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Review

Biologic therapies and systemic bone loss in rheumatoid arthritis

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ABSTRACT

Chronic inflammation affects bone metabolism leading to disequilibrium in the rates of bone resorption and repair and subsequently to local and generalized bone loss. Osteoporosis represents an important co-morbidity of rheumatoid arthritis (RA) patients, which exhibit increased fracture risk. Osteoclasts play a pivotal role in the development and progression of bone loss, while resident synovial cells such as T cells, monocytes and synovial fibroblasts have been identified as sources of osteoclast differentiation signals in RA. This process is mainly mediated through the receptor activator of nuclear-kappa B ligand (RANKL) signalling system, which is upregulated by numerous proinflammatory cytokines involved in the pathogenesis of RA. Improved knowledge of the association between cells and cytokines of the immune system and their relationship to bone remodeling has revealed several promising targets for the treatment of inflammatory bone loss in RA. In this respect, initiation of biologic therapies targeting inflammatory cytokines and/or lymphocyte activation has modified RA therapy not only by blocking local and systemic inflammatory cascades but also by providing beneficial effects against bone and joint degradation. In this article we briefly present the modern view of the mechanisms that govern inflammatory bone loss, highlighting the role of cytokine-induced molecular pathways, and discuss in detail the effects of different biologic treatment strategies on bone mass in RA patients.

Contents

1. Introduction

Bone loss has been recognized as a complication of rheumatoid arthritis (RA) for more than a century [1] and presents in two different forms: as juxta-articular osteoporosis around inflamed joints, which

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is a radiological characteristic of "early" RA, and generalized osteoporosis, which is one of the most common extra-articular manifestations of the disease [2,3]. Marginal erosions secondary to the loss of cartilage and subchondral osteolysis may develop later in the course of the disease and are included in the classification criteria for RA [4]. Given that osteoporosis is widely observed in systemic inflammatory conditions such as spondyloarthropathies [5], other autoimmune disorders [6] and inflammatory bowel disease [7], it has been postulated that reduced bone density in these conditions is mainly due to accelerated bone resorption associated with chronic inflammation [8].

In the last few decades, better understanding of the immune/inflammatory pathways that regulate synovial inflammation and bone loss has led to remarkable therapeutic advances. Tumor necrosis factor (TNF)-alpha is considered to be the predominant proinflammatory cytokine in RA and plays a pivotal role in the synovitis and destructive process of the disease. The use of TNF-alpha antagonists for treatment of RA in the last 15 years has changed the natural history of the disease and transformed the lives of people suffering from this condition. In addition to resolution of arthritic symptoms, TNF-alpha blockade in RA may arrest and even partially reverse erosive bone damage [9,10], improve quality of life [11] and attenuate the excess cardiovascular burden [12,13]. More recently, novel biologic regimens targeting other mediators of the inflammatory cascade (e.g. IL-6 inhibition), particular populations of immune cells (e.g. anti B-cell therapy) or activation pathways (e.g. anti CD28 therapy) have been developed, licensed and used for the treatment of RA with satisfactory clinical outcomes.

The aim of the present article is to review existing data about the effects of biologic therapies on rheumatoid bone disease, mainly focusing on bone loss and osteoporosis, after briefly presenting the molecular basis and therapeutic implications of the regulation of bone formation and destruction in RA.

2. Literature search strategy

A Medline search for articles published between January 1999 and December 2012 was conducted using the following keywords: rheumatoid arthritis, osteoporosis, biologic treatment, TNF-alpha inhibitors/antagonists. Articles were selected if they had been published as full journal articles or poster presentations in English. Articles could be either original research papers or review articles discussing the effect of novel biologic therapies on bone metabolism in RA.

3. Magnitude and risk factors of osteoporosis in RA

Osteoporosis is an important and severe co-morbidity as the RA population predominantly consists of post-menopausal women. RA patients exhibit a twofold higher risk of developing osteoporosis compared with general population controls [14,15], and the ensuing bone fragility leads to increased vertebral and nonvertebral fractures and has adverse socioeconomic consequences [16,17]. Case control studies [18] and a meta-analysis [19] demonstrate that RA almost doubles the risk of hip and vertebral fractures, regardless of whether steroids are used or not. Unlike postmenopausal osteoporosis, bone loss in RA is more pronounced in the peripheral bones, while bone mass is relatively preserved in the axial skeleton [20]. The cause of this is unclear but the mechanisms of bone loss in this population not only include the traditional risk factors for primary osteoporosis – for example sex, age etc. [21] – but also RA-related factors such as immobility, mediators of systemic inflammation and the use of particular anti-rheumatic drugs, all of which may affect bone remodeling [22]. Low-grade inflammation preceding the onset of clinical manifestations of RA may also contribute to systemic bone loss, as even healthy individuals with high levels of high sensitivity C-reactive protein, appear to have an increased risk of fractures [23]. Amongst these variables, disease activity and duration are considered the most important ones with regard to the risk of generalized osteoporosis. Erosive bone disease has been associated with decreased bone mass [24] and biochemical markers of bone and cartilage degradation have been described as predictors of radiographic progression of joint damage over a period of 4 years in patients with early RA [25]. More recently, accelerated hand bone mineral density loss has been correlated with progressive joint disease in hands and feet in the first year of recent-onset RA [26]. It is worth noting that bone loss occurs early in the disease process and the degree of it correlates with the disease activity [27,28], emphasizing the need for preventive and early therapeutic interventions, when the potential of reversibility is greatest [29].

