Review

The effect of biologic agents on bone homeostasis in chronic inflammatory rheumatic diseases

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ABSTRACT

Osteoporosis (OP) and increased fracture risk are widely observed comorbidities in chronic inflammatory rheumatic diseases (CIRDs). Improved knowledge of the immune/inflammatory pathways, which characterise the pathophysiology of rheumatoid arthritis (RA) and seronegative spondyloarthropathies (SpA), such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), have provided the link between inflammation and bone loss, via a complex network of bone cells, T and B cells, pro-inflammatory cytokines such as TNF-α, IL1, IL6, IL17, IL23, costimulator molecules, signalling pathways including both RANKL/RANK/OPG and Wnt signallings. The complex osteoimmunologic network in CIRDs suggested that the powerful anti-inflammatory activity of biologic drugs, beyond the control of the disease, was likely to reduce OP and fracture risk. In this respect, the available data deriving from clinical and experimental studies, conducted with TNF-α, IL6 and IL1 blockers, and B and T cell therapies, have demonstrated a beneficial effect on bone mineral density (BMD) and/or bone turnover markers (BTs). However, whether these drugs are able to positively influence also fracture risk has not yet been established, since the data available are sparse and inconclusive. Thus, systemic bone loss and increased fracture rates still remain relevant comorbidities that should be considered for screening and prevention, and proper treatment of patients with CIRDs despite the biologic therapy.

Introduction

Systemic bone loss with osteoporosis (OP) and increased fracture rates are widely observed in chronic inflammatory rheumatic diseases (CIRDs), including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) (1-6). During last EULAR initiative some important points that deserve to be considered in the course of CIRDs in order to report, screen and prevent comorbidities have been selected, OP has been included by the Task Force in the six selected comorbidities to focus on (7).

Local and systemic production of pro-inflammatory cytokines, such as TNF-α, IL1β, IL6, IL17, IL23 is central to the pathogenesis of inflammation-induced bone loss and contribute to the uncoupling of osteoclast-mediated bone resorption and osteoblast-mediated bone formation, thereby disrupting normal remodelling. In the last few decades, better understanding of the immune/inflammatory pathways which regulate synovial inflammation and bone loss has led to the modern view of the osteoimmunologic network of osteoclasts (OCs) with other cells, particularly osteoblasts, osteocytes, synovial fibroblast-like cells and activated T and B cells (8-13).

RANKL/RANK/OPG and canonical Wnt-signalling pathways also play a critical role in this complex network. RANKL is an essential factor for osteoclast differentiation, activation and survival (10) and its expression is up-regulated by pro-inflammatory cytokines (11, 12, 14). In contrast, Wnt-signalling, a key regulatory pathway for bone formation by osteoblasts (15, 16), is down-regulated by pro-inflammatory cytokines through the induction of its antagonists Dickkopf1(DKK1) and sclerostin (11, 12, 17). DKK1 is considered a master regulator of joint remodelling (18) and its expression has also been shown to contribute to systemic bone loss by inducing in turn the other antagonist sclerostin to further inhibit Wnt-signalling (15, 19). TNF-α

is a strong inducer of osteoclastogenesis through elevated expression of RANKL and directly by increasing the expression of osteoclast-associated receptor (OSCAR), a key costimulatory molecule in osteoclastogenesis (11, 12). TNF-α also inhibits osteoblastogenesis by enhancing the expression of the Wnt antagonist DKK1 and directly by inhibiting transcription factors Runx2/Cbfa and osterix which are essential regulators of osteoblast differentiation (9, 11, 12, 20).

