Emerging potential for bisphosphonates in the treatment of axial spondyloarthritis

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Ankylosing spondylitis is a chronic inflammatory condition that typically affects the joints of the spine and is characterized by inflammatory low back pain (LBP). Over time, progression of the joint inflammation leads to ankylosis of the sacroiliac joints and spine. Early diagnosis of ankylosing spondylitis is crucial for prognosis: although it is well known that nonsteroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor α (TNFα) blockers in general fail to arrest the development of ankylosis in ankylosing spondylitis,[1] recent studies have raised the possibility that treatment of early ankylosing spondylitis with TNFα antagonists can reduce radiographic progression.[2]

A diagnosis of ankylosing spondylitis is made by modified New York 1984 criteria,[3] which require clear radiographic sign of sacroiliitis. However, these criteria do not allow diagnosis at an early stage, which is largely inflammatory and potentially modifiable by TNFα blockers, because radiographic alterations can be only observed later during the course of the disease when joint inflammation has already progressed into fibrosclerosis. Because magnetic resonance imaging (MRI) is sensitive enough to detect areas of bone marrow edema (BME) resulting from early changes in bone inflammation, it is useful in detecting early-stage sacroiliitis, and may also provide indication for disease activity.[4] Moreover, BME, as well as fat infiltration detected by MRI may be useful predictors of developing syndesmophytes.[4]

Recently, the Assessment of SpondyloArthritis International Society (ASAS) has developed new criteria for classification of axial spondyloarthritis, an undifferentiated form of (conceivably early stage) sacroiliac inflammatory involvement that cannot satisfy any specific classification criteria (e.g. for ankylosing spondylitis or psoriatic arthritis).[3] The ASAS criteria were formulated with the aim of enabling an earlier diagnosis and therefore more effective treatment in the clinical setting, and require presence of LBP and evidence of sacroiliitis either on radiography (but without the spine limitation considered in the modified New York 1984 criteria for ankylosing spondylitis) or on MRI. The criteria also allow a diagnosis of axial spondyloarthritis without any imaging with Human Leukocyte Antigen B27 (HLA-B27) positivity, plus at least two clinical spondyloarthritis features (e.g. inflammatory back pain, arthritis, enthesitis, or uveitis; for complete criteria, see Table 1) being considered sufficient for diagnosis.

A recent study reported that the risk of progression from axial spondyloarthritis to defined ankylosing spondylitis in 15 years is 26%;[5] this finding has important prognostic and therapeutic implications. From a prognostic point of view, given the limited risk of disease progression, it is highly inappropriate to consider axial spondyloarthritis as a definite form of 'Early ankylosing spondylitis'; axial spondyloarthritis is a syndromic entity that includes several other clinical conditions or fruste forms of ankylosing spondylitis. From a therapeutic standpoint, considering that about one quarter of patients with axial spondyloarthritis indeed do have early ankylosing spondylitis, pharmacological intervention to prevent disease progression may be worthy of consideration. On the other hand, it must be considered that preventive treatment can expose the majority (about three quarters) of individuals with axial spondyloarthritis to unnecessary, potentially harmful, and expensive long-term treatment with biologics.

Bisphosphonates are potent inhibitors of bone resorption, with a very long half-life; 1–10 years, depending on the compound. Bisphosphonates are molecules with an intense negative charge that gives them the capacity to concentrate in sites of high bone turnover. Classically, bisphosphonates are divided into non-nitrogenous bisphosphonates (NNBPs) and nitrogenous bisphosphonates (NBPs). NNBPs generate toxic analogues of

Table 1. Classification criteria for ankylosing spondylitis and for axial-spondyloarthritis.

Modified 1984 New York classification criteria for ankylosing spondylitis	**ASAS classification criteria for axial-spondyloarthritis**
FOR DIAGNOSIS Bilateral grade 2–4 sacroiliitis OR monolateral grade 3–4 sacroiliitis plus any clinical criteria	In patients with ⩾3 months of back pain and age < 45 years 1. Sacroiliitis on imaging plus ⩾1 SpA features 2. HLA-B27 plus ⩾2 others SpA features
Radiological criteria 1. Radiographic bilateral grade 2–4 sacroiliitis OR 2. Radiographic monolateral grade 3–4 sacroiliitis	**Definition of sacroiliitis on imaging** 1. Radiographic bilateral grade 2–4 sacroiliitis OR 2. Radiographic monolateral grade 3–4 sacroiliitis 3. Acute (active) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
Clinical criteria 1. Inflammatory LBP ⩾ 3 months, improved by exercise and not relieved by rest 2. Limitation of lumbar spine in sagittal and frontal planes 3. Limitation of chest expansion (relative to normal value corrected for age and sex)	**SpA features** 1. Inflammatory back pain 2. Arthritis 3. Dactylitis 4. Enthesitis (heel) 5. Psoriasis 6. Uveitis 7. Crohn's/colitis 8. Good response to NSAIDs 9. Family history of SpA 10. HLA-B27 11. Elevated CRP

ASAS, Assessment of SpondyloArthritis International Society; CRP, C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis; LBP, low back pain; MRI, magnetic resonance imaging; HLA-B27 , Human Leukocyte Antigen B27.

adenosine triphosphate that are responsible for the accelerated apoptosis of the osteoclasts, leading to an overall decrease in bone breakdown. NBPs, instead, affect the mevalonate pathway through the inhibition of the farnesyl diphosphate synthase, leading to accumulation of isopentenyl diphosphate (IPP), which impairs osteoclastogenesis, as well as motility and survival of osteoclasts.[6] Immediately after the first infusion of NBPs, a flu-like syndrome characterized by arthromyalgia and fever is described. This reaction seems to be related to the indirect stimulation of cytotoxic γδ T cells[7] due to the buildup of IPP. Other immunomodulatory effects of NBPs have been described, including reduction of pro-inflammatory cytokines (such as IL6 and TNFα), and modulation of macrophage and osteoblast activity.[8] These effects of NBPs have mostly been exploited in cancer therapy in order to limit bone metastasis and tumor growth.

