REVIEW

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Osteoporosis in Rheumatic Diseases: Anti-rheumatic Drugs and the Skeleton

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Abstract

Osteoporosis in rheumatic diseases is a very well-known complication. Systemic inflammation results in both generalized and localized bone loss and erosions. Recently, increased knowledge of inflammatory process in rheumatic diseases has resulted in the development of potent inhibitors of the cytokines, the biologic DMARDs. These treatments reduce systemic inflammation and have some effect on the generalized and localized bone loss. Progression of bone erosion was slowed by TNF, IL-6 and IL-1 inhibitors, a JAK inhibitor, a CTLA4 agonist, and rituximab. Effects on bone mineral density varied between the biological DMARDs. Medications that are approved for the treatment of osteoporosis have been evaluated to prevent bone loss in rheumatic disease patients, including denosumab, cathepsin K, bisphosphonates, anti-sclerostin antibodies and parathyroid hormone (hPTH 1–34), and have some efficacy in both the prevention of systemic bone loss and reducing localized bone erosions. This article reviews the effects of biologic DMARDs on bone mass and erosions in patients with rheumatic diseases and trials of anti-osteoporotic medications in animal models and patients with rheumatic diseases.

Keywords Rheumatoid arthritis · Ankylosing spondylitis · Anti-rheumatic drug · Osteoporosis · Bone loss · Anti-osteoporotic medication

Introduction

Rheumatic diseases are chronic inflammatory diseases of autoimmune origin. Rheumatoid arthritis (RA) is the most prevalent rheumatic disease with both articular and extra-articular involvements. Bone loss has been recognized as a complication of RA for more than a century [1] and more recently for ankylosing spondylitis (AS) [2, 3]. The bone loss generally presents in two different forms: localized bone erosion with bone loss around an inflamed joint and systemic bone loss, or generalized osteoporosis, which is one of the most common extra-articular manifestations of the disease. The generalized bone loss associated with RA results in an increased risk of osteoporotic fractures in all age groups, both sexes, and various anatomic sites compared to non-RA patients, with an overall relative risk of 2.25 (95% CI 2.25–3.83) [4, 5]. An increased risk of osteoporosis has also been reported for patients with Ankylosing Spondylitis [6].

This paper will discuss the biology of bone loss in RA and studies that have evaluated the effects of medications prescribed for the treatment of rheumatic diseases on localized and generalized bone mass. We refer the readers to the manuscript by Paine and Richlin in this publication [7] for a more detailed description of the biology of bone loss in seronegative spondyloarthropathies, especially psoriatic arthritis (PsA). We will also review studies of localized and generalized bone loss in AS and PsA.

Methods

In order to document the currently available data on both biologic and conventional DMARDs effects on bone turnover and BMD, we performed a primary literature search in PubMed using a few search formulas. We used the following MeSH terms: rheumatoid arthritis, spondyloarthritis,

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psoriatic arthritis, ankylosing spondylitis, hydroxychloroquine, methotrexate, sulfasalazine, leflunomide, TNF-alpha inhibitors, adalimumab, infliximab, certolizumab, golimumab, etanercept, abatacept, CTLA-4 Ig, tocilizumab, rituximab, IL-6 inhibitors, tofacitinib, secukinumab, bone mineral density/BMD, and bone turnover markers. The MeSH terms were searched on PubMed and were limited to articles published in English.

Localized Bone Erosion

In RA, chronic joint inflammation with long standing synovial hyperplasia results in articular bone damage consisting of subchondral cysts, sclerosis, erosive bone damage, and cartilage loss [8, 9]. T cells in the synovium secrete IL-1, IL-6, and IL-17, which induce RANKL production in fibroblast-like synoviocytes (FLS, also known as synovial fibroblasts) [9]. The inflammatory induced increase in RANKL expression is not balanced by an increase in its physiologic inhibitors, mainly osteoprotegerin (OPG) [10]. The binding of RANKL to the RANK receptor on osteoclast precursors and mature osteoclasts leads to the stimulation of several signaling pathways for osteoclast differentiation and activation [9]. In addition, synovial inflammation results in increased production of Wnt/β-catenin signaling proteins, including dickkopf-1 (DKK-1), that inhibit the maturation of osteoblasts [11]. Thus, the interaction between the immune system and skeletal system leads to increased osteoclastogenesis and reduced osteogenesis, which is followed by bone loss.

