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Differential Effects of Inflammation on Bone and Response to Biologics in Rheumatoid Arthritis and Spondyloarthritis

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Abstract
Purpose of review We review the pathways, cytokines, and concepts important to the pathogenesis of bone resorption and formation in rheumatoid arthritis (RA) and spondyloarthritis (SpA).
Recent findings Research in bone biology has shed light on the pathogenesis of the joint destruction that occurs in RA and in peripheral SpA. However, understanding the mechanisms behind the bone formation seen in peripheral and axial SpA has been challenging. Mouse models have been used to gain an understanding of key signaling pathways, cytokines and cells regulating inflammation in these diseases. Biologic therapies directed against these targets have been developed to control both inflammation and effects on bone.
Summary Although biologic therapies improve joint inflammation in both RA and SpA, leading to a decrease in pain and improving quality of life for patients, the long-term effects of such therapies must also be evaluated by assessing their impact on structural progression. Inhibition of radiographic progression in both RA and peripheral SpA has been easier to demonstrate than in axial SpA. Here, we discuss the similarities and differences among biologic therapies as they pertain to radiographic progression.

Keywords Rheumatoid arthritis · Spondyloarthritis · Bone · Biologics · Radiographic imaging

This article is part of the Topical Collection on *Spondyloarthritis*

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Introduction

Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are diseases in which inflammation can lead to significant changes in bone homeostasis, resulting in patient morbidity and loss of function. SpA is a unifying term that encompasses psoriatic arthritis (PsA), ankylosing spondylitis (AS), reactive arthritis, and inflammatory bowel disease-associated arthritis. Features common to both RA and SpA include peripheral joint involvement, in which inflammation is associated with focal articular erosions, and systemic bone loss. The term "SpA" also includes a subset known as "axial SpA (axSpA)," in which axial skeletal involvement is a major clinical component of the disease.

There are fundamental clinical and pathologic differences between RA and SpA, especially axSpA, which suggest different local responses of bone to inflammation. Whereas periarticular osteopenia and bone erosions with destruction of peripheral joints are typical clinical features of RA and peripheral SpA, osteoproliferation/bone formation occurs in axSpA. In addition, in the SpA spectrum of disease, but not in RA, enthesitis (inflammation at sites of insertion of tendons and ligaments on bone) and new bone formation are prominent. Features of axSpA that are not seen in RA include syndesmophytes (new areas of bony growth at intervertebral sites) and osteophytes (areas of bone formation occurring

peripherally at periosteal surfaces) [1]. Research aimed at elucidating the pathogenesis of bone changes in RA and SpA has focused on pathways regulating osteoclast and osteoblast function, on the interplay between these two cell types, and on cytokines and factors released by cells within the inflamed synovium and at entheses.

Drawing upon this research, targeted biologic therapies directed against specific cytokines, pathways and cells of the immune response have been developed that have revolutionized the treatment of both RA and SpA. This review will provide a synopsis of current knowledge regarding the mediators and effects of inflammation on bone and joints in RA and SpA, focusing on recent relevant discoveries; summarize the effects of the various biologic agents on structural progression in these diseases; and correlate basic mechanisms of bone biology with clinical outcomes in these diseases.

Rheumatoid Arthritis: Inflammation and Bone Loss

Bone Pathways in RA

Bone homeostasis requires coupled bone formation (mediated by osteoblasts) and bone resorption (mediated by osteoclasts). Thus, the development of osteopenia/osteoporosis and bone erosions in the joints of patients with RA demonstrates that, in this disease, bone resorption is favored over bone formation. Osteoclast-driven joint destruction as a consequence of chronically active inflammation has been widely studied and is well defined in RA [2•]. Currently available drug therapy can prevent the development and progression of erosions; however, even in patients who have achieved clinical remission, previously established erosions persist and rarely heal, suggesting that there is also an inhibition of bone formation by osteoblasts in this disease.

Osteoblasts are derived from mesenchymal precursor cells and produce and mineralize bone matrix. These cells produce two important factors in varying amounts: receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG). RANKL binds to the RANK receptor on osteoclast precursor cells, providing a signal for osteoclastogenesis and bone resorption. OPG, the soluble decoy for RANKL, blocks the effects of RANKL on osteoclasts, acting as an inhibitor of its function. Immature osteoblasts produce RANKL, and as these cells mature, RANKL production decreases and production of OPG increases. In RA, additional cellular sources of RANKL, including synovial fibroblasts, T and B cells, enter into the bone microenvironment, and the RANKL/OPG balance is altered, resulting in bone loss [3]. Synovial tissues of RA patients express a higher ratio of RANKL to OPG mRNA that results in a microenvironment that is favorable for bone resorption and erosion [4], and osteoclasts are required for articular bone erosion in inflammatory arthritis [5, 6]. Furthermore, treatment with DMARDs leads to a reduction of the RANKL/OPG ratio in RA synovium, correlating with a reduction in erosion scores in hand and foot radiographs [7].

