playing a role in the pathogenesis of arthritis such as inflammation, angiogenesis or pain.

Effect on Angiogenesis

Arthritis development in the joint is associated with an increased angiogenesis. Changes to the endothelium are among the first pathophysiological events that occur in the human RA synovium with increase in the vascularisation being detected as early as the first month. The main cytokine involved in this process is the vascular endothelial growth factor (VEGF), produced mainly by the cells of the synovial lining layer. VEGF promotes endothelial

migration and proliferation in the synovial tissue [25]. In turn, activated endothelial cells express adhesion molecules and present chemokines, leading to leukocyte migration from the blood into the pannus tissue [26]. An anti-VEGF-Receptor 1 antibody, tried in the murine collagen-induced arthritis (CIA), has suppressed arthritis and decreased the number of leukocytes and endothelial cells in the inflammatory tissue [27]

BPs have been shown, *in vitro*, to inhibit the main steps of the angiogenic process, from cell proliferation to tube formation [3]. This has been demonstrated in a model using human umbilical vein and aortic explants [28]. ZA has been shown to induce a long lasting decrease in the serum level of VEGF in patients treated for bone metastasis cancer [29]. However, the high affinity of BPs to bone may lead *in vivo* to a short exposure of the endothelial cells to BPs. Thus, only high dosage of BPs has demonstrated an antiangiogenic effect *in vivo* in a mouse model of myeloma or prostate cancer [30,31]. In contrast, an equivalent of one year 5 mg infusion ZA could not inhibit bone vascularisation in a rat model of bone healing [32]. Studies are needed to evaluate any potential antiangiogenic effect of BPs in arthritis.

Effect on inflammation

The potential anti-inflammatory effect of BPs is more controversial. They are believed to have anti-inflammatory properties but can also induce fever and other inflammatory symptoms after infusions. Some data derived from *in vitro* studies first showed that BPs could act on the monocyte/macrophage cells or osteoblast-like cells to inhibit the release of pro-inflammatory cytokines [33,34]. However, *in vivo* studies are more contradictory with the effect depending on the type of BPs or the model of inflammation [35]. In the context of arthritis, two studies using a rat model of collagen-induced arthritis have even demonstrated potential pro-inflammatory effects of these drugs when used at high dosage [36,37].

One of the most frequent adverse effects with BPs is the acute-phase reaction observed mainly after infusion of IV BPs. It is characterised by an influenza-like syndrome with fever, myalgia and arthralgia. An increase of serum pro-inflammatory cytokines like IL-6 or TNF has been described after BPs infusion. One of the mechanisms suggested for this reaction is that the inhibition of the FPP synthase leads to the accumulation of the metabolite upstream which is IPP (isopentenyl phosphate) (Figure 1). By an unknown mechanism, IPP is presented by the monocytes of the peripheral blood to a subtype of gamma-delta T lymphocytes, activating the production of pro-inflammatory cytokines by these cells such as TNF alpha [38]. Pre-treatment in vitro by statin prevents such reaction because the statin inhibits the mevalonate pathway upstream to IPP [39]. However, a controlled randomized study conducted on children had not demonstrated any effect of pre-treatment with atorvastatin on pain, CRP or peripheral gamma delta after BPs infusion [40].

Effect on Pain

Besides their powerful antiresorptive effect, it is suggested that BPs could also have a specific analgesic effect. BPs are known to provide a rapid improvement in pain associated with bone metastasis [41]. The most common explanation for that analgesic effect is that, inhibiting bone resorption, BPs are able to increase the pH inside the bone microenvironment, resulting in a decrease of acid-sensing ion channel nerve stimulation. The analgesic effect could also be mediated by the decrease of pro-inflammatory cytokines, prostaglandins, lactic acid, and/or various neuropeptides and neuromodulators release during bone degradation which are known to stimulate sensitive nerves. As described previously, Nitrogen-containing BPs inhibit the prenylation of the GTPases such as Ras, Rac, Rho, and Cdc42 which are involved into the postsynaptic plasticity and then signal transmission in the spinal cord [42]. In a mice model of pain using the tail flick test (testing the sensitivity of the tail to temperature changing),

intravenous BPs have also proved a peripheral antinociceptive effect independent of their action on bone although its mechanism remains unclear [43].