Systemic Bone Loss

The prevalence of osteoporosis in RA subjects is higher than that observed in an age and gender matched reference group [12]. The risk of fracture is increased at vertebral and appendicular sites of the skeleton [4], and the fracture risk assessment tool FRAX, the most frequently used tool to determine fracture risk worldwide, has RA as one of the seven most important risk factors for fragility fractures [13]. The systemic bone loss in RA is known to involve at least three risk factors: glucocorticoid use, reduced physical activities, and chronic systemic inflammation [14]. The effect of glucocorticoids on bone loss in RA is now interpreted with caution as glucocorticoids have dual effects on bone in RA. Since glucocorticoids reduce the inflammation in RA, they theoretically can reduce some of the localized bone loss [15]; however, glucocorticoids initially increase bone resorption, followed by a delayed and prolonged suppression of bone formation and osteoblast and osteocyte apoptosis [9, 16]. Yao et al. reported glucocorticoid excess in mice resulted in a rapid upregulation of genes involved with osteoclast activation and function, followed by the expression of genes

associated with matrix degradation [16]. After a few weeks, the expression of genes associated with osteoblast activation and maturation decreased, and expression of Wingless (Wnt) antagonists, including DKK-1, Wnt inhibitory factor 1, and sclerostin, increased. In addition, there was early increased expression of genes associated with adipogenesis. Mesenchymal stem cells are the precursors of both osteoblasts and adipocytes, and glucocorticoids appear to favor the production of adipocytes [16]. This could lead to a reduction in the number of potential progenitor cells that differentiate into osteoblasts, indirectly affecting bone formation and bone mass.

The pro-inflammatory cytokines that are present in the systemic circulation with inflammatory arthritis stimulate bone resorption, while simultaneously suppressing bone formation. Macrophage colony stimulating factor (M-CSF) and tumor necrosis factor alpha (TNF-α) stimulate the RANK/RANKL pathway [8], and TNF-α is a potent inducer of DKK-1 [17]. The Wnt signaling pathway regulates bone formation via interaction with several signaling pathways, including Wnt/β-catenin pathway (designated as the canonical Wnt pathway), the non-canonical Wnt/planar cell polarity pathway, and the Wnt/calcium pathway [18]. The binding of Wnt ligands to a dual receptor complex, comprising frizzled and either low-density lipoprotein receptor-related protein (LRP) 5 or LRP6, initiates the signaling of the canonical pathway, which leads to inactivation of a multiprotein β-catenin complex. β-Catenin then accumulates in the cytoplasm, and subsequently translocates to the nucleus, where it mediates the transcription of genes that control osteoblast differentiation and OPG, an inhibitor of osteoclast differentiation [19]. The elevated production of DKK-1 by TNF-α reduces Wnt-induced production of OPG, which results in an increase in the RANKL/OPG ratio [17, 18]. The imbalance of RANKL/OPG contributes to accelerated osteoclast resorption, leading to decreased bone mass.

Conventional Synthetic DMARDs, Biologic DMARDs, and Bone Mass in RA

Medications prescribed to reduce joint inflammation for RA and other rheumatic diseases can have effects on bone mass. Conventional synthetic disease modifying agents (DMARDs) including hydroxychloroquine, sulfasalazine (SSZ), methotrexate (MTX), and leflunomide effects on bone mass have been evaluated in a few studies. A study of hydroxychloroquine's effects on bone turnover in RA patients before and after 3–6 months of treatment, found the level of β-CTx, a marker of bone resorption, at 3 months was not different from the baseline value; however, β-CTx was significantly decreased after 6 months [20]. A cross-sectional study evaluated the effects of SSZ on BMD at the lumbar spine and hip in RA subjects compared to a patient

cohort treated with all other available oral DMARDs (MTX, cyclosporin A, chloroquine, injectable gold, auranofin, podophyllin, or penicillamine) and found significantly increased trochanteric BMD with SSZ with no change in the other group [21]. Another study assigned RA patients to treatment with either MTX (15 mg/week) or leflunomide (20 mg/day) for 2.5 years and reported no change in periarticular BMD measured by digital X-ray radiogrammetry or erosions [22].

MTX is the most common DMARD used to treat RA. MTX is frequently used in very high doses to treat malignancies especially in children, and there have been reports of reduced bone mass [23]. A meta-analysis was performed to determine the effect of MTX on bone mass in RA subjects, and of the six studies analyzed, there was no change in femoral neck or lumbar spine BMD for RA or juvenile RA patients on long-term, low-dose MTX [24–30]. Other studies have evaluated the effects of MTX on bone turnover markers. One study randomly assigned RA subjects to treatment with either salazosulfapyridine ($n = 13$), actarit ($n = 14$), or 4–10 mg of MTX ($n = 30$) per week and assessed study subjects after 3 and 6 months of treatment. There were only changes in the MTX group that included significantly reduced bone resorption marker urine NTX/Cr from the baseline value, and urine DPD/Cr, another resorption marker, also declined; however, it was only significantly different from the baseline value after 6 months, and serum bone alkaline phosphatase (BAP) had no significant change during the 6-month study period [31]. A retrospective study of RA subjects treated with MTX at 7.5 mg/week ($n = 30$) or SSZ 2 g/day ($n = 30$) found no significant differences in BMD measured at the lumbar spine and femoral neck between MTX and SSZ groups, or in change in BMD from the baseline value in either group [32]. Studies have also reported fracture risk changes associated with MTX treatment. A cross-sectional and longitudinal study of 117 RA patients over a 4-year period found no change in fracture risk for RA patients taking MTX compared to those not receiving MTX [33].