In normal bone homeostasis, osteoblast differentiation and function are dependent, in part, on the canonical Wnt (Wingless) signaling pathway. Wnt ligands induce downstream signaling, leading to activation of gene transcription that enhances osteoblast differentiation and bone formation. Countering this are endogenous inhibitors of Wnt signaling, including secreted frizzled-related proteins (sFRPs), Dickkopf (DKK) family members and sclerostin [8]. We have demonstrated increased expression of the Wnt signaling antagonists sFRP-1 and -2 in inflamed synovial tissues in an animal model of RA and shown that there is an abundance of immature rather than mature osteoblasts at sites of inflammation and erosion, suggesting that inflammation impairs osteoblast maturation, at least in part, through the inhibition of Wnt signaling [9]. In a follow-up study, complete resolution of inflammation was noted to lead to repair of articular bone erosions, accompanied by downregulation of Wnt antagonist expression and the induction of the Wnt agonist Wnt 10b [10]. These results imply a role for persistent subclinical inflammation in uncoupling of bone formation and bone resorption in RA and may explain, at least in part, the lack of significant repair of bone erosions in RA patients.

In an important related study in the TNF-transgenic (TNFtg) murine model of arthritis, an antibody to an inhibitor of the Wnt signaling pathway, DKK1, was administered from the time of disease onset. Blockade of DKK1 prevented the development of bone erosions [11] and also resulted in periosteal bone formation at sites where bone erosion would have occurred. This suggested that the Wnt signaling pathway, and in particular DKK1, may be a critical "switch," regulating whether bone is lost or formed in inflammatory arthritis. DKK1 blockade has also been shown to reduce the TNF-mediated expression of the Wnt pathway inhibitor sclerostin in mature osteoblasts in vitro and in vivo [12]. Furthermore, DKK1 levels are elevated in the serum of rheumatoid arthritis patients [13], and TNF induces DKK1 in synovial fibroblasts [11, 14].

While the Wnt signaling pathway appears to play an important role in the pathogenesis of bone changes in inflammatory arthritis, other local factors may also influence osteoblast function. In the RA joint, synovial tissue is infiltrated by many cell types including macrophages and leukocytes that produce cytokines including TNF, IL-1, IL-6, IL-17, and a growth factor, M-CSF, which all have the potential to regulate remodeling of bone [15].

Selected Cytokines that Regulate Bone in RA

TNF is an important cytokine that promotes osteoclast differentiation and function [6]. TNF has also been shown in vitro to suppress osteoblast-lineage commitment by inhibiting

expression of the transcription factor RUNX2 [16], a factor essential for osteoblast differentiation, leading to a decrease in mineralized bone. The TNFtg mouse model has been used to investigate effects of TNF in inflammatory arthritis. Blocking TNF in this mouse model decreases osteoclastogenesis and bone erosions [17]. TNF is also upstream of interleukin-1 (IL-1), and IL-1, in turn, provides a positive feedback loop for TNF expression. The effects of TNF on bone remodeling have been reviewed previously [1, 18, 19].

IL-6 is another cytokine that is expressed by many cell types (including macrophages, chondrocytes, and fibroblast-like synoviocytes) that are present in the inflamed joint. Its expression is elevated both in serum and synovium of RA patients [20]. IL-6 is a pleiotropic cytokine that plays a role in B cell differentiation and antibody production and in T cell development, as well as in pannus proliferation via VEGF stimulation [21]. Some controversy still exists regarding the direct effects of IL-6 on osteoclastogenesis. However, it has been shown that in the bone microenvironment, IL-6 interacts with its receptor sIL-6R complex present on osteoblast lineage cells, leading to upregulation of PGE2 synthesis and to an increased RANKL/OPG ratio, enhancing osteoclastogenesis [22]. Inhibiting IL-6 in mouse models of inflammatory arthritis attenuates the development of arthritis [23–25].

IL-6 also promotes the differentiation of Th17 cells to produce IL-17 and IL-17 indirectly increases IL-6 levels in osteoblasts [26]. IL-17 is a potent activator of osteoclastogenesis by increasing RANKL expression in osteoblast-lineage cells and in synovial fibroblasts in RA [27]. Similar to IL-6, IL-17 promotes PGE2 secretion from osteoblasts [28]. IL-17 levels are elevated both in serum and in synovial fluid from RA patients [29]. In animal models of inflammatory arthritis, both joint inflammation and bone erosions are reduced by IL-17 blockade [30••].