Bisphosphonates in the treatment of RA

Treatment and prevention of osteoporosis

Patients with RA are at greater risk of developing osteoporosis [44]. The increased fracture risk is more prominent at the hip and spine and is associated with RA severity, disease duration and glucocorticoid use [45]. The mechanism of this bone loss is multifactorial, including effects of chronic inflammation on bone, decrease of activity or corticoid use. Control of inflammation is important to prevent this bone loss as several studies have demonstrated that anti-TNF alpha antibodies were able to prevent bone loss and to increase bone formation markers [46,47]. BPs are widely used to prevent or treat osteoporosis associated with arthritic conditions. Since they have mainly been evaluated in the context of corticoid-induced osteoporosis, a direct action on inflammation-induced bone loss is likely yet remains difficult to prove.

Glucocorticoids (GCs) are one of the mainstay therapies for RA, having a rapid anti-inflammatory effect. They have also been proved to have a beneficial long term effect in the prevention of structural damage [48]. However, their use is associated with an increased risk of osteoporosis and fractures that is correlated with prolonged or high dose treatment [45]. Randomised controlled studies have demonstrated that alendronate and risedronate were efficient in the prevention of GCs induced osteoporosis [49,50]. ZA seems to be the most efficient in that context. In the HORIZON study, ZA was non-inferior and even superior to risedronate at 12 months for increase of lumbar spine bone mineral density (mean 4.06% vs

2.71%), even in the patients treated for less than 3 months with GCs (2.60% vs 0.64%). ZA showed a faster, more substantial inhibitory effect on bone turnover biomarkers than did risedronate [51]. Around 40% of the patients enrolled in this study suffered from RA. Of note, about 6-8% of the patients experienced a worsening of their RA in both ZA and risedronate group but the absence of any placebo group prevents us to draw any conclusion. Finally, although BPs are one of the best options to treat or prevent osteoporosis associated with RA, questions remain about the indications and duration of treatment in view of the secondary effect associated with their long term use [52].

Effect of bisphosphonates on clinical and biological parameters of RA

Several studies have tried to assess any beneficial effect of BPs on clinical symptoms and biological inflammation in RA (Table 1) [53-66]. The first work was published in 1988 and studied the effect of etidronate 5 mg/kg/day on inflammation [53]. In this study, Bird et al. demonstrated an early but transient improvement in clinical index but no effect on serum level of inflammatory proteins. In a randomised controlled study, Eggelmeijer et al treated 30 RA patients with IV pamidronate (either 20 to 40 mg) and showed a mild but significant decrease in clinical inflammation and the level of CRP and ESR with a relation with the dosage use [56]. Another study confirmed a potential anti-inflammatory effect of BPs as pamidronate 1000 mg/day for 12 months significantly decreased the clinical and biological parameters of inflammation compared to the placebo [55]. However, pre-existing differences existed in the 2 groups of treatment in this last study. Since these first studies were published before 1995, several authors have failed to see any effect of BPs on inflammatory symptoms [58-63]. The relatively small sample size of all studies is likely to result in a lack of power, explaining the conflicting results reported. Overall, even if an anti-inflammatory effect exists, the use of BPs

in that indication is not justified in view of the efficacy of new treatments to treat inflammatory symptoms in RA.

Effect of bisphosphonates in the prevention of bone erosions

The effect of BPs on bone erosions was initially assessed in animal model of arthritis. In two of them ZA was shown to strongly inhibit focal joint erosions [36,37]. ZA acted directly on mature osteoclasts and was able to down regulate the number of osteoclasts inside the joint.