Ankylosing spondylitis is characterized by the simultaneous presence of bone erosion and aberrant bone apposition that can lead to ankyloses.[9] Molecular pathophysiology of the condition involves the pro-inflammatory cytokines IL6, TNFα, IL17 and IL23 (the latter two being important mediators of lymphocyte-induced inflammation in ankylosing spondylitis), as well as a notable macrophage activation and the dysregulation of Dickkopf-related protein 1 (also known as DKK1), an inhibitor of the Wnt pathway implicated in osteoblast functions. Therefore, infusional NBPs could be useful in the treatment of early ankylosing spondylitis/axial spondyloarthritis *via* the reduction in pro-inflammatory cytokines, and inhibition of macrophage and osteoblast activity.

In consideration of their promising immunomodulatory effects, NBPs have been tested in small proof-of-concept studies of patients with ankylosing spondylitis/axial spondyloarthritis. The initial results have been largely conflicting; however, after the introduction of the ASAS criteria, promising results have been published. Viapiana and colleagues[10] have compared the effect of infliximab (a TNFα antagonist) and intravenous neridronate (a third generation NBP; at dosage of 100 mg monthly) in 60 patients with established ankylosing spondylitis. Over the 6-month follow-up period, the groups showed similar improvements in terms of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), but only the neridronate group showed an improvement in

Bath Ankylosing Spondylitis Functional Index (BASFI), a somewhat surprising finding given that substantial reductions in circulating inflammatory markers [i.e. erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were seen only in the infliximab study group.[10]

A second study compared the efficacy of golimumab, another TNFα antagonist, with pamidronate (a second-generation NBP) for 6 months in 50 patients with axial spondyloarthritis. The study reported similar improvement in BASDAI in both groups. Similar to findings by Viapiana *et al.*, a significant improvement in ESR and CRP was only reported in patients treated with the TNFα antagonist. Moreover, BASFI and axial inflammation evaluated with MRI according to Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system improved only in the golimumab group.[11]

These studies suggest that bisphosphonates can have clinical benefit and may modulate the pathogenetic mechanism of ankylosing spondylitis, possibly by acting simultaneously on bone erosion by inhibiting the osteoclasts, on the immune system by modulating macrophage and γδ lymphocyte activity, and on bone aberrant apposition by reducing osteoblast activity. Of note, bisphosphonates showed a satisfactory safety profile (the most common adverse effect is self-limiting arthromyalgia; the more severe, although rare jaw osteonecrosis has never been reported in the context of bisphosphonate treatment of ankylosing spondylitis or axial spondyloarthritis). Given the promising efficacy and tolerability findings, bisphosphonates should be now investigated in large prospective studies. Moreover, the high concentration of bisphosphonates in the bone region characterized by active turnover are maintained for several years and can prevent both evolution and any subsequent inflammatory reactivations, possibly without the necessity of repeated dosing of these drugs.

Given the positive results in terms of BASDAI disease activity and the much lower cost compared with TNFα blockers, axial spondyloarthritis and early ankylosing spondylitis may well represent an interesting target where NBPs could be tested as stand-alone first-line therapy in refractory or incomplete responders, or in combination with NSAIDs. Exploitation of their synergic anti-inflammatory effects can be attained by combining NBPs with biologics as second-line therapeutics, or in a later-stage ankylosing spondylitis.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Ramiro S, Stolwijk C, van Tubergen A, *et al.* Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. *Ann Rhem Dis* 2015; 74: 52–59.
2. Haroon N, Inman RD, Learch TJ, *et al.* The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013; 65: 2645–2654.
3. Akgul O and Ozgocmen S. Classification criteria for spondyloarthropathies. *World J Orthop* 2011; 2: 107–115.
4. Weber U, Jurik AG, Lambert RG, *et al.* Imaging in spondyloarthritis: controversies in recognition of early disease. *Curr Rheumatol Rep* 2016; 18: 58.
5. Wang R, Gabriel SE and Ward MM. Progression of nonradiographic axial spondyloarthritis to ankylosing spondylitis: a population-base cohort study. *Arthritis Rheumatol* 2016; 68: 1415–1421.
6. Drake MT, Clarke Bl and Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; 83: 1032–1045.
7. Iannitti T, Rosini S, Lodi D, *et al.* Bisphosphonates: focus on inflammation and bone loss. *Am J Ther* 2012; 19: 228–246.
8. Basso FG, Silveira Turrioni AP, Hebling J, *et al.* Zoledronic acid inhibits human osteoblast activities. *Gerontology* 2013; 59: 534–541.
9. Mahmoudi M, Aslani S, Nicknam MH, *et al.* New insights toward the pathogenesis of ankylosing spondylitis; genetic variations and epigenetic modifications. *Mod Rheumatol* 2016; 18: 1–12.
10. Viapiana O, Gatti D, Idolazzi L, *et al.* Bisphosphonates vs infliximab in ankylosing spondylitis treatment. *Rheumatology* 2014; 53: 90–94.
11. Mok CC, Li OC, Chan LY, *et al.* Effect of golimumab and pamidronate on clinical efficacy and MRI inflammation in axial spondyloarthritis: a 48-week open randomized trial. *Scand J Rheumatol* 2015; 44: 1–7.