4. Osteoimmunology in RA

Osteoimmunology is a new research field originally initiated by Arron and Choi [30] when T cells were described as inducers of proteolytic pathways leading to bone loss. It investigates the interaction of the immune system with the skeleton, two at first glance fundamentally different organ systems, which however are in close relation to each other, particularly in the context of inflammatory arthritides [31].

4.1. The role of osteoclasts

RA represents an excellent model for gaining insights into the local and systemic effects of inflammation on bone metabolism. Although focal bone erosions, periarticular and generalized osteoporosis in RA involve different regions of the skeleton, dysregulation of the balance between bone formation and resorption in favor of the latter has been suggested as the common underlying mechanism of all these forms of bone loss. It is believed that disturbance of bone homeostasis in RA is driven by the cellular action of osteoclasts, the sole bone-resorbing cell type in the human body. In various models of inflammatory arthropathy no bone erosions were noticed after genetic depletion or blockade of osteoclasts or their function, indicating that these cells are essential for the evolution of structural damage in such conditions [32,33].

The enhanced osteoclast formation in RA is due to the increased accumulation in the inflamed synovium of cells that serve as osteoclast precursors, such as dendritic and mononuclear cells of the monocyte/macrophage lineage [34]. Local and systemic production of cytokines including TNF-alpha, interleukin (IL)-1, IL-6 and IL-17 is responsible for the recruitment of osteoclast precursors to the bone microenviroment where they are induced to differentiate to fully functional osteoclasts [35]. This process requires intensive crosstalk with other cells, particularly osteoblasts, osteocytes, synovial fibroblast-like cells and activated T- and B cells which express the receptor activator of nuclear-κB ligand (RANKL), an essential mediator of osteoclastogenesis [36,37]. Binding of RANKL to the RANK receptor on osteoclast precursors and mature osteoclasts, leads to stimulation of several signalling pathways of osteoclast differentiation and activation. RANKL synthesis is precipitated by pro-inflammatory cytokines (Fig. 1) which are abundantly present in the inflamed synovium and the systemic circulation [38], and this high level of RANKL expression is not balanced by the production of its physiologic inhibitors, mainly osteoprotegerin (OPG)—a decoy receptor of RANKL which blocks osteoclast formation [39]. Since the RANKL/OPG ratio determines the degree of proliferation and activity of osteoclasts, this imbalance appears to be of great importance in yielding a negative net effect on bone mass in RA [40]. A clinical case study showed that RANKL/OPG ratio was significantly different amongst groups with normal bone density, osteopenia and osteoporosis in a small population of RA patients with serum RANKL levels being negatively related to bone density in multiple regression analysis [41]. Macrophage colony-stimulating factor secreted by bone marrow stromal cells represents another key cytokine which modulates multiple steps in human osteoclastogenesis by promoting fusion and maturation of precursor cells, as well as by augmenting RANKL-induced bone-resorbing activity [42].