The preliminary encouraging results obtained in animal models were followed by several studies that have assessed the effect of BPs on structural damage in RA patients. Maccagno et al first demonstrated in 1994 in a double blind controlled study, that a daily dose of oral pamidronate prevented bone erosion in RA patients [55]. Indeed, although patients treated with BPs had a more active disease before introduction of BPs therapy, they did not show X-Ray damage after 1 year of pamidronate 1000 mg/day whereas progression was observed in the placebo group. Hasegawa et al showed in 31 RA patients treated with cyclic etidronate during 1.5 year that this drug was able to prevent the systemic bone loss but also the structural damage assessed by the Larsen score compared to the placebo [61]. However, conclusions are difficult to draw in view of the small patients sample in the first study and the absence of randomization in the second. Moreover, several later studies failed to demonstrate any protective effect on bone erosions [62,63]. More recently, one double bind randomized controlled proof-of-concept study has compared ZA, the most powerful BP, to placebo in the prevention of structural damage [64]. Thirty-nine patients with early RA were randomized to receive either two infusions of 5 mg of ZA at 0 and 3 months or a placebo. Bone erosions in hand and wrist were assessed with MRI after 6.5 months. The study showed that there were 61% less erosions in the ZA group compared to control with also a reduction in the number of

new erosions. However, these results did not reach statistical significance because of the high variability between patients in the evolution of the X-ray score. Since that study, no new randomised controlled study have evaluated the effect of BPs in RA, may be because new treatments targeting cytokines or intra-cellular pathway have become available. However, the lack of superiority of these new treatments in the prevention of bone erosions shows that osteoclasts are still a potential therapeutic target in RA. Overall, the effect of BPs on bone erosions in RA remains controversial. New randomised studies with more patients and use of last generation BPs are necessary to conclude on any beneficial effect in this indication.

Of note, intra-articular injections of BPs have been trialed in RA patients after promising preliminary data in animal models of arthritis [65]. Liposome encapsulation of the bisphosphonates was used as it allows the drug to penetrate in the synovial tissue and have its action on the cells in the inflammatory infiltrate. Barrera et al demonstrated in patients with longstanding RA that after 2 weeks, the intra-articular injection of clodronate-containing liposomes leads to macrophage depletion and decreased expression of adhesion molecules in the synovial lining [66]. However, no study has been carried on since that first description.

Long term or high dose BPs are associated with rare but serious adverse effects like osteonecrosis of the jaws or the more recently described atypical fractures of the femur. It seems that RA patients are not at higher risk to develop such complications. Thus, although jaws osteonecrosis has been described in RA patients treated with oral BPs for osteoporosis [67,68], there is no evidence of any causal relation between the treatment which was given orally at low dose and the occurrence of the osteonecrosis. However, a special care should be taken during dental surgical procedure in these patients treated by corticosteroids, having a higher risk of parodontopathies. Concerns have also been raised about potential

oversuppression of bone turnover and the development of atypical skeletal fragility associated with long-term use of BPs [69]. A number of case reports in the literature have documented atypical insufficiency fractures in patients on long-term BPs therapy. Someford et al reported the case of a RA patient who was treated with alendronate for 8 years and developed spontaneous bilateral subtrochanteric/diaphyseal fractures [70]. Being the only case reported so far, no conclusion can be drawn but follow-up of RA patients treated with long term BPs therapy remains necessary.