TNF-α and IL1β are synergistic in promoting bone loss, as TNF-α induces IL1β and the IL1β receptor in stromal cells, while IL1β in turn mediates TNF-α-induced osteoclastogenesis both *in vitro* and *in vivo* (11, 21). IL1β up-regulates RANKL expression, thus stimulating osteoclastogenesis (11, 21) and decreasing the apoptotic rate of preformed OCs to further promote bone resorption (11). Furthermore, IL1β induces secretion of prostaglandin E2 to increase bone resorption and down-regulates osteoblastogenesis by increasing the expression of the Wnt antagonists DKK1 and sclerostin (21). IL6 is another pro-inflammatory cytokine abundantly present in blood circulation, which may have a major role in the development of systemic OP (20). IL6 is a pleiotropic cytokine strongly connected to osteoclast physiology, as it interacts synergistically with IL1β and TNF-α to support the fusion of osteoclast precursors, prolong the survival and increase the activity of mature osteoclasts mainly through RANKL-mediated pathways (22). In contrast to other soluble receptors, the soluble IL6-receptor (IL6-R) serves as an agonist of IL6; the IL6/IL6-R complex activates the osteoclastogenic pathway mediated by Janus inases (JAKs), which dramatically contributes to joint destruction (20, 23). IL6 plays also a critical role in the generation of pro-inflammatory Th17 cells, thereby enhancing IL17 levels (11). Apart from its osteometabolic effects, IL6 takes an endocrine role through the activation of the hypothalamic-pituitary-adrenal axis by IL1 and TNF-α, which leads to the release of glucocorticoids which contribute in bone loss (20).

IL17 is the most recently described subclass of pro-inflammatory cytokines, enhancing the production of TNF-α, IL1β and IL6 and *vice versa*. In addition, IL17 directly stimulates the expression of RANKL and prostaglandin E2 (12, 13, 22, 24). This cytokine is in large amount expressed by Th17 cells, a new subset of Th-cells which are an important trigger for focal and systemic bone loss in CIRDs. The mechanisms related to Th17 differentiation appear to involve IL1α and IL6, but also IL23, which plays a paramount role in maintenance of Th17 population (IL23/Th17- axis) (13, 24). Although pro-inflammatory cytokines and T cells have been suggested to provide the essential link between inflammation and bone loss, other mechanisms are additionally involved. Along with activated T cells, B cells express RANKL and IL6, therefore contributing to osteoclastogenesis. Moreover, B cells differentiate into plasma cells which inhibit bone formation through the expression of the Wnt antagonist DKK1 (8). On the contrary CTLA4, a T cell-associated antigen, contributes to the anti-osteoclastogenic effect of Treg cells competing with the surface protein CD28 for binding with CD80 and CD86, potent co-stimulators of T cells and OC precursors (8, 20, 25). In addition to RANKL/RANK/OPG, other osteoclastogenic pathways have recently focused the attention in CIRDs. JAK family of tyrosine kinases is one of these and has been proved to contribute to joint destruction and potentially to systemic OP, via the action of IL6 (20, 23, 26). Increased understanding of CIRDs pathophysiology has led to identify biologic agents as novel therapeutic strategy that could dramatically improve clinical outcomes of these diseases (8, 26-29).

Available biologics are characterised by a different pharmacological activity targeted on different levels of immune response, including IL6 inhibitor tocilizumab, anti-CD20 rituximab, anti-IL1 anakinra, CTLA4-Ig recombinant soluble fusion protein anti-CD28 abatacept, anti-IL12/23 ustekinumab, anti-IL17 secukinumab and anti-TNF-α agents such as adalimumab, etanercept, infliximab, golimumab, certolizumab pegol (28). Additionally, synthetic small molecules which selectively inhibit JAK-STAT pathways are being recently developed (baricitinib, tofacitinib) (20, 26, 29, 30). As discussed above, the relationship between inflammation and bone loss which emerged from the complex osteoimmunologic network well documented in CIRDs (8, 9, 11, 12), suggests that biologic drugs, all characterised by powerful anti-inflammatory activity in disease control, are likely to reduce OP and fracture risk (20, 22, 31). Several cross-sectional and longitudinal studies evaluating the effect of biologic therapies on bone mineral density (BMD) and/or bone turnover markers (BTs) in RA, AS and PsA have provided conflicting results 32–34. However, most of these studies had small sample sizes, rather short observational period and only a minority had a control group; additionally, there is a lack of long-term follow-up from the early phase of the disease. A review about the effect of biologic drugs on bone loss and OP in RA, which evaluated articles published between January 1999 and December 2012, indicated beneficial effects against bone loss (22). Zerbini *et al*. recently conducted a search on the effect of biologics on BMD in RA patients including articles from 2003 to 2015 (29). The results demonstrated that the biologic treatment was associated with decreased bone loss. Most of the studies were conducted with TNF-α inhibitors and there were few studies with tocilizumab, rituximab and abatacept. In both these two reviews denosumab (DNB), a monoclonal antibody against RANKL, was also included. This drug, which is a well-known effective biologic agent for OP treatment, significantly increased BMD at the lumbar spine (LS) and hip and reduced BTs after 6 and 12 months in patients with active RA. Notably, at 12 months, both x-ray erosion score and total Sharp score were significantly lower in the DNB group than in the untreated group (35). However, DNB treatment did not influence disease activity parameters. Tables I–III summarise some of the most relevant studies focusing on the effects of biologic drugs on BMD in RA and SpA and relative fracture risk.