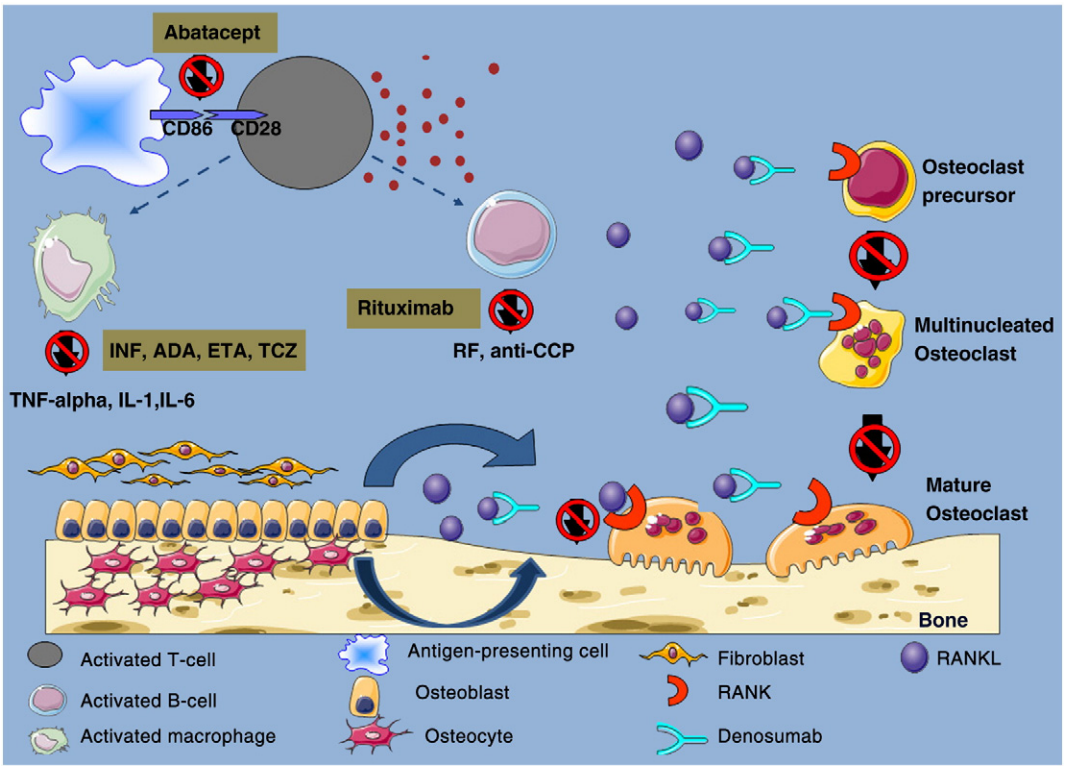

Fig. 1. Osteoimmunology in RA and targets of biologic regimens. $CD4^+$ T cells are responsible for initiating and perpetuating RA. The T cell inappropriately recognizes autoantigens on the surface of antigen-presenting cells. This process is inhibited by abatacept which interrupts the CD28–CD80/86 co-stimulatory pathway—a mechanism shown to reverse osteoclastogenesis via CTLA4. Activated T cells release cytokines that directly activate synovial macrophages and B cells. The former produce large amounts of proinflammatory cytokines (TNF-alpha, IL-6, IL-1) which stimulate the expression of RANKL in osteoblasts and synovial fibroblasts and mediate the differentiation of pre-fusion osteoclasts through RANKL independent pathways. Blockade of these pathways may diminish the degree of immune responses with direct and indirect beneficial effects on bone metabolism. Depletion of activated B cells with rituximab compromises antigen presentation, production of autoantibodies and formation of immune complexes. Finally denosumab's binding to RANKL blocks the maturation of pre-fusion osteoclasts to multinucleated osteoclasts and inhibits the activation, development and fusion of mature cells in bone microenvironment. ADA: adalimumab, anti-CCP: anticitrullinated protein antibodies, ETA: etanercept, IL: interleukin, INF: infliximab, RANK: receptor activator of nuclear factor-kappa B, RANKL: receptor activator of nuclear factor-kappa B ligand, RF: rheumatoid factors, TCZ: tocilizumab, TNF-alpha: tumor necrosis factor—alpha.

4.2. Inflammatory mediators as triggers of bone loss

In addition to their involvement in overexpression of RANKL, proinflammatory cytokines directly or indirectly regulate osteoclastogenesis by mediating different intracellular pathways to initiate osteoclast development and survival. For example TNF-alpha exerts direct effects on osteoclast precursors by inducing the expression of receptors such as TNF-receptor type-1 on the surface of monocytes, stimulating their differentiation to osteoclasts [43]. TNF-alpha-dependent secretion of macrophage colony-stimulating factor by bone marrow stromal cells has also been demonstrated as an alternative pathway through which the formation of mature osteoclasts is promoted [44].

A significant component contributing to the residual and generalized bone loss in RA is the suppression of osteoblast function and the subsequent low rates of bone repair. TNF-alpha directly inhibits osteoblast differentiation and bone nodule formation by suppressing the expression of positive regulators of their development and growth such as nephronectin [45]. It also interacts with the wingless signalling pathway, a critical pathway that regulates bone formation by enhancing the differentiation of osteoblasts from their mesenchymal cell precursors [46]. Wingless proteins induce OPG expression and therefore diminish the RANKL/OPG ratio, thus blocking osteoclast activation [47]. On the other hand TNF-alpha is a strong inducer of dickkopf-1, a protein inhibitor of wingless signalling [48], which is upregulated in the inflamed synovial tissue [49]. In RA patients, elevated serum concentrations of dickkopf-1 have been reported in several studies [50,51]. The imbalance between wingless signalling and their inhibitors triggered by TNF-alpha may account for reduced osteoblast function and the suppressed bone repair in RA resulting in further derangement of bone homeostasis and accelerated bone loss.

In RA, activated macrophages, synovial fibroblasts and T cells are sources of IL-1 and IL-6 which are considered to play a key role in synovial inflammation, bone damage and the systemic manifestations of the disease. Both cytokines are strongly connected to osteoclast physiology, as they support the fusion of osteoclast precursors, prolong the survival and increase the activity of mature osteoclasts mainly through RANKL-mediated pathways [52–54]. Additionally IL-6 promotes the adhesion of osteoclast precursors by enhancing the expression of intercellular adhesion molecule-1 on endothelial cells [55]. The critical significance of IL-6 signalling for the altered modulation of RANKL/OPG ratio in postmenopausal women with RA has recently been described [56].