Tumor Necrosis Factor Alpha Inhibitors

The introduction of biologic DMARDs for the treatment of RA has had a significant influence on both the reduction of inflammation and associated bone loss. TNF-α inhibitors were the first biologic DMARDs to be used in the treatment of RA, and remain the most widely used in clinical practice. At present, there are five TNF-α antagonists approved for the treatment of RA: infliximab, adalimumab, etanercept, certolizumab, and golimumab. In an animal model of collagen-induced arthritis, TNF-α blockage led to a decrease in joint erosions, generalized bone loss, and synovial inflammation [34]. In RA patients, the effect of TNF-α blockade on bone has also been extensively studied. Initial studies of the effect of infliximab on bone turnover markers reported conflicting results. A study of 36 RA patients treated with infliximab and MTX found both the bone resorption marker N-terminal telopeptide (NTX) and the bone formation marker osteocalcin significantly decreased from baseline levels after 14 weeks, while bone resorption marker deoxypyridinoline (DPD) reduction was delayed until 6 months of treatment. Additional follow-up determined no significant changes occurred in any of the bone turnover markers between the 6- and the 12-month measurement, indicating short-term effects on bone turnover in infliximab-treated patients [35]. This observation was supported by a study with 48 infliximab-treated RA patients that showed decreased levels of CTX-1 at 6 and 22 weeks after biologic administration, but levels returned to baseline at 54 weeks [36]. However, another study of 68 RA patients treated with infliximab found after 6 weeks of treatment, there was an increase in the bone formation markers osteocalcin and N-propeptide of type I procollagen (P1NP) from 21.2 to 23.9 ng/mL and 43.9 to 50.1 µg/mL respectively, and a decrease in the bone resorption marker C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinases (ICTP) from 8.9 to 7.8 µg/mL [37]. Another study of 90 RA subjects treated with infliximab for 1-year reported no change in the serum level of osteocalcin and the bone resorption marker CTX-1 [38]. In addition, 102 infliximab-treated RA patients had significant reductions in the resorption marker B-CTX at 14, 30, and 46 weeks [39]. Finally, Lange et al. reported data on 26 RA patients treated with infliximab for 1 year, and found a significant increase in osteocalcin and a significant decrease in CTX-1 [40]. In summary, changes in markers of bone formation and resorption are present with TNF blocking agents. Also, the baseline bone turnover of the RA patients at the time of the initiation of the biologic appears to influence the changes induced by the biologic and bone resorption generally declines.

The introduction of TNF inhibition for the treatment of RA patients has been associated with decreased generalized bone loss [17]. In an open label study, 50 RA patients treated for 1 year with adalimumab + MTX, with or without less than 10 mg/day of prednisone, had no reduction in BMD of the lumbar spine or femur [41]. Another open label study treated 36 RA patients with infliximab for 1 year, measured lumbar spine and hip BMD, and a found a non-significant decrease in hip and increase in lumbar spine BMD [42]. When comparing 90 RA infliximab-treated patients after 1 year of treatment to retrospective data on 99 MTX-treated patients, there was less BMD decrease in the infliximab-treated cohort at lumbar spine and hip [38]. A larger study, the BeST study, randomized 342 RA patients to receive (1) sequential monotherapy (MTX, SSZ, then leflunomide), (2) step-up combination therapy (MTX, SSZ, then hydroxychloroquine), (3) initial combined therapy with glucocorticoids

(MTX or SSZ with prednisone), and (4) initial combined therapy with infliximab (MTX with infliximab). At 1-year follow-up, median lumbar spine and hip BMD decreased by 0.8 and 1%, and showed no variation between groups [43].

Multiple other studies reported on both central and localized bone changes. An open cohort study on 102 RA patients treated with infliximab for 1 year reported no reduction in BMD of lumbar spine and hip; however, there was progressive metacarpal cortical bone loss of 0.8% [39]. Also, 52 RA patients treated for more than 2 years with infliximab had BMD measurements at baseline, and after 2 years and had no change in the BMD of the lumbar spine and hip, while bone mass of the metacarpal bones declined [44]. In another cohort study consisting of 184 RA patients treated with adalimumab for 1 year, there was no change in BMD at lumbar spine and hip, but metatarsal BMD was significantly decreased by 1.41%. The study also included a follow-up after 4 years of treatment and found a significant decrease in BMD measured at the hip, but no change in BMD measured at the lumbar spine. The metatarsal bone loss continued to decrease by an additional 0.83%/year [45].