Table I. BMD and biologic drugs in RA.

Authors and year	Drug	Pts/studies	Osservation time	BMD spine	BMD total Hip	BMD femoral neck
Haugeberg *et al*. 2014	DMARDs + Biologics	92 pts	0–2 yrs 2–10 yrs	↔ ↔	↓ ↔	↓ ↔
Krieckaert *et al*. 2013	ADA	184 pts	1 yr 1–4 yrs	↔ ↔	↔ ↓	NA
Kume *et al*. 2014	TCZ	78 pts	1yrs	↑	NA	↑
Briot *et al*. 2015	TCZ	103 pts	1 yrs	↔	↔	↔
Ricciardi *et al*. Review 2013	Anti-TNF	9 studies	6 mos – 2 yrs	↑	↑	↑
Manara *et al*. Review 2015	Anti-TNF	17 studies	6 mos – 2 yrs	↔	↔	↔
Dimitroulas *et al*. Review 2013	Anti-TNF, DNS	14 studies	6 mos – 4 yrs	↔	↔	↔
Zerbini *et al*. Review 2016	Anti-TNF, TCZ, DNS	28 studies	6 mos – 10 yrs	↔	↔	↔
Vivian K. Kawai *et al*. Review 2012	Anti-TNF	14 studies	6 mos – 2 yrs	↔ ↑	↔	↔
Siu *et al*. Meta-analysis 2015	Anti-TNF	4 studies	1–2 yrs	↔	↔	

Table II. BMD and biologic drugs in SpA.

Authors and year	Drug	Pts/studies	Osservation time	BMD spine	BMD total Hip	BMD femoral neck
Visvanathan *et al*. 2009	Anti-TNF	157pts	2 yrs	↑	↑	↑
Kang *et al*. 2013	Anti-TNF	26 pts	2 yrs	↑	↑	↔
Durnez *et al*. 2013	Anti-TNF	59 pts	1–4 yrs	↑	↔	↑
Ricciardi *et al*. Review 2013	Anti-TNF	9 studies	6 mos – 2 yrs	↑	↑	↑
Vivian K. Kawai *et al*. Review 2012	Anti-TNF	9 studies	6 mos – 2 yrs	↑	↑	↑
Siu *et al*. Meta-analysis 2015	Anti-TNF	4 studies	1–2 yrs	↑	↑	↑
Haroon *et al*. Review 2015	Anti-TNF	8 studies	1–2 yrs	↑	↑	↔

Table III. Biologic drugs and fracture risk.