Expert commentary

Their action on osteoclasts and their potential extra-skeletal effects have made BPs an attractive alternative therapeutic in arthritis. As underlined in this review, clinical studies have been able to only confirm their interest in the treatment and prevention of osteoporosis associated with inflammation and corticosteroid use. Any beneficial effect of this treatment on inflammation or pain has not been confirmed in patients despite promising in vitro and animal data .Their ability to protect from focal joint erosions remains interesting but needs to be further explored. ZA, the most potent BP, has shown an interesting potential in a small proof-of-principal study in early arthritis. However, although osteoclasts are involved in focal and systemic bone loss associated with arthritis, the mechanisms of these two types of bone loss may differ and could explain the lack of efficacy observed with BPs in clinical trial. In view of the in vivo data, it is likely that higher dosages are needed for BPs to have a beneficial effect on bone erosion. As a high variability exists between patients disease, a more targeted population of RA patients must be included in the future studies like patients with rapid joint destruction or resistant to conventional therapy. Recently, Sojeima et al described a case of a 38 year old man presenting with a recent rheumatoid arthritis associated with hepatitis C [71]. X-Ray of the hands showed erosions and demineralization of the carpus. In view of relative

contraindication of immunosuppressive therapy, alendronate was started at the dosage of 5 mg/day. After 4 months, symptoms and control radiography showed an improvement and sometimes healing of bone erosions. However, in the context of potential secondary effects associated with high dose or prolonged use of BPs, the justification of any therapeutic has to be carefully evaluated.

Five years view

Although new therapeutics are available to treat RA patients, some patients are still resistant to conventional and biological therapy or continue to experience radiological progression despite a good control of the disease activity. A complementary treatment may be prescribed with the goal to prevent radiological progression. Besides BPs, other therapeutics primarily used in osteoporosis should be evaluated in the context of arthritis in the future. Cohen et al demonstrated recently that denosumab, a monoclonal antibody targeting RANKL, was able to efficiently prevent bone erosions in patients with RA, confirming the therapeutic potential of osteoclast inhibition in this indication [72]. If BPs will still be a therapeutic option in this indication, dose ranging and a more targeted population of RA needs to be evaluated. Moreover, new therapeutic promoting bone formation as anti-sclerostin antibodies will be currently trialed in osteoporosis and could also be an alternative solution to not only prevent bone erosions but also promotes bone healing [73].

Key issues:

- BPs, targeting osteoclasts, are indicated in all the pathologic processes associated with an increase of resorption like osteoporosis, bone metastasis or Paget's disease of bone
- Besides their effect on bone, BPs have extraosseous properties acting on tumor cells, inflammation, angiogenesis or pain
- Inflammatory arthritis is characterised by a chronic inflammation of the joint but is also associated with a bone loss
- Osteoclasts are involved in the local (bone erosions) and systemic (osteoporosis) bone loss association with inflammatory arthritis
- BPs are a therapeutic of choice in the treatment or prevention of osteoporosis associated with rheumatoid arthritis
- Although promising preliminary data are available on the effect of BPs on the prevention of joint destruction, more study are needed to confirm a potential indication in clinical practice
- Therapeutic targeting osteoclasts are a therapeutic option in rheumatoid arthritis, more particularly in patients with osteoporosis or having rapid joint damage

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

please highlight 6–8 references that are of particular significance to the subject under review as “* of interest” or “** of considerable interest” and provide a brief (1–2 line) synopsis.

[1] Favus MJ. Bisphosphonates for osteoporosis. *N Engl J Med.* 363, 2027-35 (2010).

[2] Clezardin P. Bisphosphonates antitumor activity: an unravelled side of a multifaceted drug class. *Bone.* 48, 71-9 (2011).

* of interest : comprehensive review on the anti-tumoral effect of BPs

[3] Stresing V, Daubin  F, Benzaid I, M nkk nen H, Cl zardin P. Bisphosphonates in cancer therapy. *Cancer Lett.* 257, 16-35 (2007).

[4] Le Goff B, Berthelot JM, Maugars Y, Romas E. Alternative use of bisphosphonate therapy for rheumatic disease. *Curr Pharm Des.* 27, 3045-52 (2010).

[5] Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, P stlberger S, Menzel C et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med.* 360, 679-91 (2009).

[6] Romas E, Gillespie MT. Inflammation-induced bone loss: can it be prevented? *Rheum Dis Clin North Am.* 32, 759-73 (2006).