IL-23 is a cytokine that is functionally linked to IL-17. IL-23 levels are elevated in patients with early RA [31]. IL-23 deficiency [32] and IL-23 targeting prior to disease onset [33, 34] prevented the development of collagen-induced arthritis in mice. These data suggest a potential role for IL-23 in early RA. In vitro studies have described both inhibition and stimulation of osteoclastogenesis by IL-23, leaving the role of IL-23 in bone homeostasis unclear [35, 36]. IL-23 also induces expression of IL-22, which in turn can promote osteoblast differentiation [37, 38••]. The IL-23/IL-17 (Th17) axis is considered to be important in mouse models of inflammatory arthritis, and these cytokines may exert different effects in various stages of RA development. It has been proposed that blockade of IL-23 or IL-17 might be more effective treatment for patients with early, rather than established RA or when administered in combination with drugs targeting other cytokines (such as TNF) [30••]. This might merit further investigation, although a clinical trial of an oral IL-12/IL-23 inhibitor in RA patients did not demonstrate significant efficacy [39].

Spondyloarthritis: Inflammation and Bone Remodeling

The prominent new bone formation that is a feature of axSpA suggests that different mechanisms are involved in bone remodeling at periosteal sites than at articular sites of inflammation in diseases within the SpA spectrum. Some pathways may be shared at both sites, including the Wnt signaling pathway, the IL-23/IL-17/IL-22 axis, and other cytokine pathways, as outlined below and summarized in Table 1. The enthesis and the synovio-enthesial complex (SEC) have been considered as a site of initiation of the disease in animal models of SpA, with inflammation first affecting the enthesis and subsequently involving the synovium, rather than vice versa [40, 41].

The Wnt Signaling Pathway in SpA

It is important to note that several mouse models of inflammatory arthritis used to investigate RA pathogenesis and effects on bone have also been used to study effects on bone in SpA. This is because many of these models develop both articular erosions *and* enthesial bone formation; such models include the K/BxN serum transfer model, collagen-induced arthritis (CIA), and the SKG mouse model. TNF transgenic (TNFtg) mice (overexpressing TNF) also develop an RA-like peripheral arthritis and concomitantly develop bilateral sacroiliitis. However, no syndesmophytes are formed in these mice. This model of inflammatory arthritis, nevertheless, has shed some light on the pathogenesis of bone formation in SpA; particularly, it has highlighted the importance of the Wnt signaling pathway [11], the activation of which leads to bone formation on periosteal surfaces. This is contrary to what is observed in RA, where inhibitors of Wnt signaling may promote bone erosion, by inhibition of osteoblast function, and inhibit erosion healing. In associated translational studies, lower serum levels of functional DKK1 were found in ankylosing spondylitis (AS) patients who had greater numbers of syndesmophytes than those patients with higher levels of DKK1, again implicating DKK1 (and the Wnt signaling pathway) as a regulator of outcomes for bone [42].

The Wnt pathway inhibitor sclerostin (gene name SOST) has also been implicated in AS pathogenesis. Decreased sclerostin levels (and presumably increased Wnt signaling and osteoblast differentiation) in AS patients are associated with an increased number of syndesmophytes [43]. Treatment of TNFtg mice with anti-sclerostin antibody was shown to inhibit periarticular and systemic bone loss and to repair erosions when combined with a TNF inhibitor (TNFi) [44•], suggesting that this antibody may have clinical utility in inflammatory arthritis. However, a recent study by Wehmeyer et al. found significant worsening of inflammation in arthritic mice treated with anti-sclerostin antibody [45••]. In fact, the administration of anti-sclerostin antibody augmented synovial