In summary, there is compelling evidence that inflammatory mediators in RA alter the relationship between bone formation and resorption by stimulating osteoclasts and inhibiting osteoblasts. Better understanding of these pathways may allow amelioration of the deleterious effects of inflammation on bone metabolism with novel treatments targeting the molecular interactions between immune activation and the skeletal system.

5. Effects of anti-rheumatic treatment on bone metabolism: kill two birds with one stone?

Treatment with anti-inflammatory and disease-modifying drugs has been shown to have a beneficial effect on bone mass in patients with RA. Effective control of inflammation with conventional agents

resulted in partial recovery of initial bone loss in patients with early RA [28], whereas improvement of the disease activity score was associated with stabilization of bone density in an open prospective 2-year study [57]. These findings indicate the importance of controlling disease activity to prevent generalized bone loss in RA.

5.1. Corticosteroids and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) in RA: effects on bone density

The effects of low-dose corticosteroids on bone metabolism in RA have been a matter of debate: on one hand their use associates with increased bone loss and fracture risk [58], but on the other it effectively dampens systemic inflammation. Randomized control studies have found a beneficial effect of steroids compared to placebo on femoral [59] and hand [60] bone density in early RA. Low-dose steroids also appeared to have a synergistic effect with the TNF-alpha antagonist, adalimumab, accounting for 18.5% of the improvement observed in femoral neck bone density in 50 patients with active RA [61]. Of interest, in a 1-year case-control study [62], the beneficial effect of another TNF-alpha antagonist, infliximab, on femoral bone density was no longer significant when steroid treatment was included in the multivariate model, indicating that clinical remission and increased mobility after successful control of inflammation with steroids may contribute to the favorable effects on bone turnover reported in this study. In line with these observations, a recent study showed that steroids are associated with a lower risk of vertebral fractures in RA, further supporting the view that appropriate control of disease may protect against bone fragility [63]. Future studies will help clarify which particular subgroups of RA patients may or may not benefit from low-dose steroids and will potentially lead to a re-evaluation of the role of these drugs in the management of bone loss in RA.

High-dose methotrexate has been linked with bone loss in patients with malignant diseases [64] but an observational study did not show any impairment of bone formation in RA patients treated with low-dose methotrexate (mean 10 mg/week) [65]. The view that low-dose methotrexate does not interfere with bone remodeling has been supported by other studies too [66,67], but contradictory results have also been reported [68]. Treatment with sulphasalazine decreases excretion of bone turnover markers in the urine of RA patients, suggesting a lower rate of bone loss [69], but direct evidence of this is lacking. There is no information on the effects of other non-biologic DMARDs on bone turnover in patients with RA.

5.2. Biologic DMARDs and bone metabolism in RA

The fact that proinflammatory cytokines induce the uncoupling between bone destruction and formation in RA may explain the ability of novel anti-cytokine biologic treatments not only to suppress systemic inflammation, but also to halt systemic bone loss [70,71]. It is not surprising therefore that several studies have reported beneficial effects on bone mass in patients with RA following treatment with such drugs.

5.2.1. TNF-alpha inhibition

TNF-alpha blockers were the first class of biologics used in RA. They have beneficial effects on inflammatory disease activity and joint degradation by achieving high rates of sustained clinical remission. Initial studies in estrogen-deficient (by ovariectomy) animal models showed that direct blockade or diminished production of TNF-alpha prevented bone loss [72,73]. These findings suggested that TNF-alpha antagonists may prevent the inflammatory bone demineralization in TNF-alpha driven systemic arthritides. This hypothesis was confirmed in the collagen-induced arthritis model, in which TNF-alpha blockade reduced bone resorption assessed by urinary deoxypyridinoline excretion and prevented bone mineral density reduction in parallel with improvement in disease activity scores [74].