IL-6 Inhibition

Interleukin-6 (IL-6) inhibitors approved for the treatment of RA are known to inhibit osteoclast activity, which may over time influence local and generalized bone mass in RA subjects. The first approved IL-6 inhibitor, tocilizumab, effects on bone turnover and BMD have been studied, and results vary. The OPTION study was the first to analyze tocilizumab effects on bone turnover markers. This multicenter, double-blind, placebo-controlled trial included 416 patients, analyzed the bone resorption markers CTX-1 and ICTP, and found a significant decrease in both bone resorbing markers at 4, 16, and 24 weeks, and an increase in the bone formation marker PINP, which was only significant 4 weeks after treatment initiation [46]. A second large, randomized, double-blind, placebo-controlled, trial analyzed 299 patients treated with either tocilizumab + MTX, or placebo + MTX and found a significant reduction in the CTX-1/osteocalcin ratio at 24 weeks [47]. Briot et al. studied RA patients, treated with standard DMARDs for RA and 8 mg/kg of tocilizumab for 44 weeks, and found no change in lumbar spine or total hip BMD, while Chen et al. treated RA patients with tocilizumab for 2 years and reported an increase in femoral neck BMD, but a non-significant increase in lumbar spine BMD for a subgroup of anti-citrullinated protein antibody (ACPA) positive patients. However, there was no change in the subgroup of RA patients negative for ACPA [48, 49]. Both studies also measured bone formation using P1NP and bone breakdown using CTX, and Chen et al. also measured osteocalcin. While Briot et al.

reported an increase in P1NP and no change in CTX, Chen et al. reported a decrease in CTX and no change in P1NP or osteocalcin. An additional study measured BMD at the lumbar spine and femoral neck 52 weeks after initiating tocilizumab treatment, and found no change in BMD at either the lumbar spine or femoral neck for patients without osteopenia, but a significant increase in both locations for patients with baseline osteopenia [50]. In summary, tocilizumab appears to reduce the increased bone turnover observed in inflammatory arthritis and to improve bone mass in subgroups of RA patients that are ACPA positive, with low bone mass when initiating therapy and treated for 2 years.

Currently, information on bone turnover and mass changes for Kevzara, another IL-6 antagonist recently approved, are not yet available.

Janus Kinase 1 and 3 Inhibitor

Tofacitinib is a selective inhibitor of Janus kinase 1 (JAK1) and Janus Kinase 3 (JAK3) that interferes with the dimerization of signal transducers and activation of transcription (STAT) molecules. This results in inhibition of STAT1 and STAT3 of the JAK-STAT signaling pathway [51]. The efficacy and safety of tofacitinib in active moderate-to-severe RA has been demonstrated, and the inhibition of structural damage in patients receiving tofacitinib has been shown using radiographs [52, 53]. Clinical studies evaluating local and generalized bone mass have not yet been reported with tofacitinib. However, a recent study evaluated the bone effects of tofacitinib in the adjuvant-induced arthritis rat model [54]. Tofacitinib treatment did not prevent inflammation-induced loss of cortical and trabecular bone structure and strength, although at the tissue level bone hardness, measured by nanoindentation, was conserved compared to placebo controls. The difference between local and systemic bone effects of tofacitinib could be explained by complex interactions with bone-related cells by intracellular molecules [54]. JAK1 is expressed in bone cells and is involved in bone formation. Thus, depletion of JAK1 may cause a delay in bone growth. STAT1 inhibits transcription of Runx2 in osteoblasts, and the inactivation of STAT1 leads to an osteoporotic bone phenotype in both Chinese and Caucasians [55]. The JAK-STAT3 signal transduction pathway promotes osteoblastic differentiation. Inactivation of STAT3 in osteoblasts led to lower bone mass and STAT3 mutations increased osteoclast number, bone resorption, and was associated with recurrent fractures in mice [56]. Clinical studies are now underway to determine the long-term effects of tofacitinib on localized and generalized bone mass in rheumatic disease patients.