Table 1 Proinflammatory cytokines regulating bone cells: key effects

	RANKL	TNF	IL-6	IL-17A	IL-22	IL-23
Effects on osteoclasts/ bone erosion	Binds to RANK receptor on osteoclast precursor cells leading to their differentiation Expression is upregulated by proinflammatory cytokines in RA	Expands osteoclast precursor pool Promotes osteoclast differentiation and function [6]	Indirectly enhances osteoclastogenesis by interacting with sIL-6 receptor on osteoblast lineage cells, upregulating PGE2 synthesis and increasing RANKL/ OPG ratio [22] Inhibits differentiation of osteoclast precursor cells by disrupting RANK signaling pathways Promotes Th17 cell differentiation	Activates osteoclastogenesis by inducing RANKL expression in osteoblast-lineage cells and synovial fibroblasts in RA [27]		Reported both to inhibit and to stimulate osteoclastogenesis [35, 36]
Effects on osteoblasts/ bone formation	Expressed on osteoblasts, synovial fibroblasts and T and B cells present in the bone microenvironment in RA	Suppresses osteoblast-lineage commitment by inhibiting expression of RUNX2 [16] Inhibits osteoblast differentiation by inducing DKK1	Decreases DKK1 levels in cultured fibroblast-like synoviocytes from inflamed peripheral joints and thus may promote osteoblast differentiation	Suppresses bone formation by inhibiting Wnt signaling in osteoblasts [59] Promotes bone formation by stimulating differentiation of osteoblast mesenchymal progenitor cells in a mouse model of bone fracture repair [58]	Promotes osteoblast function by inducing pro-osteogenic factors [38]	Overexpression in mice promotes enthesial bone formation [38] Induces expression of IL-22 [38]

inflammation in several murine arthritis models driven by TNF. It was further demonstrated that sclerostin inhibits signaling pathways downstream from TNF. Thus, inhibition of sclerostin in patients with inflammatory arthritis could enhance inflammation. Furthermore, it has been accepted that sclerostin is expressed only by osteocytes within the bone matrix; however, this study demonstrated sclerostin expression in fibroblast-like synoviocytes derived from synovial tissues of RA patients [45••]. Clarification of the potential role of sclerostin in the pathogenesis of both SpA and RA thus requires further study.

Selected Cytokines That Regulate Inflammation and Bone in SpA

The IL-23/IL-17/IL-22 axis has emerged as an important pathway in the pathogenesis of SpA and is the target of biological therapies approved for treatment of patients with diseases within the SpA spectrum. The enthesis (and interestingly the aortic root) is an anatomic site where a unique subset of ROR-$\gamma t^{+}CD4^{-}CD8^{-}$T cells expressing the IL-23 receptor resides. These cells were first described by Sherlock et al. in mice in which overexpression of IL-23 was introduced [38••]. These mice developed enthesitis before progressing to overt peripheral arthritis. In addition, expansion of periosteal osteoblasts was observed, with subsequent entheseal and periosteal bone formation. IL-23 induced expression of IL-17A, IL-17F, IL-6, and IL-22, as well as other cytokines/factors. Administration of IL-23p19 antibody at the time of disease induction reduced clinical disease scores, as well as histological evidence of entheseal inflammation. However, inhibition of TNF or IL-6 did not result in improvement of clinical disease. Depletion of Th17 cells also did not have an effect on clinical disease or histological enthesitis scores. Further, supporting an important role for IL-23 in SpA is the elevation of serum IL-23 levels observed in patients with AS [46] and the clinical efficacy of anti-IL-12/IL-23p40 in psoriatic arthritis and AS [47–49]. IL-23R polymorphisms have been identified in patients with diseases in the SpA spectrum, including inflammatory bowel disease and psoriatic arthritis [50, 51]. The exact source of IL-23 in SpA has not been established. However, IL-23 production could occur in the intestine, as a result of HLA-B27 misfolding [52] or in response to endoplasmic reticulum stress triggered by *Chlamydia trachomatis* (a pathogen implicated in reactive arthritis) [53], suggesting additional mechanisms that may contribute to bone formation in SpA.

IL-23 signaling promotes Th17 cell differentiation, resulting in increased IL-17A production [54]. IL-17A is a member of the IL-17 cytokine family, which also includes IL-17B-F. Of these, IL-17A and IL-17F have been implicated in the pathogenesis of inflammation [55]. The number of circulating memory Th17 cells is increased in patients with SpA

[56]. IL-1β and IL-23p19 activate γδ T cells to produce IL-17A, and expression of both IL-1β and IL-23p19 is upregulated in repair tissue in the early stages of bone regeneration [57, 58•]. IL-17A has been shown to promote osteoclastogenesis and bone resorption; however, the effects of IL-17A on osteoblast function are likely complex (see "Biologics"). Further evidence for a role of IL-17A in SpA includes the increase in systemic bone mass and improved osteoblast function after IL-17A inhibition in a mouse model of psoriasis, as well as increased IL-17A serum levels in psoriasis patients [59•]. Finally, IL-17A inhibition has proven efficacious in SpA clinical trials [60–62].