[7] Saag KG. Bisphosphonates for osteoarthritis prevention: "Holy Grail" or not? *Ann Rheum Dis.* 67, 1358-9 (2008).

[8] Cremers SC, Pillai G, Papapoulos SE. Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet.* 44, 551-70 (2005).

[9] Rogers MJ, Crockett JC, Coxon FP, Mönkkönen J. Biochemical and molecular mechanisms of action of bisphosphonates. *Bone.* Nov 26. (2010). [Epub ahead of print]

** of considerable interest: The insight of the mechanisms of action of BPs

[10] Lehenkari PP, Kellinsalmi M, Näpänkangas JP, Ylitalo KV, Mönkkönen J, Rogers MJ, Azhayev A, Väänänen HK, Hassinen IE. Further insight into mechanism of action of clodronate: inhibition of mitochondrial ADP/ATP translocase by a nonhydrolyzable, adenine-containing metabolite. *Mol Pharmacol.* 61:1255-62 (2002).

[11] Zhang Q, Badell IR, Schwarz EM, Boulukos KE, Yao Z, Boyce BF et al. Tumor necrosis factor prevents alendronate-induced osteoclast apoptosis in vivo by stimulating Bcl-xL expression through Ets-2. *Arthritis Rheum.* 52, 2708-18 (2005).

[12] Sutherland KA, Rogers HL, Tosh D, Rogers MJ. RANKL increases the level of Mcl-1 in osteoclasts and reduces bisphosphonate-induced osteoclast apoptosis in vitro. *Arthritis Res Ther.* 11:R58(2009).

[13] Russell RG, Xia Z, Dunford JE, Oppermann U, Kwaasi A, Hulley PA et al. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci.* 1117, 209-57 (2007).

[14] Szabo CM, Matsumura Y, Fukura S, Martin MB, Sanders JM, Sengupta S, Cieslak JA, Loftus TC, Lea CR, Lee HJ, Koohang A, Coates RM, Sagami H, Oldfield E. Inhibition of geranylgeranyl diphosphate synthase by bisphosphonates and diphosphates: a potential route to new bone antiresorption and antiparasitic agents. *J Med Chem.* 45:2185-96 (2002).

[15] Mönkkönen H, Auriola S, Lehenkari P, Kellinsalmi M, Hassinen IE, Vepsäläinen J, Mönkkönen J. A new endogenous ATP analog (ApppI) inhibits the mitochondrial adenine nucleotide translocase (ANT) and is responsible for the apoptosis induced by nitrogen-containing bisphosphonates. *Br J Pharmacol.* 147:437-45 (2006).

[16] Schett G, Teitelbaum SL. Osteoclasts and Arthritis. *J Bone Miner Res.* 24, 1142-1146 (2009).

* of interest: Interesting review on the role of osteoclasts in arthritis

[17] Gravallesse EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol.* 152, 943-51 (1998).

* of interest: First report of the role of osteoclasts in bone erosions

[18] Pettit AR, Ji H, von Stechow D, Muller R, Goldring SR, Choi Yet al. TRANCE/RANKL knockout mice are protected from bone erosion in a serum transfer model of arthritis: *Am J Pathol.* 159, 1689-1699 (2001).

[19] Romas E, Sims NA, Hards DK, Lindsay M, Quinn JW, Ryan PF, et al. Osteoprotegerin reduces osteoclast numbers and prevents bone erosion in collagen-induced arthritis. *Am J Pathol.* 161, 1419-27 (2002).