Anti-CD20 Depletion Rituximab

Rituximab is a CD20 B cell depleting antibody that is approved for the treatment of RA after an ineffective response to oral DMARDs or other biologic agents. To evaluate the effects of rituximab on bone metabolism, a prospective study consisting of 13 patients treated with rituximab measured serum bone turnover markers including alkaline phosphatase, CTX, tartrate-resistant acid phosphatase, and DPD 15 months after treatment was initiated. No changes were found in bone formation markers or tartrate-resistant acid phosphatase, but there was a significant decrease in DPD [57], suggesting a reduction in osteoclast activity. Another open label study measured osteocalcin and NTX in 28 patients before and after 16 weeks of rituximab treatment. There was a non-significant increase in osteocalcin, and no change in NTX [58]. Finally, 16 patients with RA were treated with rituximab for 18 months and subjects classified as clinical responders had an improvement in lumbar spine BMD, and no change in femoral BMD, while in non-responders, there was an improvement in lumbar spine BMD, but a decrease in femoral BMD [59].

Anti-CTLA-4Ig Abatacept

Abatacept is fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4 that is approved for the treatment of RA after an ineffective response to other DMARDs or biologic agents. A murine model of inflammatory arthritis showed that CTLA-4Ig inhibited differentiation and maturation of osteoclasts, suggesting that this antibody may have anti-resorptive effects. This observation was confirmed in an in vitro study, as the addition of CTLA-4Ig dose-dependently decreased osteoclast formation and osteoclast activity measured by a resorption assay [60]. One study in humans randomized 165 RA patients to abatacept or a treatment group receiving either infliximab, etanercept, adalimumab, tocilizumab, or golimumab, and measured BMD before and after 1 year of treatment. They found no significant difference in BMD measured at the lumbar spine, but found a significantly higher increase in BMD measured at the femoral neck in the abatacept treatment group compared to the group receiving other treatments [61].

Ankylosing Spondylitis (AS)

AS is a chronic systemic inflammatory disease that affects the spine and sacroiliac joints [62]. Osteoporosis is considered a common feature of AS, even in early stages of the disease [63]. The prevalence of osteoporosis was 25% at mean age of 38.9 years in AS patients according to the WHO classification, and vertebral fracture was detected in 43%. In a clinical series of 111 AS patients, 23 patients had either a compression or biconcave spinal fracture [3].

The skeletal phenotype of seronegative spondyloarthropathies (e.g., AS and Psoriatic Arthritis, PsA) is different from that observed in RA, as in the former there can be pathologic bone formation. This new bone formation may present as syndesmophytes that are usually symmetric and can be bridging in AS, sacroiliitis, or sacroiliac joint ankylosis. Bone formation in the peripheral skeleton may present with enthesophytes, periosteal new bone formation, and ossification of the enthesis.

The biologic bone mass changes in the axial and peripheral skeleton in AS differ from RA. In AS, there is increased bone resorption in the axial and peripheral skeleton due to systemic inflammation, while there can be an increase in bone formation at the enthesis sites. Recent studies from the mouse enthesis have identified T cells with an IL23 receptor, which when stimulated with IL-23 increase the production of other pro-inflammatory cytokines including TNF, interleukin-17 (Il-17), and interleukin-22 [7, 64, 65]. Also IL-23 can increase the production of bone morphogenetic proteins that can stimulate new bone formation. Overexpression of the IL-23 in mice produced enthesitis and arthritis with features like SpA [66]. These new observations help to explain how our anti-rheumatic treatments help patients with AS (Fig. 1).

Conventional Oral DMARDs

Conventional oral DMARDs, including sulfasalazine and MTX, have not been studied for their effects on localized and generalized bone loss in AS subjects.

Biologic Agents and BMD in AS

TNF blockers have been successfully used to reduce disease activity in the treatment of ankylosing spondylitis [67]. Infliximab was shown to increase BMD in 29 AS patients by 3.6% at the lumbar spine and 2.2% at the total hip, compared to baseline after 6 months [68]. In support of these results, when 279 patients were randomly assigned to placebo or infliximab, the infliximab group showed significantly greater increased BMD measured at the spine and hip than placebo at 24 weeks [69]. Another study assessed BMD in 90 AS patients in four different treatment groups: (1) conventional treatment (NSAID, SSZ, or MTX), (2) bisphosphonate + conventional, (3) anti-TNF agent (infliximab, etanercept, and adalimumab) + conventional, or (4) bisphosphonate + Anti-TNF agent + conventional. At follow-up of less than 3 years, there was a significant increase in lumbar spine BMD for all groups except bisphosphonate + conventional treatment. There was no significant