While inhibitors of IL-17A and IL-23 are the newer biologic agents used to treat the SpA spectrum of disease, TNFi have been the mainstay of biologic therapy to control inflammation for more than a decade. TNFi have proven successful in reducing inflammation in SpA [63–71]. Treatment of AS patients with TNFi is also associated with improvement in lumbar spine and total hip bone mineral density [72]. However, TNF induces DKK1 and thus could provide a brake to Wnt signaling, osteoblast differentiation, and bone formation [11]. Due to the potential effects of TNF on the Wnt signaling pathway, it has been hypothesized that TNF inhibition may promote bone formation in patients with SpA, a concept known as the "TNF brake hypothesis." This hypothesis arose when syndesmophytes were noted more likely to form after resolution rather than persistence of MRI inflammation of vertebral lesions in AS patients treated with TNFi [73, 74]. Details of the specific sequence of MRI features (inflammation vs fatty degeneration at vertebral edges) that predict syndesmophyte formation have been debated and have raised questions as to the validity of the "TNF brake hypothesis" [75]. Nevertheless, the component of time is proposed to be important in relation to radiographic progression in AS with TNF blockade. Alternating periods of inflammation (high TNF, high DKK1) and its resolution (low TNF, low DKK1) could alter the cytokine milieu and bone microenvironment in favor of bone formation [76•]. If inflammation were to be prevented entirely, early in disease, subsequent bone formation might be unlikely to occur. In support of this concept, initiating TNFi therapy 10 years after the onset of AS is associated with faster radiographic progression than when TNFi treatment is initiated earlier [77].

IL-6 is another pro-inflammatory cytokine that may regulate inflammation in SpA. IL-6 levels are increased in psoriatic skin lesions [78] and in synovial fluid of PsA patients, at levels similar to those in RA [79, 80]. IL-6 serum levels correlate with disease activity, specifically with the number of joints affected, and with ESR and CRP [81]. However, except as mentioned above, the available data do not support a significant, specific role for IL-6 in bone remodeling in SpA.

Biologics in Spondyloarthritis and Rheumatoid Arthritis

Study of the pathogenic mechanisms of bone resorption and formation in inflammatory arthritis, as outlined above, has suggested therapeutic approaches in SpA, some of which have been adopted after they demonstrated success in treating RA. Prior reviews have discussed the effects of therapeutic interventions on bone erosion and osteopenia/osteoporosis in RA [1, 2•, 82]. Here, we will focus on therapeutic responses in peripheral and axial SpA with an emphasis on outcomes for bone, as summarized in Table 2.

Assessment of Radiographic Progression in Axial and Peripheral SpA

Structural damage in AS is associated with a decline in physical function [86]. A goal of clinical trials of targeted biologic agents in SpA is to slow or halt structural progression, both in peripheral joints and in the spine. Ideally, therapeutic

Table 2 Inhibition of structural damage progression on imaging by biologics in SpA and RA

Drug	Target	RA	PsA*	AS**
Currently in clinical use				
etanercept	TNF	+	+	ND
infliximab	TNF	+	+	ND
adalimumab	TNF	+	+	ND
certolizumab pegol	TNF	+	+	+ [83]
golimumab	TNF	+	+	ND
abatacept	T cell activation	+	+	ND
tocilizumab	IL-6R^{O}	+	ND	ND
rituximab	B cell	+	ND	ND
ustekinumab	IL-12/IL-23	ND	+	+
secukinumab	IL-17A	ND	+	+ [84]
Currently under investigation				
sirukumab	IL-6	+ [85]	ND	ND
sarilumab	IL-6	+	ND	ND
ixekizumab	IL-17A	ND	+	ND
brodalumab	IL-17R^{O}	ND	ND	ND

+ indicates inhibition of structural damage progression either by MRI or plain radiographs

- indicates no effect on inhibition of strutural damage progression on imaging

ND no imaging data available

*Peripheral arthritis in PsA

**Axial arthritis in AS

^{O} R denotes "Receptor"

intervention would prevent both erosion and ankylosis of joints, thereby reducing disability and improving quality of life.

To assess structural progression in patients with SpA in clinical trials, both plain radiographs and MRI have been used. Scoring methods used to quantitate structural change on plain radiographs of the spine include the Bath Ankylosing Spondylitis Radiology Index (BASRI), the Stoke Ankylosing Spondylitis Spine Score (SASSS), and the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Of these three scoring systems, the mSASSS has been shown to be the most sensitive to structural change [87]. This system scores the presence of syndesmophytes; vertebral body erosion, sclerosis, or squaring; and bridging at the anterior vertebral corners on plain radiographs of the cervical and lumbar spine on a scale of 0 to 72 [88]. Interestingly, structural changes in the sacroiliac joints (SI) would contribute minimally to the overall mSASSS score and thus have been excluded from this scoring system [87].