- [20] Li P, Schwarz EM, O'Keefe RJ, Ma L, Looney RJ, Ritchlin CT, et al. Systemic tumor necrosis factor alpha mediates an increase in peripheral CD11bhigh osteoclast precursors in tumor necrosis factor alpha-transgenic mice. *Arthritis Rheum.* 50, 265-76 (2004).
- [21] Ghishan FK, Kiela PR. Advances in the understanding of mineral and bone metabolism in inflammatory bowel diseases. *Am J Physiol Gastrointest Liver Physiol.* 300, G191-201 (2011).
- [22] Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest.* 111, 821-31 (2003).
- [23] Herman S, Müller RB, Krönke G, Zwerina J, Redlich K, Hueber AJ et al. Induction of osteoclast-associated receptor, a key osteoclast costimulation molecule, in rheumatoid arthritis. *Arthritis Rheum.* 58, 3041-50 (2008).
- [24] Ma YD, Park C, Zhao H, Oduro KA Jr, Tu X, Long F et al. Defects in osteoblast function but no changes in long-term repopulating potential of hematopoietic stem cells in a mouse chronic inflammatory arthritis model. *Blood.* 114, 4402-10 (2009).
- [25] Koch AE, Harlow LA, Haines GK, Amento EP, Unemori EN, Wong WL, et al. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. *J. Immunol.* 152, 4149-4156 (1994).

- [26] Middleton J, Americh L, Gayon R, Julien D, Aguilar L, Amalric F, et al. Endothelial cell phenotypes in the rheumatoid synovium: activated, angiogenic, apoptotic and leaky. *Arthritis Res. Ther.* 6, 60-72 (2004).
- [27] Choi ST, Kim JH, Seok J, Park Y, Lee S. Therapeutic effect of anti-vascular endothelial growth factor receptor I antibody in the established collagen-induced arthritis mouse model. *Clin. Rheumatol.* 28, 333-337 (2009).
- [28] Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM, Castronovo V, Green JR. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther.* 302, 1055-61 (2002).
- [29] Santini D, Vincenzi B, Dicuonzo G, Avvisati G, Massacesi C, Battistoni F, et al. Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients. *Clin. Cancer Res.* 2893-2897 (2003).
- [30] Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 62, 6538-44 (2002).
- [31] Biver E, Vieillard MH, Cortet B, Salleron J, Falgayrac G, Penel G. No anti-angiogenic effect of clinical dosing regimens of a single zoledronic acid injection in an experimental bone healing site. *Bone.* 46, 643-8. (2010).

- [32] Croucher PI, De Hendrik R, Perry MJ, Hijzen A, Shipman CM, Lippitt J, et al. Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. *J Bone Miner Res* 18, 482–92 (2003).
- [33] Giuliani N, Pedrazzoni M, Passeri G, Girasole G. Bisphosphonates inhibit IL-6 production by human osteoblast-like cells. *Scand J Rheumatol*. 27, 38-41 (1998).
- [34] Pennanen N, Lapinijoki S, Urtti A, Monkkonen J. Effect of liposomal and free bisphosphonates on the IL-1, IL-6 and TNF- secretion from RAW264 cells in vitro. *Pharmacol Res*. 12, 916–22 (1995).
- [35] Richards PJ, Amos N, Williams AS, Williams BD. Pro-inflammatory effects of the aminobisphosphonate ibandronate in vitro and in vivo. *Rheumatology*. 38, 984-91 (1999).
- [36] Sims NA, Green JR, Glatt M, Schlicht S, Martin TJ, Gillespie MT et al. Targeting osteoclasts with zoledronic acid prevents bone destruction in collagen-induced arthritis. *Arthritis Rheum*. 50, 2338-46 (2004).
- [37] Le Goff B, Soltner E, Charrier C, Maugars Y, Rédini F, Heymann D, Berthelot JM. A combination of methotrexate and zoledronic acid prevents bone erosions and systemic bone mass loss in collagen induced arthritis. *Arthritis Res Ther*. 11, R185 (2009).
- [38] Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: Different mechanisms of action and effects. *Bone*. Dec 9 (2010)