Fig. 1 Site of action of biologic anti-rheumatic medications and osteoporosis medications
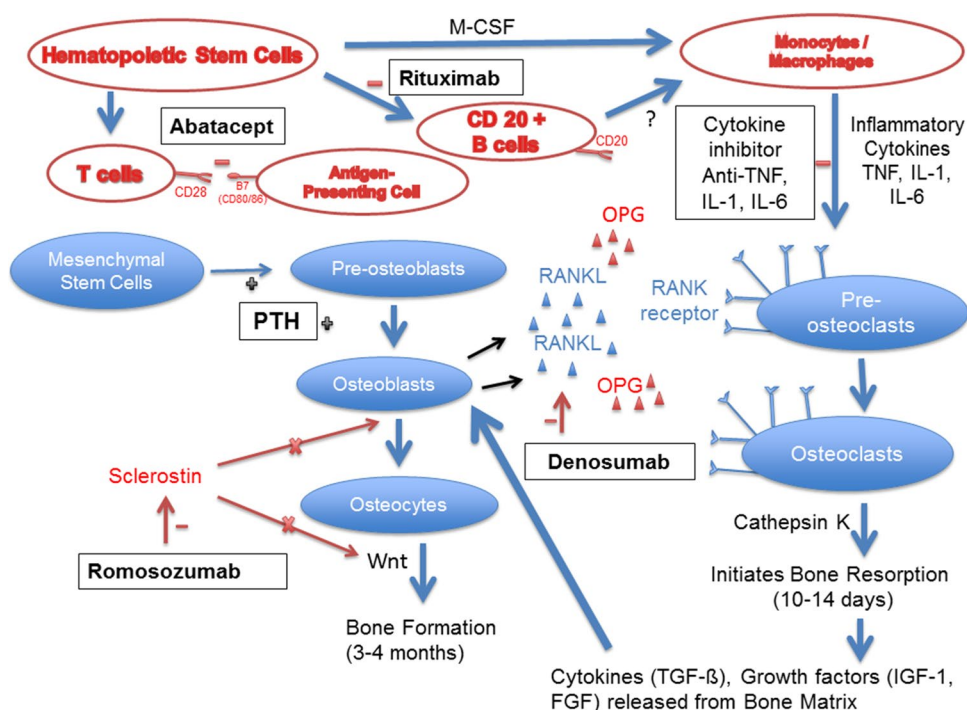
change in BMD measured at femoral neck, upper neck, or trochanter for any groups [70]. The increased BMD are likely confounded by the spine ossification, a chronic post-inflammatory feature that is characteristic of AS, because these ossifications usually require many years to develop, and the effect of the biologics on BMD in AS is usually fairly rapid [20]. Another study evaluated bone formation in 29 patients with SpA unresponsive to MTX, SSZ, or NSAIDs after 6 months of infliximab treatment, and found the bone formation marker osteocalcin to be elevated with the median change of 1.45 μg/L (− 2.10 to 42.10, $p = 0.013$) compared to the baseline value [68]. Radiographs of the cervical and lumbar spine from 257 AS patients treated with etanercept for up to 96 weeks were compared with radiographs from 175 AS patients in a large prevalence cohort who had not been treated with anti-TNF agents, and there was no structural benefit for AS patients received etanercept [63]. When the inhibition of progression of structural damage in the spine was measured by the mean change in the modified Stoke AS Spine Score (mSASSS) (range 0–72) from baseline to 2 years, the failure of inhibition of structural damage progression in AS was confirmed also for adalimumab [69] and infliximab [70].

A number of recent studies have evaluated peripheral joint destruction in AS patients on TNF blocking agents and found that these agents are effective in reducing structural deterioration. These data are summarized in a recent publication [71].

Interleukin-17 Inhibition with AS

Recently, the Th17 T cell and the cytokine it produces, interleukin-17 (IL-17), have been reported to increase joint inflammation and induce osteoclast differentiation and bone destruction in autoimmune arthritis [72]. Preclinical studies have reported that IL-17 can stimulate synoviocytes to produce RANKL and activate osteoclastogenesis [73]. Secukinumab is a fully human IgG1 monoclonal antibody that selectively binds to and neutralizes IL-17A. Secukinumab is approved for the treatment of moderate-to-severe AS. Two phase III studies evaluated the efficacy and safety of secukinumab (loading dose 10 mg/kg baseline, weeks 2 and 4) followed by either 300 mg every 4 weeks or 150 mg every week for 4 weeks. After 16 weeks, significant improvements in the AS International Society criteria for 20% improvement (ASAS20) were nearly 60% for both secukinumab IV-300 mg and IV-150 mg compared to placebo at 37%, and the improvements were maintained at week 52 [74]. Other studies of secukinumab in AS have reported similar results [75, 76]. Currently, there are no studies with secukinumab that evaluated localized or systemic bone mass changes; however, the reduction in structural changes within the inflamed joints suggests that bone mass may be improved with the treatment.