MRI of the SI joints and spine is assessed using the Berlin scoring system that evaluates changes in vertebral units, which include facet joints and spinous processes [89]. Such changes include erosion and bone proliferation (syndesmophytes with and without bridging) reflecting progression of structural damage, as well as fatty bone marrow deposition and osteitis (bone marrow inflammation) that can be the earliest signs of inflammation. MRI may be the better imaging modality to assess structural damage in relatively brief trials of biologics in axial SpA, since it detects osteitis in early bone lesions as increased T2-weighted signal on STIR images. Furthermore, MRI can assess SI joint inflammation with greater sensitivity than plain radiographs, which demonstrate only structural changes that have developed as a result of chronic inflammation.

Progression of structural damage in peripheral joints of patients with SpA is evaluated using methods that were developed to assess structural progression in RA. Plain radiographs of the hands and feet are assessed using the van der Heijde modification of the total Sharp score (SvH), which quantitates erosions and joint space narrowing on a scale of 0 to 448 [90]. MRI of the wrists and MCP joints is assessed for synovitis, bone erosion, and bone edema and is graded using the Rheumatoid Arthritis MRI scoring system (RAMRIS) [91].

TNF Inhibitors

The effects of TNF inhibitors (TNFi) in suppressing joint inflammation and preventing structural progression of articular disease in RA and of peripheral arthritis in PsA are well known [92–102]. However, it has been difficult to demonstrate the effects of TNFi on the progression of spinal involvement in axSpA. Each of the five commercially available TNFi has demonstrated efficacy in controlling inflammation in randomized, placebo-controlled, double-blind, phase 3 clinical trials in patients with axSpA [63–67] and, other than infliximab, also in patients with non-radiographic axSpA [68–71]. In these prospective studies, MRI evidence of osteitis improved with TNFi treatment. Inhibition of syndesmophyte formation was demonstrated in a retrospective study that compared AS patients treated continuously with infliximab over 8 years to a historical cohort of AS patients who had not received a TNFi. Patients treated with infliximab developed significantly fewer new syndemophytes compared to the historical cohort. However, overall progression of structural change, as assessed by the mSASSS, was similar in both groups [103].

In a prospective study that included patients with early disease, plain radiographs of the spine were performed every 2 years in 334 patients with AS who were receiving both an NSAID and a TNFi. Over longer than 4 years, TNFi treatment was associated with a 50 % reduction in the likelihood of structural progression (defined as an increase of ≥1 mSASSS unit/year). Patients who delayed initiating TNFi treatment for >10 years were more likely to exhibit structural progression than those who began treatment earlier [77]. This study differed from previous trials in that it followed patients on treatment over a longer period of time, which might account for its ability to demonstrate inhibition of structural progression.

IL-6 Inhibitors

IL-6 inhibition has demonstrated clinical efficacy in patients with RA [104]. In patients with early RA, circulating IL-6 levels correlate with synovitis, as evaluated by musculoskeletal ultrasound, and with progression of structural damage, as assessed on plain radiographs using the SvH score [105]. Treatment with tocilizumab has resulted in inhibition of progression of structural joint damage, both in patients with established RA [106] and in those with early RA [107]. Similarly, treatment with sarilumab, another monoclonal antibody to the IL-6R, inhibited structural progression in patients with established RA who had been inadequately responsive to methotrexate [108].

The reduction in signs and symptoms and prevention of structural progression by IL-6 inhibition in patients with RA confirms the role of IL-6 in the pathogenesis of this disease. However, in randomized, placebo-controlled clinical trials in patients with AS, neither tocilizumab nor sarilumab demonstrated clinical efficacy for treating signs or symptoms of axial disease [109, 110]. Both studies were of relatively brief duration (12 weeks) and neither evaluated the effect of treatment on progression of joint erosion. These negative studies suggest that, despite elevated levels of circulating IL-6 in patients with AS, this cytokine does not appear to be an important therapeutic target in AS. Nonetheless, clazakizumab, a monoclonal anti-IL-6 antibody, has demonstrated efficacy in treating joint inflammation, enthesitis, and dactylitis in patients with psoriatic arthritis, but studies have not yet been conducted to assess the effect of IL-6 inhibition on structural progression in patients with psoriatic arthritis [111].