- [39]Thompson K, Rogers MJ. Statins prevent bisphosphonate-induced gamma,delta-T-cell proliferation and activation in vitro. *J Bone Miner Res.* 19:278-88(2004).
- [40] Srivastava T, Haney CJ, Alon US. Atorvastatin may have no effect on acute phase reaction in children after intravenous bisphosphonate infusion. *J. Bone Miner. Res.* 24, 334-337 (2009).
- [41] von Moos R, Strasser F, Gillessen S, Zaugg K. Metastatic bone pain: treatment options with an emphasis on bisphosphonates. *Support Care Cancer.* 16, 1105-15 (2008).
- [42] Reszka AA, Rodan GA. Nitrogen-containing bisphosphonate: mechanism of action. *Mini Rev Med Chem.* 4, 711-9 (2004).
- [43] Bonabello A, Galmozzi MR, Canaparo R, Serpe L, Zara GP. Long-term analgesic effect of clodronate in rodents. *Bone.* 33, 567-74 (2003).
- [44] Haugeberg G, Ørstavik RE, Kvien TK. Effects of rheumatoid arthritis on bone. *Curr Opin Rheumatol.* 15, 469-75 (2003).
- [45] van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum.* 54, 3104-12 (2006).

- [46] Chopin F, Garnero P, le Henanff A, Debiais F, Daragon A, Roux C, et al. Long-term effects of infliximab on bone and cartilage turnover markers in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 67, 353-357 (2008).
- [47] Vis M, Havaardsholm EA, Haugeberg G, Uhlig T, Voskuyl AE, van de Stadt RJ, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 65, 1495-1499 (2006).
- [48] Hoes JN, Jacobs JWG, Buttgerit F, Bijlsma JWJ. Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis. *Nat Rev Rheumatol.* 6, 693-702 (2010).
- [49] Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *N Engl J Med.* 339, 292-9 (1998).
- [50] Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 42, 2309-18 (1999).
- [51] Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY et al. HORIZON investigators: Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet.* 373, 1253-63 (2009).

** of considerable interest: The confirmation of the efficacy in the prevention and treatment of glucocorticoid-induced osteoporosis

[52] Pazianas M, Cooper C, Ebtino FH, Russell RG. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. *Ther Clin Risk Manag.* 21, 325-43 (2010).

[53] Bird HA, Hill J, Sitton NG, Dixon JS, Wright V. A clinical and biochemical assessment of etidronate disodium in patients with active rheumatoid arthritis. *Clin. Rheumatol.* 7, 91-94 (1988).

[54] Ralston SH, Hacking L, Willocks L, Bruce F, Pitkeathly DA. Clinical, biochemical, and radiographic effects of aminohydroxypropylidene bisphosphonate treatment in rheumatoid arthritis. *Ann. Rheum. Dis.* 48, 396-399 (1989).

[55] Maccagno A, Di Giorgio E, Roldan EJ, Caballero LE, Perez Lloret A. Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 23, 211-214 (1994).

[56] Eggelmeijer F, Papapoulos SE, van Paassen HC, Dijkmans BA, Breedveld FC. Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J. Rheumatol.* 21, 2016-2020 (1994).

[57] Cantatore FP, Acquista CA, Pipitone V. Evaluation of bone turnover and osteoclastic cytokines in early rheumatoid arthritis treated with alendronate. *J. Rheumatol.* 26, 2318-2323 (1999).

[58] Van Offel JF, Schuerwegh AJ, Bridts CH, Bracke PG, Stevens WJ, De Clerck LS. Influence of cyclic intravenous pamidronate on proinflammatory monocytic cytokine profiles and bone density in rheumatoid arthritis treated with low dose prednisolone and methotrexate. *Clin. Exp. Rheumatol.* 19, 13-20 (2001).

[59] Valleala H, Laitinen K, Pylkkänen L, Konttinen YT, Friman C. Clinical and biochemical response to single infusion of clodronate in active rheumatoid arthritis--a double blind placebo controlled study. *Inflamm. Res.* 50, 598-601 (2001).

[60] Mazzantini M, Di Munno O, Metelli MR, Bulleri M, Giordani R. Single infusion of neridronate (6-amino-1-hydroxyhexylidene-1,1-bisphosphonate) in patients with active rheumatoid arthritis: effects on disease activity and bone resorption markers. *Aging Clin Exp Res.* 14, 197-201 (2002).