Osteoporosis and Psoriatic Arthritis (PsA)

PsA is a systemic inflammatory arthritis in which subjects with a long disease duration can have both localized and systemic bone loss secondary to systemic inflammation, medications used to treat the disease and reduced activity related to joint pain. A cross-sectional study of BMD in patients with PsA reported that low bone mass and osteoporosis were associated with longer average duration of disease [77]. Another cross-sectional and longitudinal study of PsA subjects found the frequency of low BMD and osteoporosis no different from the general population [78].

The Skeletal Phenotype of PsA

The skeletal phenotype of PsA patients is more similar to AS than RA. PsA is associated with increased bone formation at the sites of inflammation. The bone formation in the axial skeleton can take the form of marginal or paramarginal syndesmophytes that are asymmetrically distributed, and sacroiliitis that is frequently asymmetric. In the peripheral skeleton bone formation can be present in the periosteum within the joints as ankylosis, and within the enthesis [7].

The biology of the bone changes in PsA is an active area of research and is reviewed in detail by Paine and Richlin [7]. Briefly, in PsA, there is altered bone remodeling due to an increase in inflammatory cytokines including TNF, IL-1, and Il-17, growth factors, and ill-defined biomechanical factors. Inflammatory cytokines including TNF alpha and IL-17 are released from the synovitis, and stimulate osteoclast maturation and activity indirectly through RANKL production or directly by stimulating osteoclast activity. However, simultaneously, the localized production of IL-23 in the inflamed enthesis can stimulate IL-22 and BMP production, thereby stimulating new bone formation in the inflamed joint [7, 66]. The biology of the bone changes in PsA have informed clinicians about optimal treatments.

Conventional DMARDs and Bone in PsA

There are no studies of the effects of PsA on localized or systemic bone mass in PsA.

Biologic Agents, Bone Mass, and PsA

There are no studies that have evaluated the effect of biologic agents used to treat the inflammatory joint activity in patients with PsA on localized or systemic bone mass. However, there are now seven biologic agents and apremilast FDA approved to inhibit structural damage from PsA, and these studies have been reviewed recently [7]. While all agents, but apremilast, have demonstrated an ability to slow radiographic progression, none have been able to inhibit the new bone formation [7]. Interestingly, many years ago, it was shown that treatment with non-steroidal anti-inflammatory agents (NSAIDs) was able to inhibit the new bone formation in AS patients [79], and additional studies are needed to determine if the NSAIDs may be effective in PsA.

IL-12/23 and Interleukin-17 Inhibition with PsA

While a number of new biologic agents are approved for the treatment of PsA, nearly all of these agents were originally studied and received approval in RA. However, the inhibition of IL-17 and IL-12/23 and IL-23 were initially studied in PsA and we will review the studies briefly.

Interleukin-23 (IL-23) is an inflammatory cytokine and expression is increased in animal models of arthritis. It is associated with enthesitis via activation of T cells that produce Il-17, TNF, and Il-22. A monoclonal antibody to IL-12/23, ustekinumab, was studied in patients with active PsA, and it slowed radiographic progression both in TNF previously treated or TNF naïve PsA subjects [80–82].

Secukinumab is a fully human IgG1 monoclonal antibody that selectively binds to and neutralizes IL-17A. Secukinumab is approved for the treatment of moderate-to-severe psoriasis, PsA. Secukinumab significantly reduced radiographic progression, measured by change from baseline to week 24 in the modified total Sharp/van der Heijde score (SHS) for PsA compared with placebo [83]. In a phase III study of active PsA, radiographic progression using SHS for PsA was inhibited in all secukinumab-treated patients through 52 weeks [84]. Currently, there are no studies with secukinumab that evaluated localized or systemic bone mass changes; however, the reduction in structural changes within the inflamed joints suggests that bone mass may be improved with the treatment.

Anti-osteoporotic Medication in Rheumatic Disease Patients

Bisphosphonates

Bisphosphonates are widely used as anti-osteoporotic medication for decades. Recently, its role for a structural benefit in RA has been highlighted. A study on early RA randomized 39 patients to receive zoledronic acid or placebo, with both groups receiving MTX. Patients were evaluated at 26 weeks for MRI measured hand and wrist erosion, and were 61% lower in the zoledronic acid + MTX group compared to the placebo + MTX group [85]. Also, PsA patients treated with zoledronic acid had a significant reduced MRI measured bone edema [86]. Further studies on bisphosphonates and DMARDs are warranted.