IL-17 Inhibitors

IL-17 inhibition has shown variable clinical efficacy when studied in patients with RA. In a randomized, placebo-controlled phase 2 clinical trial of secukinumab monotherapy, this monoclonal antibody directed against IL-17A failed to achieve the primary endpoint of ACR20 response at week 16, a result that may have been due in part to the mix of patients that included TNFi non-responders [112, 113]. In a subsequent randomized, placebo-controlled phase 2 clinical trial conducted in RA patients inadequately responsive to methotrexate and naïve to TNFi, the proportion of ACR20 responders to secukinumab plus methotrexate also was not statistically significantly greater than that to methotrexate alone [114•]. In these studies, however, significantly more patients treated with secukinumb achieved secondary endpoints, including reduction in DAS28 and of CRP, than did patients treated with placebo.

In contrast, treatment with ixekizumab, another monoclonal anti-IL-17A antibody, yielded a significantly greater proportion of ACR20 responders than did placebo in RA patients who either were naïve *or* had been inadequately responsive to TNFi [115•]. However, a randomized, controlled phase 2 clinical trial in which RA patients inadequately responsive to methotrexate and naïve to TNFi received either monotherapy with brodalumab, a monoclonal antibody directed against the IL-17 receptor (IL-17R), or placebo also did not achieve statistically significant improvement in its primary endpoint of ACR50 response or in the secondary endpoint of ACR20 response, each at week 12 [116].

Additional studies may be warranted before concluding that IL-17 inhibition is ineffective treatment for RA. IL-17 inhibition may be more effective in early RA than in established disease, and combined inhibition of IL-17 and other cytokines may be more effective in treating inflammatory arthritis than inhibition of IL-17 alone [30••]. In support of this hypothesis is the inverse relationship between Th17 levels at baseline and the response of RA patients to TNFi [117]. Additionally, the inhibition of both IL-17 and TNF using a bispecific anti-TNF/IL-17 antibody more effectively reduced inflammation and bone destruction in a mouse model of inflammatory arthritis than did inhibition of either cytokine alone [118•].

Two prospective randomized, placebo-controlled clinical trials have demonstrated efficacy of secukinumab in PsA [60, 61]. However, in only one of these studies were radiographic data obtained to assess progression of structural damage in peripheral joints [61, 119]. Among secukinumab-treated patients, 72 % of whom were TNF-naïve and 59 % of whom were receiving concomitant methotrexate, inhibition of structural damage progression was sustained over 52 weeks, as assessed with the SvH score. Notably, progression of structural damage was reduced, irrespective of prior TNFi or concomitant methotrexate use. Ixekizumab and brodalumab each has also shown clinical efficacy in PsA [120, 121], but only the clinical trial of ixekizumab acquired radiographic data to assess structural progression. Ixekizumab treatment significantly reduced the change in the SvH score, compared to that observed with placebo. Although inhibition of structural damage progression in peripheral joints has been established with IL-17A inhibitors in SpA, no imaging data regarding progression of axial skeletal structural damage in AS have been published to date for secukinumab in manuscript form. However, one abstract [84] reports initial data that suggest inhibition of radiographic progression in AS (see Table 2). Additional studies are needed to address this subject.

It is difficult to predict the response to IL-17A blockade on bone formation, as there have been conflicting results regarding the effects of IL-17A on osteoblast function. Several studies have demonstrated that IL-17A inhibits the differentiation of calvarial osteoblasts [59•, 122] and there is a growing body of evidence that IL-17A suppresses osteoblast differentiation by inhibiting Wnt signaling in osteoblasts and osteocytes in the setting of inflammatory conditions associated with arthritis, such as psoriasis [59•]. Thus, IL-17A blockade could promote periosteal bone formation by osteoblasts. However, it has also been shown that IL-17A promotes bone formation by stimulating the differentiation of osteoblast mesenchymal progenitor cells [58•]. This has been demonstrated in a mouse model of bone fracture repair and in human mesenchymal cell differentiation studies [123]. It is likely that IL-17A has differential effects on osteoblasts, depending on their stage of cellular differentiation at the time when they encounter the cytokine. It also may be that injury-associated bone repair differs from the mechanical type of bone formation that occurs at periosteal/enthesial sites. In any case, if inflammation (and not just mechanical stress) is promoting periosteal/enthesial bone formation and IL-17A blockade reduces inflammation, the direct effects of this cytokine on osteoblasts may be far less relevant.

IL-12/23 Inhibitors

Ustekinumab is a monoclonal antibody directed against the p40 subunit present in both the IL-23 and IL-12 heterodimers. Hence, this antibody binds to and inhibits the action of both cytokines. The efficacy of ustekinumab in psoriatic arthritis has been demonstrated in two phase 3 randomized, placebo-controlled clinical trials: PSUMMIT-1 [48] and PSUMMIT-2 [47]. Ustekinumab was effective even in patients previously treated with TNFi, among whom the proportion of ACR20 responders was 35.6 % in ustekinumab-treated patients and 14.5 % in placebo-treated patients. In both PSUMMIT-1 and PSUMMIT-2, structural damage observed in radiographs of the hands and feet, assessed using the SvH score modified for PsA, progressed significantly less over 24 weeks among patients treated with ustekinumab than among those who received placebo [124]. This inhibition of structural damage progression

was maintained through 52 weeks in both studies and for up to 2 years in the PSUMMIT-1 extension study [125].