Authors and year	Drug	Pts	Osservation time	Disease	Vertebral fractures	Non-vertebral fratures	Overall fractures
Coulson *et al*. 2009 CORRONA	Anti-TNF *vs*. DMARDs *vs*. combo	8419/11429	13 yrs	RA	↔	↔	↓
Kim *et al*. 2012	Anti-TNF *vs*. DMARDs	5856/16412	???	RA	NA	↔	NA
Roussy *et al*. 2013	Anti-TNF, ABA, RTX	1515/7578	6 mos	RA	NA	↔	NA
Vivian K. Kawai *et al*. 2013	Anti-TNF *vs*. DMARDs	20814/8964 4302/6593	2 yrs	R PsA/AS	↔ ↔	↔ ↔	↔ ↔

TNF-α blockade

A study evaluating the effect of synthetic DMARDs and biologics on systemic bone loss in RA patients, followed for 10 years (36) adds evidence that aggressive anti-inflammatory strategy, including biologic agents (TNF-α inhibitors mostly) on systemic bone loss in RA patients, followed for 10 years reduces bone loss rate. Krieckaert *et al*. documented that adalimumab treatment over 4 years arrested bone loss in the spine in 184 patients with severe RA, whereas hip BMD continued to decrease (37). A review by Kawai *et al*. has not demonstrated any advantages by TNF-α inhibitors use over synthetic DMARDs in patients with RA and spondyloarthropathies (SpA) (38). Interestingly, a recent meta-analysis on TNF-α inhibitors on BMD in RA and

AS trials (39) demonstrated no effects on LS and hip BMD in RA patients, while in AS patients both LS and hip BMD resulted significantly improved. It is important to consider that none of the included trials had BMD as the primary outcome and some of them may have been too short or underpowered to detect meaningful changes. In line with previous results, a 6-year follow-up study in AS showed significantly increased LS and trochanter BMD in patients treated with TNF-α inhibitors compared with that in untreated patients (40). A systematic review and meta-analysis on the effect on BMD of TNF-α inhibitors in AS patients with a minimum follow-up period of 1 year, showed increased LS and total hip (TH) BMD and maintained femoral neck (FN) BMD (41). Recently Manara *et al*. (42) evaluated the effects on BMD of TNF-α inhibitors in clinical studies on RA patients between 2005 and 2014 demonstrating that TNF-α inhibitors were able to arrest systemic bone loss assessed by BMD and BTs.

The effect of TNF-α blockade on fracture risk remains still uncertain. Data from 11,429 RA patients enrolled in the CORRONA database (43) which were treated with synthetic DMARDs or TNF-α inhibitors as monotherapy or synthetic DMARDs combined with TNF-α inhibitors showed that only anti-TNF-α treatment was associated with significantly decreased overall fractures, when compared with other treatments. On the contrary, in a population-based cohort study aimed to evaluate the risk of non-vertebral fractures in patients with RA, Kim *et al*. found a similar risk in patients treated with TNF-α inhibitors with or without a synthetic DMARD, methotrexate (MTX) alone or a synthetic DMARD alone. Multivariate regression did not show any differences between patients on TNF-α inhibitors *versus* MTX (44). More recently, a nested case-control study in 1,515 RA patients treated with TNF-α blockers, abatacept and rituximab and 6,023 controls, with a median duration of exposure of 735 and 645 days, was unable to demonstrate a reduction of non-vertebral fracture rate (45). The same results have been documented in a large retrospective cohort of patients with RA and SpA, who initiated either TNF-α blockers or synthetic DMRDs; the risk of combined fractures did not differ between initiators of a synthetic agent and a TNF-α blocker (46). Also the recent review by Manara *et al*. (42) concluded that there is poor evidence of clinically relevant effect of TNF-α inhibitors in preventing fractures and Zerbini *et al*. (29) concluded that there are still unmet needs for studies regarding this aspect.

IL6 blockade

Garnero *et al*. demonstrated rapid and significant increase of markers of bone formation associated with a significant decrease of markers of bone resorption following the initiation of tocilizumab combined with MTX in 416 patients with active RA (47). These results provide evidence of a reduced joint damage and possibly of beneficial effects on systemic bone homeostasis. Also in the RADIATE study, tocilizumab significantly decreased bone resorption markers and increased bone formation markers, although not significantly, in RA patients (48). A critical role of tocilizumab on bone metabolism was also suggested by a pilot study which in a smaller sample of RA patients (22 women) documented the effect of IL6 blockade on RANKL- and Wnt-mediated pathways with increased OPG/RANKL ratio associated with DKK1 decreased levels after 2 months of treatment (49). More recently the effect of tocilizumab on BMD was evaluated in patients with MTX-resistant active RA (50). Interestingly tocilizumab maintained BMD stable in patients with normal baseline BMD and increased BMD in osteopenic patients at baseline. In contrast, an open prospective study, with a duration of one year in RA active patients receiving tocilizumab and MTX (51), did not show significant changes in BMD. However**,** a significant decrease of serum levels of DKK1 and a significant increase of bone formation marker PINP were associated with tocilizumab. As confirmed by the two recent reviews by Dimitroulas *et al*. (22) and Zerbini *et al*. (29), no data are available on the anti-fracture activity of this agent.