Several cross-sectional studies have assessed the effect of TNF-alpha blockade on bone metabolism in humans (Table 1), but there is no robust data available on bone fractures. Recently published studies suggest that the risk for nonvertebral fractures is the same amongst patients with RA or other inflammatory conditions treated with TNF-alpha inhibitors, methotrexate or other non-biologic DMARDs [75,76]. Bone formation markers such as osteocalcin and N-terminal propeptide of type I collagen significantly improved after 6 weeks of treatment with infliximab in an open label study of 68 RA patients [77]. The extension of the study to 102 patients with a follow-up period of 12 months showed that clinical remission following treatment with infliximab was associated with an arrest in generalized bone loss, which however was not accompanied by improvement of localized bone loss in the hands [78]. In the same study, clinical response was related to a decrease of bone resorption parameters such as RANKL/OPG ratio. In that respect, lower baseline serum levels of RANKL and RANKL/OPG ratio have been described as predictors of clinical remission in RA patients treated with TNF-alpha antagonists [79]. In another study, infliximab resulted in normalization of OPG and soluble RANKL, without influencing RANKL/OPG ratio [80]. The long term impact of TNF-alpha inhibition on biochemical markers of bone turnover has provided conflicting results. Whereas Chopin et al. [81] demonstrated a transient decrease in bone turnover indices in the first 6 weeks, which however was not sustained after 12 months, other studies [82–84] reported a persistent improvement both in markers of bone resorption and formation. Anti-TNF alpha therapy also regulates the wingless signalling pathway by reducing serum dickkopf-1 concentrations [85] and by increasing synovial OPG expression [86]. In summary, TNF-alpha inhibition appears to have at least a short-term positive effect

Table 1
Overview of the studies assessing the effects of biologic treatment on biochemical markers of bone turnover in RA.

Study	Type of study	Patients	Molecule	Follow-up period	Outcome
Vis et al. [77]	Prospective	68	INF	6 weeks	↑ PINP, ↑OC
Lange et al. [81]	Prospective	26	INF	1 year	↑ OC ↓ serum cross laps
Vis et al. [78]	Prospective	102	INF	1 year	↓ beta-CTX, ↓ RANKL, (−)OPG, (−)OC, ↓ RANKL/OPG
Seriolo et al. [88]	Prospective	11 ETA/9 INF/10 controls	INF/ETA	6 months	↑ OC ↓ DPD/Cr
Marotte et al. [62]	Prospective	90 INF/99 controls	INF	1 year	(−)0C, (−)CTX-1
Chopin F et al. [81]	Prospective	48	INF	1 year	(−)P1NP, (−) CTX-1 ↑ PINP/CTX-
Torikai E et al. [83]	Prospective	17	INF	6 months	↓ NTX, ↓ DPD
Ziolkowska M et al. [80]	Prospective	43INF/30 controls	INF	6 months	↓ OPG, ↓ sRANKL
Garnero et al. [100]	Randomized	416	TCZ	6 months	↑ PINP ↓ CTX-1 ↓ ICTP
Terpos et al. [102]	Prospective	22	TCZ	2 months	↓ dickkopf-1
Yasunori et al. [84]	Prospective	30	ETA	6 months	↑BAP, ↓DPD ↑sRANKL, (−)OPG
Boumans et al. [105]	Prospective	28	RIT	12 months	↓ OPG, ↓ sRANKL ↑ OPD/RANKL
Dore et al. [118]	Randomized	143 DEN/75 controls	DEN	1 year	↓ CTX-I, ↓PINP

BAP: bone alkaline phosphatase, beta-CTX: beta-isomerized carboxy terminal telopeptide of type 1 collagen, Cr: creatinine, CTX-I: serum C-terminal cross-linked telopeptide of type I collagen, DEN: denosumab, DPD: deoxypyridinoline, ICTP: C-terminal crosslinking telopeptide of type I collagen generated by matrix metalloproteinases NTX: N-telopeptide of type I collagen, OC: osteocalcin, OPG: osteoprotegerin, PINP: N-terminal propeptide of type I collagen, RIT: rituximab, sRANKL: (soluble) receptor activator of the NFkappaB ligand.

on bone remodeling in RA, as assessed by alterations of the balance between biomarkers of bone formation and resorption.

Similarly to what occurs with biochemical parameters, TNF-alpha antagonists have an effect on bone mineral density (Table 2). A significant increase in the bone mass measured in the spine and the hip of 36 RA patients after 1 year of treatment with infliximab was observed in an open label study [87]. Seriolo et al. reported the same trend in bone density after a 6 month follow-up amongst RA patients treated with infliximab or etanercept in comparison with patients on stable dose of prednisolone or methotrexate [88]. However the lack of appropriate control groups in these studies, attributed to ethical considerations, was a major limitation that does not really allow a true estimation of the effect of TNF-alpha inhibition on the bone. In an attempt to overcome this limitation, Marotte et al. performed a historical group study by comparing 90 RA patients treated with infliximab, to 99 patients with RA who were treated with methotrexate at the time biologics were not available [62]. They demonstrated a significant decrease of bone mineral density at the femoral neck and the lumbar spine in the control group, while no deterioration of bone density was observed in the group treated with combination of methotrexate and infliximab, after controlling for demographic parameters and the use of steroids or biphosphonates. A potentially important unexpected finding was that the benefit on bone mass was also observed in clinical non-responders: this may indicate that the systemic effects of TNF-alpha on bone differ from those on RA activity, suggesting a more specific role in the inhibition of osteoclastogenesis. In his regard the reduction of the bone resorptive potential of circulating osteoclast precursor cells detected in patients with RA and ankylosing spondylitis may provide an alternative explanation to the anticatabolic effect of TNF-alpha inhibition on bone metabolism [89].