Ustekinumab has also demonstrated efficacy in AS [49]. In a prospective, open-label, single-arm, proof-of-concept trial that excluded TNFi non-responders, 20 patients with active AS received ustekinumab 90 mg at baseline, week 4 and week 16: MRI of the sacroiliac joints and spine was performed at baseline and week 24. The primary endpoint of an ASAS40 response at week 24 was achieved by 65 % of patients. Clinical responses were observed more often in younger patients who had a shorter duration of symptoms, less functional limitation, higher CRP levels, and more evidence of sacroiliac joint and spine inflammation on MRI at baseline. Evidence of active inflammation (osteitis and bone marrow edema) on MRI, scored according to the Berlin scoring system, decreased significantly by 31 % in the spine and 41 % in the sacroiliac joints. Although the data from this study are encouraging, additional studies of longer duration that acquire conventional radiographs are needed to assess the potential inhibitory effect of ustekinumab on bone proliferation and ankylosis in axial SpA.

Targeting B and T Cells

Rituximab, a chimeric monoclonal antibody that targets CD20+ B cells, effectively reduces signs and symptoms and inhibits progression of structural joint damage in RA. A multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trial of rituximab demonstrated significant reduction of disease activity and a modest effect on slowing of structural progression over 24 weeks [126]. In another phase 3 study in which RA patients who had been inadequately responsive to TNFi were treated with the combination of rituximab and methotrexate, progression of structural joint damage was slowed over 56 weeks; the mean change from baseline in the total Genant-modified Sharp score was significantly lower for the combination of rituximab plus methotrexate than for methotrexate alone [127]. This inhibition of structural damage progression was sustained through 2 years after the initial rituximab treatment, with re-treatment administered every 6 months if needed [128]. Similar results were observed in patients with early RA treated with the combination of rituximab plus methotrexate in the randomized, double-blind, placebo-controlled IMAGE trial [129]. However, data on the efficacy of rituximab in SpA are limited. Preliminary studies in patients with SpA suggest that rituximab may have only a modest effect on inflammation and no effect on progression of structural damage in axial disease [130, 131].

Abatacept is a recombinant Fc fusion protein containing the extracellular domain of human CTLA4, which interferes with T cell co-stimulation by inhibiting the interaction between T cells and antigen presenting cells. In an open label, 24-week pilot study [132] abatacept was administered to patients with active AS who either had responded inadequately or were naïve to TNFi. Only 13 % of TNFi-naïve patients and none of the TNFi inadequate responders achieved the primary endpoint of an ASAS40 response. Thus, abatacept appears to have limited efficacy in AS, and there are no data regarding its effect on progression of structural damage in the axial skeleton.

Conclusion

Inflammation in RA and SpA disrupts normal bone homeostasis leading to an imbalance of bone resorption and formation that favors resorption in peripheral joints in both RA and SpA and formation at periosteal/enthesial sites in SpA. Research conducted in animal models of inflammatory arthritis and observation of the responses of human disease to therapeutic interventions have contributed to a greater understanding of the pathways and cytokines involved in the response of bone to inflammation in RA and SpA, including the IL-23/IL-17 axis. As more data emerge regarding both the clinical and radiographic outcomes of targeted biological treatment in RA and SpA, the role of these pathways in disease pathogenesis will be elucidated.

Compliance with Ethical Standards

Conflicts of Interest EG reports grants from AbbVie Inc, personal fees from AbbVie Inc, Eli Lilly and Company, GlaxoSmithKline PLC, Novartis Pharmaceuticals Corporation, Sanofi, and UpToDate.

JK reports grants and personal fees from AbbVie Inc, Genentech Inc, GlaxoSmithKline PLC, UCB Inc, Eli Lilly and Company, Pfizer Inc, Roche Laboratories Inc, personal fees from Amgen, Inc, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Crescendo Bioscience Inc, Epirus Biopharmaceuticals Inc, Hospira Inc, Janssen Biotech Inc, Merck Sharp & Dohme Corp, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals Inc, Samsung Bioepis, Sandoz Inc, and UpToDate.

KU and ZS declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any primary studies with human or animal subjects performed by the authors.

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- • Of importance
- •• Of major importance

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