Inhibition of B and T cells

There is a lack of detailed data on the effect on systemic bone loss of rituximab, a CD20 specific antibody which depletes B cells. However, due to the evidence that B cells highly express RANKL and, through their differentiation into plasma cells also activate DKK1, it can be speculated that rituximab can also positively influence bone mass (8). Boumans *et al*. (52) showed that 12 month treatment with rituximab was associated with increased OPG/RANKL ratio in the serum of 28 RA patients. On the contrary, in a prospective study with a follow-up of 15 months evaluating 13 RA patients, a non significant decrease of RANKL was observed after rituximab treatment (53). Wheater *et al*. (54) documented a significant decrease of bone resorption marker CTX associated with a significant increase of bone formation marker PINP after 6 months of treatment with rituximab in 46 RA patients. So far, only a study by Salvin *et al*. specifically documented an improvement in BMD in a small number of RA patients treated with this agent (55).

Although there is a lack of clinical studies with primary outcomes of BMD and/or BTs in RA patients treated with abatacept, preclinical data provide an attractive explanation for a potential antiresorptive effect of this drug (21, 23, 27). In a model of TNF-α-induced arthritis, CTLA4 dose-dependently directly inhibited OC differentiation and maturation by binding their precursor cells (25). Recently, Bozec *et al*. (56) reported that the binding of CTLA4 to CD80/86 in OC precursors induced their apoptosis.

Other agents

To date there are no studies on the effect on BMD, BTs or fracture risk in course of different new biologic agents therapies, also including new selective JAK-inhibitors (tofacitinib and baricitinib). However, beneficial effect on systemic inflammation of all these drugs is likely to positively influence also systemic bone health.

Conclusions

In the last few decades, greater knowledge on immune/inflammatory pathways regulating synovial inflammation and local bony damage has led to remarkable therapeutic advances by introducing biologic agents. Mostly important, powerful and early anti-inflammatory activity evidenced by these drugs suggested their extended effect also on systemic bone homeostasis beyond the control of the disease. Overall, accumulated data deriving from studies, most of them conducted with TNF-α blockers, have reported positive effects on BTs as well as on BMD leading to reduced risk of systemic OP. Whether TNF-α blockers and other biologic agents are ultimately effective in reducing fracture risk remains so far inconclusive. Studies evaluating larger cohorts of patients with longer follow-up, also including newer biologic agents and small molecules, are needed to determine if positive changes in BTs and BMD translate into changes in fracture risk.

Key messages

- OP with increased fracture risk has been reported as one of the most clinically meaningful comorbidities to be screened, prevented and treated in CIRDs.
- Improved understanding of the osteoimmunologic network regulating inflammatory pathway provided evidence that inflammation plays a harmful role on both local and systemic bone loss, which may ultimately lead to disability and mortality. Early and powerful inhibition of inflammation is paramount in counteracting local and systemic bony damage.
- Biologic agents have proved to positively influence disrupted bone homeostasis documented in all CIRDs by interfering with BTs and systemic bone loss. However, if these effects can also translate into reduced fracture risk remains to be determined.
- Whether the co-administration of biologic agents with DNB, the monoclonal antibody against RANKL successfully used in systemic OP, could offer a better outcome in preserving BMD and possibly reduce fracture risk, is not fully investigated.
- Rheumatologists should improve their awareness, so far largely suboptimal, of the need for screening, and prevention, or proper treatment of systemic bone loss and increased fracture rates also in patients placed on biologics.

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