Denosumab

RANK/RANKL/OPG pathway plays an important role in osteoclast differentiation, activity, and survival. OPG is a natural inhibitor of RANKL, and the idea of inhibition of RANKL led to the development of denosumab, a fully human antibody that binds to, and inhibits, RANKL [87]. In a study of RA patients with active disease treated with MTX, denosumab successfully reduced radiographic progression and improved BMD of lumbar spine and total hip 6 and 12 months after treatment, regardless of concomitant glucocorticoid administration, while bone turnover markers were suppressed [88]. In the denosumab treatment group receiving 180 mg of denosumab and no glucocorticoids, BMD at the lumbar spine increased by 2% compared to placebo at 6 months, and 4% at 12 months. In the same treatment group also receiving glucocorticoids, lumbar spine BMD increased by approximately 2.4% at 6 months, and 3.2% at 12 months, compared to placebo. Measurements of total hip BMD showed 1 and 1.7% at 6 and 12 months, respectively, for denosumab without glucocorticoids, and 1.2 and 1.7% for denosumab with glucocorticoids [88].

In a randomized clinical trial, 40 patients with RA received either alendronate or denosumab for 6 months. A post-hoc analysis of changes in bony erosions at the second metatarsal head reported a significant reduction in bone erosion in the denosumab group, but a significant increase in erosions in the alendronate-treated group [89]. However, denosumab had negligible effects on the RA disease activity based on the American College of Rheumatology (ACR) response parameters [90, 91].

Treatment with denosumab was also shown to decrease joint erosion measured with MRI. Metacarpophalangeal joints and wrists were analyzed on 218 patients receiving either placebo or denosumab for 12 months. Patients receiving 180 mg of denosumab showed a decrease in joint erosion measured by MRI at 6 months after treatment; however, those treated with 60 mg showed no significant improvement [91]. 12 months after treatment, patients treated with denosumab showed a significant decrease in the total modified Sharp erosion scores, but no difference in the modified Sharp joint space narrowing score. In addition, bone turnovers markers, serum CTX-1 and serum PINP, significantly decreased in denosumab treated groups compared to the placebo groups at 12 months [91]. An additional analysis of the same study measured lumbar spine and hip BMD and denosumab significantly increased the BMD at the lumbar spine and hip compared to the placebo group at 12 months [91].

Recent publications report that cessation of denosumab therapy can lead to a rapid decrease of BMD, thus increasing risk of fracture [92]. Therefore, it is recommended that either denosumab should be continued without drug holiday, or denosumab should be switched to other osteoporotic medication upon discontinuation, even if BMD is well above values recommended for treatment.

Parathyroid Hormone (PTH) and Analogs

PTH exerts its efficacy depending the route of administration. The continuous administration of PTH leads to increased bone remodeling with bone loss, whereas intermittent, daily, low-dose administration of PTH has an osteoanabolic effect [93]. Since PTH can stimulate bone formation and glucocorticoids reduce bone formation, rheumatic disease patients on chronic glucocorticoids have been treated with PTH. Lane et al. studied osteoporotic postmenopausal women with rheumatic diseases on glucocorticoids and determined that hPTH (1–34) and estrogen increased bone mass at the lumbar spine and hip after 12 months of treatment significantly more than estrogen alone [94]. Saag et al. compared alendronate to teriparatide in glucocorticoid-induced osteoporosis and reported teriparatide was associated with increased bone mineral density at the lumbar spine and total hip with reduced incidence of new vertebral fracture compared with alendronate [95]. Another study in glucocorticoid treated men found treatment with hPTH (1–34) had greater improvements in BMD, microstructure and bone strength than risedronate [96]. Moreover, patients with RA showed greater response to daily hPTH (1–34) administration at the femoral neck at 18 months than postmenopausal osteoporotic patients, and there was a positive effect of biologics combined with teriparatide in elevating bone formation markers [97]. However, a pilot study randomized 20 patients to receive etanercept or etanercept + teriparatide and evaluated patients at 12 months for changes in arthritis erosions. They reported that concomitant administration of etanercept and PTH did not affect healing erosions in early RA patients [98]. Also, another study evaluated the effect of teriparatide on joint erosions in RA patients and reported no significant reduction in erosion volume of hand or wrists following 1 year of treatment with teriparatide or placebo [99].

Conclusion

Inflammatory arthritis results in both generalized and localized changes in bone mass and bone structure. While biologic agents appear to reduce structural deterioration, and periarticular bone loss, the effects on systemic bone mass are limited. Blockade of TNF appears to maintain or modestly increase localized and systemic BMD in subjects with inflammatory arthritis. However, other non-TNF biologic agents approved for rheumatic diseases effects on bone have not been well studied. Additional studies that include biochemical markers of bone turnover, bone density, and

fracture outcomes are needed to better inform the medical community of the long-term impact of these medications on bone health in subjects with rheumatic diseases.

Compliance with Ethical Standards

Conflict of interest Alanna M. Dubrovsky, Mie Jin Lim, Nancy E. Lane have no conflicts of interest related to this work.

Human and Animal Rights and Informed Consent There were no human or animal studies that were performed by the authors that were described in this work.

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