On the other hand, data obtained from the BEST study did not show any significant difference in bone density measurements performed at baseline and after 1 year between four different treatment strategies (sequential monotherapy, step-up combination therapy, initial combination therapy with prednisolone or initial combination therapy with infliximab) [90]. These observations were attributed to the relatively low baseline bone mass loss in the patients of this study, the tight control of inflammation achieved in all treatment groups and the concomitant use of antiresorptive treatment: this highlights once more that effective suppression of inflammation in early RA, irrespective of the exact treatment approach, helps to maintain bone integrity and prevent accelerated bone mass loss.

With respect to localized osteoporosis a few studies have demonstrated that hand bone loss continues to deteriorate despite effective control of inflammation and improvement of lumbar spine and hip bone density [91,92]. In line with previous observations, a cohort-study of 184 patients with established RA treated with adalimumab for at least 1 year showed that improvement in lumbar spine bone density, was not accompanied by a halt of hand bone loss [93]. In a subanalysis of the PREMIER trial, metacarpal cortical bone loss was arrested in patients on combination of adalimumab plus methotrexate compared to methotrexate alone only in the group with high disease activity. For patients in remission and low disease activity, levels of bone loss were similar [94]. These findings suggest that TNF-alpha inhibition stabilizes systemic but has a lesser effect on peripheral osteoporosis supporting the hypothesis that despite clinical remission, local joint inflammation remains to a greater or lesser extent sub-optimally controlled leading to localized bone loss and structural joint damage [95].

5.2.2. Altering IL-6 signalling: a novel therapeutic approach

IL-6 is a pleiotropic proinflammatory cytokine and in conjunction with IL-6 receptor alpha elicits a broad spectrum of inflammatory events involved in the onset and progression of RA, such as initiation of hepatic acute phase response, stimulation of synoviocyte proliferation, recruitment of inflammatory cells in the joints, and promotion of bone and cartilage destruction. Tocilizumab is a humanized anti IL-6 receptor monoclonal antibody which has been effective in reducing clinical signs and systemic inflammation in RA, in particular decreasing joint swelling and controlling the acute phase response [96]. Moreover, tocilizumab was found to reduce structural joint damage in the SAMURAI study [97]. This concurs with published data suggesting that IL-6 inhibition specifically blocks inflammatory osteocalcinogenesis in vitro and in vivo independent of its anti-inflammatory properties [98], reinforcing the hypothesis that the IL-6 pathway is one of the major contributing factors to the disrupted bone metabolism in RA.

Despite the fact that serum IL-6 levels have been inversely correlated with bone density in RA [99], the effects of IL-6 blockade on the skeleton are still under investigation without any data available on fracture risk or on bone mineral changes. Garnero et al. [100] demonstrated rapid and sustained improvement in bone metabolism

Table 2
Changes in local and systemic bone mineral density in patients with RA following treatment with biologic drugs.

Study	Type of study	Patients	Drug	F/up period	Generalized osteoporosis		Localized osteoporosis
					All patients	Clinical non-responders	
Vis et al. [78]	Prospective	102	INF	1 year	(−) spine/hip BMD	NA	↓ MCP BMD
Lange et al. [82]	Prospective	26	INF	1 year	↑ spine/hip BMD	NA	NA
Vis et al. [87]	Prospective	36	INF	1 year	Nonsignificant ↑ spine BMD Nonsignificant ↓ hip BMD	NA	NA
Seriolo et al. [88]	Prospective	11 ETA/9 INF/10 controls	INF/ETA	6 months	Nonsignificant improvement in anti-TNF-alpha treated group	NA	NA
Marotte et al. [62]	Prospective	90 INF/99 controls	INF	1 year	Stabilization of spine/hip BMD in INF-treated group	++	NA
Chopin F [81]	Prospective	48	INF	1 year	(−) spine/hip BMD	NA	NA
Güler-Yüksel et al. [90]	Randomized	81 sequential 84 step-up combination 89 PRE combination 88 INF combination	INF	1 year	Nonsignificant ↓spine BMD Nonsignificant ↓ hip BMD without differences within treatment groups	NA	NA
Eekman et al. [91]	Prospective	52	INF	2 years	↑ spine BMD (−) hip BMD	NA	↓ MCP BMD
Krieckaert et al. [93]	Prospective	184	ADA	4 years	(−) spine BMD (−) hip BMD (decreased after the first year)	NA	↓ MCP BMD
Wijbrandts et al. [61]	Prospective	50	ADA	1 year	(−) spine/hip BMD	NA	NA
Hoff et al. [94]	Randomized	261 ADA + MTX/261 ADA/246 MTX	ADA	2 years		++	Stabilization of MCP BMD in ADA groups
Deodhar et al. [116]	Randomized	43 DEN/13 controls	DEN	6 months			↑ MCP BMD
Dore et al. [118]	Randomized	143 DEN/75 controls	DEN	1 year	↑ spine/hip BMD	NA	NA
Sharp et al. [117]	Randomized	143 DEN/75 controls	DEN	1 year		NA	↓ MCP bone loss in DEN group