[61] Hasegawa J, Nagashima M, Yamamoto M, Nishijima T, Katsumata S, Yoshino S. Bone resorption and inflammatory inhibition efficacy of intermittent cyclical etidronate therapy in rheumatoid arthritis. *J. Rheumatol.* 30, 474-479 (2003).

[62] Valleala H, Laasonen L, Koivula M, Mandelin J, Friman C, Risteli J, et al. Two year randomized controlled trial of etidronate in rheumatoid arthritis: changes in serum

aminoterminal telopeptides correlate with radiographic progression of disease. *J. Rheumatol.* 30, 468-473 (2003).

[63] Lodder MC, Van Pelt PA, Lems WF, Kostense PJ, Koks CHW, Dijkmans BAC. Effects of high dose IV pamidronate on disease activity and bone metabolism in patients with active RA: a randomized, double-blind, placebo-controlled trial. *J. Rheumatol.* 30, 2080-2081 (2003).

[64] Jarrett SJ, Conaghan PG, Sloan VS, Papanastasiou P, Ortmann C, O'Connor PJ, et al. Preliminary evidence for a structural benefit of the new bisphosphonate zoledronic acid in early rheumatoid arthritis. *Arthritis Rheum.* 54, 1410-1414 (2006).

* of interest: Last study showing a beneficial effect of bisphosphonate in the prevention of bone erosions using MRI.

[65] Ceponis A, Waris E, Mönkkönen J, Laasonen L, Hyttinen M, Solovieva SA et al. Effects of low-dose, noncytotoxic, intraarticular liposomal clodronate on development of erosions and proteoglycan loss in established antigen-induced arthritis in rabbits. *Arthritis Rheum.* 44, 1908-16 (2001).

[66] Barrera P, Blom A, van Lent PL, van Bloois L, Beijnen JH, van Rooijen N et al. Synovial macrophage depletion with clodronate-containing liposomes in rheumatoid arthritis. *Arthritis Rheum.* 43, 1951-9 (2000).

[67] Yarom N, Yahalom R, Shoshani Y, Hamed W, Regev E, Elad S. Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome. *Osteoporos Int.* 18, 1363-70 (2007).

[68] Grana J, Mahia IV, Meizoso MO, Vazquez T. Multiple osteonecrosis of the jaw, oral bisphosphonate therapy and refractory rheumatoid arthritis (Pathological fracture associated with ONJ and BP use for osteoporosis). *Clin Exp Rheumatol.* 26, 384-5 (2008).

[69] Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: A systematic review of case/case series studies. *Bone.* 47, 169-80 (2010).

[70] Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. *J Bone Miner Res.* 24, 1736-40 (2009).

[71] Soejima M, Kawaguchi Y, Hara M, Saito S, Kamatani N, Yamanaka H. Therapeutic effects of alendronate on bone erosion and atrophy in a patient with rheumatoid arthritis and hepatitis C virus infection. *J. Rheumatol.* 35, 2284-2286 (2008).

[62] Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum.* 58, 1299-309 (2008).

[73] Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res.* 19-26 (2011).

Figure 1. Mechanisms of action of bisphosphonates. Simple-BPs are incorporated with an AMP to form an AppCp-type non-hydrolyzable cytotoxic analogues of ATP. The mitochondrial ADP/ATP translocase is one of its molecular target, leading to caspase activation and apoptosis. Nitrogen-containing-BPs (N-BPs) inhibits the farnesyl pyrophosphate synthase (FPP Synthase) and geranylgeranyl pyrophosphate synthase (GGPPS) which catalyses the condensation of dimethylallyl pyrophosphate (DMAPP) with 2 units of 3-isopentenyl pyrophosphate (IPP) to form FPP. Accumulated IPP is converted to a cytotoxic ATP analogue called ApppI, inducing apoptosis.