ADA: adalimumab, BMD: bone mineral density, DEN: denosumab, ETA: etanercept, INF: infliximab, MCP: metacarpal, MTX: methotrexate, PRE: prednisolone.

following the initiation of combination treatment – tocilizumab plus methotrexate – in 416 patients with active RA. They reported an increase in markers of bone formation which remained significant after 24 weeks and was associated with a drop in serum levels of bone degradation markers, especially C-terminal crosslinking telopeptide of type-1 collagen and C-terminal crosslinking telopeptide of type-1 collagen generated by matrix metalloproteinases. The authors concluded that pharmacological blockade of IL-6 signalling attenuates local and systemic bone loss predominantly but not exclusively in clinical responders, dissociating the tight link between disease activity and bone turnover in RA.

Tocilizumab may also improve coupling of bone formation and resorption by regulating the wingless signalling pathway. Kanbe et al. [101] investigated histological changes of bone marrow in response to tocilizumab in 10 RA patients who underwent total knee replacement. Specific immunohistochemical examinations demonstrated increased OPG expression in the bone marrow of patients treated with tocilizumab compared to patients on conventional treatment. Recently it has been reported that IL-6 blockade resulted in decrease of circulating dickkopf-1 levels and in normalization of OPG/RANKL ratio in 22 women with active RA just after 2 monthly infusions [102]. These findings may indicate a positive influence of tocilizumab on bone formation by altering the balance of wingless proteins and their inhibitors in favor of the former; in general they suggest a potential role of IL-6 in the modulation of the wingless signalling pathway.

5.2.3. Antilymphocyte biologic therapeutic strategies

In spite of the introduction of biologic regimens, which inhibit proinflammatory cytokines, a significant part of RA patients remain non-responders and/or cannot tolerate such treatment due to severe side effects [103,104]. This fact has focused the interest of rheumatologists on the role of lymphocytes in the pathogenesis of local and systemic inflammation in RA and the development of therapeutic approaches targeting these types of immune cells [105].

Rituximab is a chimeric anti CD20 antibody which eliminates B-lymphocytes and induces their apoptosis. In the context of RA, the number of Ig-producing cells is drastically reduced, diminishing the synthesis of rheumatoid factors or anti-citrullinated protein antibodies and leading to the inhibition of T-to B cell activation process (Fig. 1). Rituximab has been registered for the treatment of RA in patients with primary or secondary failure to TNF-alpha antagonists since 2006. Although the role of B-cells in inflammatory bone loss is unclear, there is preliminary evidence that B-cell depletion has positive effects on bone metabolism in RA. Boumans et al. [106] showed that 12 month treatment with rituximab is associated with decreased number of synovial osteoclast precursors and increased OPG/RANKL ratio in the serum of 28 RA patients. Similarly a small study demonstrated reduction in circulating markers of bone resorption in 13 active RA patients resistant to therapy with TNF-alpha inhibitors [107]. Improvement in bone density following rituximab – more pronounced in clinical responders – has also been reported but these findings should be interpreted cautiously due to the small number of patients, the relatively short period of follow-up and the absence of appropriate controls [108].

It has been suggested that B cells are able to secrete RANKL and contribute to ovariectomy-induced osteoporosis [109]. Interestingly a recent study using cytokine messenger RNA profiling identified B cells as important mediators of RANKL synthesis in rheumatoid synovium [110]. Taking into account the role of B cells in stimulating cytokine secretion by T cells, it can be speculated that B cells can also upregulate RANKL expression and support osteoclastogenesis. The pathophysiological pathways of inflammatory bone loss driven by B cells as well as the long term impact of B-cell depletion therapy on bone remodeling in patients with refractory RA warrant further investigation in well-controlled studies in large cohorts of patients.

T cell-mediated processes have long been considered central to the initiation and perpetuation of RA. Abatacept also known as CTLA4-Ig, is a recombinant soluble fusion protein that blocks the co-stimulation of T cells by inhibiting the CD28–CD80/CD86 pathway between T cells and antigen presenting cells which is essential for T cell activation (Fig. 1). Abatacept has been successfully evaluated in RA and it is currently licensed as an alternative treatment in patients failing to respond to other biologic agents [111]. Recent insights have revealed that the binding of CTLA-4 on CD80/CD86 molecule on the surface of monocytes which act as osteoclast precursors restrains their maturation and development providing an attractive explanation for a potential antiresorptive effect of abatacept in RA [112]. In addition it has been reported that CTLA4-Ig may have a direct regulatory influence on osteoclast differentiation and bone resorption by altering the expression of gene encoding factors involved in osteoclast development [113]. It has been shown in mice that abatacept prevents PTH-induced bone loss [114] but the outcome of T cell targeting therapy on bone mineral density in RA patients has not been investigated so far.

6. Biologic antiresorptive treatment: targeting osteoclast biology

The demonstration that focal, periarticular and systemic bone loss in RA is generated by osteoclasts suggests that blockade of development, differentiation and activity of these cells would be a rational target for preventing inflammatory bone loss (Fig. 1). Denosumab, a humanized antibody that specifically binds RANKL, has been found to reduce the risk of vertebral and non-vertebral fractures in women with postmenopausal osteoporosis [115]. In RA it inhibits the radiographic progression of erosive bone damage and increases the bone mineral density in the hands after 12 months of treatment [116]. Inhibition of osteoclast-mediated bone loss with denosumab has also resulted in prevention of metacarpal shaft cortical bone loss in patients with erosive RA treated with methotrexate [117].

The effects of denosumab on bone mineral density were also investigated in a randomized double-blinded placebo-controlled phase II study in patients with RA receiving treatment with biphosphonates or glucocorticoids [118]. Denosumab increased bone mineral density in the lumbar spine and the hip and reduced markers of bone turnover after 6 months. These findings were observed in all subgroups of patients regardless of the concomitant administration of steroids and/or biphosphonates and the dose of denosumab-60 mg or 180 mg subcutaneously every 6 months. In combination with the previous reports, this study suggests that the pharmaceutical blockade of RANKL suppresses the accelerated bone turnover and may represent a new therapeutic option for local and systemic bone loss in RA. Particularly in view of juxta-articular osteoporosis, the potential therapeutic role of denosumab is of outmost importance as inhibition of the TNF-alpha pathway has failed to arrest local bone loss in metacarpal bones. Whether the co-administration of denosumab with other biologic regimens such as TNF-alpha inhibitors may have a better outcome in ameliorating and reversing the impact of systemic inflammation on bone hemostasis and structure in this population remains to be determined.

7. Conclusion

Secondary osteoporosis is a well-known co-morbidity in RA and bone loss is a frequent and clinically serious event. The great progress achieved in delineating the pathophysiological pathways of synovial and systemic inflammation in RA, has led to a deeper understanding of the mechanisms involved in the disturbance of bone hemostasis and emphasized the complex interrelations between immune and bone cells. In particular, the molecular regulation of osteoclast formation and its control by systemic and local production of inflammatory mediators suggests that inflammation itself triggers bone turnover resulting in marginal erosions and osteoporosis. Several lines of evidence indicate that biologic therapies targeting specific inflammatory signalling pathways have provided potent therapeutic effects in protecting bone demineralization in RA. The effective suppression of inflammation contributes to the stabilization of bone density in patients with

RA but the fact that beneficial effects of treatment have also been reported in clinical non-responders suggests that inhibition of osteoclasts is potentially another important mechanism. It remains unclear whether these findings will translate into better hard outcomes and diminish the risk of fracture, as numerous questions have not been answered yet. For example the lesser effect of TNF-alpha antagonists on localized bone loss may suggest that intra-articular inflammatory activity is not sufficiently blocked and underline the importance of tight control of inflammation for the improvement of bone density in metacarpals, which on the other hand may be achievable with RANKL inhibition. These new insights will hopefully allow the development of new therapeutic strategies by incorporating both antirheumatic and bone-directed treatments in the RA management paradigm.

Take-home messages

- Localized and systemic osteoporosis is an important co-morbidity of RA.
- Adequate control of the disease prevents bone loss.
- Novel biologic drugs may offer better and sustained outcomes.

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Efficacy and safety of mycophenolate mofetil in Japanese patients affected with lupus nephritis

Mycophenolate mofetil (MMF) has been found to be effective as intravenous cyclophosphamide (IVC) in patients affected with lupus nephritis (LN). However, the treatment response depends on several variables, including race. It has been shown that Asian and white patients have similar response rates while black or Hispanic patients seem to respond better to MMF than IVC.
Considering that no studies have compared the efficacy of MMF vs IVC in Japanese patients, Onishi et al (**Mod Rheumatology 2013;23:89-96**) retrospectively investigated the efficacy and safety of MMF compared with IVC in the induction therapy of active LN (class III, IV and V) in 21 Japanese patients.
Eleven of them were treated with MMF 0.5-1.5 g twice daily and ten with biweekly or monthly pulses of IVC 0.2-1 g/m2. Patients receiving MMF achieved complete or partial remission in 81.8% of cases compared with 40% of patients treated with IVC ($p=0.081$) and no differences were found in other parameters such as anti-dsDNA title, C3 and C4 concentration and urine protein/creatinine ratio.
Moreover, MMF showed a better safety profile, especially for hematologic toxicity, and no differences between infection and gastrointestinal disorders were found.
MMF was not superior to IVC in this cohort of patients but showed a better overall safety profile than IVC.

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