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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

The Effect of TNF Inhibition on Bone Density and Fracture Risk and of IL17 Inhibition on Radiographic Progression and Bone Density in Patients with Axial Spondyloarthritis: a Systematic Literature Review

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Abstract

Purpose of Review Osteoporosis in axial spondyloarthritis may be modified by therapy. The purpose of this systematic review is to describe (i) the effect of TNFi on BMD, (ii) the effect of secukinumab on BMD, and (iii) the effect of secukinumab on radiographic disease progression in axSpA.

Recent Findings We searched PubMed, Embase, and Cochrane using the following retrieval languages: spondyloarthritis, ankylosing spondylitis, TNF, IL-17, x-rays, and osteoporosis. Twenty-nine studies were included; 27 re: TNFi and BMD, and 2 re: IL-17 blockers and x-ray progression. TNFi over 2–4 years increased BMD of the lumbar spine (3.2–14.9%) and hip (2.26–4.7%) without reducing vertebral fractures. Secukinumab reduced radiographic progression; none (73%) and minimal (79%) at 4 years. No data on IL-17 blockade and bone were found.

Summary TNFi therapy improves bone density but not vertebral fracture rates. Secukinumab improves symptoms and may slow radiographic progression. Data is lacking regarding the effects of secukinumab on BMD and fractures. These are important questions which may impact the choice of therapy.

Keywords Axial spondyloarthritis · Ankylosing spondylitis · Osteoporosis · Bone density · TNF inhibitors IL-17 · Secukinumab · Radiographic progress · Vertebral fracture

Abbreviations

axSpA	Axial spondyloarthritis
AS	Ankylosing spondylitis
TNFi	Tumor necrosis factor (TNF) inhibitor
RCT	Randomized control trial
PRISMA	Preferred reporting items for systematic review and meta-analysis
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
ACR	American College of Rheumatology
LS	Lumbar spine
TH	Total hip
FN	Femoral neck
VFx	Vertebral fractures
OTW	Occiput to wall
BASFI	Bath Ankylosing Spondylitis Functional Index
VEs	Vertebral edges

Topical Collection on *Spondyloarthritis*

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Introduction

Axial spondyloarthritis (axSpA), and its prototype, Ankylosing spondylitis (AS), are characterized by new bone formation that produces syndesmophytes that bridge vertebrae resulting in the classic features of the disease. Paradoxically,

axSpA patients simultaneously reabsorb bone and many develop osteoporosis at the spine and hip [1–4], increasing the risk of fractures.

TNF inhibitor (TNFi) therapy is currently recommended for the treatment of axSpA, and studies have demonstrated an associated improvement in bone mineral density (BMD) at the spine and hip [5–7]. The effect of TNFi on the osteoproliferation typical of structural damage in axSpA is not well established. However, recent randomized control trials suggest that patients started on TNFi early in the course of their disease had less progression after 8 years of treatment [8–10].

Recently, the critical role of the IL-23/IL-17 pathway in the development and persistence of AS and axSpA has been discovered [11]. IL-17 is an important mediator of immune response against pathogens but is also a potent mediator of inflammation and tissue damage [12]. Evidence of the involvement of the IL-23/IL-17 pathway in axSpA was initially observed in genetic association studies which demonstrated that polymorphisms in the IL-23 receptor gene were associated with AS [13], and animal studies revealed that IL-23 driven inflammation can lead to new bone formation in an animal model of AS [14]. The PGISp mouse model of AS suggests that inflammation and new bone formation occur sequentially and in fact suggests that inflammation drives increased osteoproliferation through the IL-17/IL-23 pathway [15].

In addition to playing a role in the pathogenesis of axSpA, IL-17 also plays a role in osteoporosis, promoting bone loss by upregulating N-cadherin and inhibiting canonical Wnt signaling, thus inhibiting osteoblast activation [16•]. Tyagi et al. demonstrated that in an oophorectomy mouse model of osteopenia, anti-IL17 antibody protects against bone loss by suppressing osteoclast function and promoting osteoblast differentiation. These osteoprotective effects were superior to the effects seen by blocking osteoclast activation by RANKL or TNFi [17]. Molnar et al. reported that post-menopausal women with higher IL-17A levels had lower lumbar spine BMD and higher sRANKL [18]. Azizieh et al. reported that women with low BMD produced higher levels of IL-17 along with other pro-resorptive cytokines such as TNF alpha, as compared with women with normal BMD [19].

As a result of these data, IL-17 blocking agents have recently been introduced for the treatment of AS/axSpA. Recent randomized controlled trial (RCT) results suggest that IL-17 blockade with secukinumab may provide structural modification at 2 and 4 years [20••, 21]. There is limited data on the effects of IL-17 blockade on bone density and effects on bone turnover markers and fracture risk are not known.

In this paper, we review the available literature on the effects of treatment of axial spondyloarthritis on bone health. The majority of studies have focused on TNF inhibition. More recent data from studies of IL-17 inhibitors was also included.

Methods

Systematic Review

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [22]. Eligible studies for inclusion met the following criteria: our population of interest was participants aged 18 years or older who had AS defined by 1984 modified New York criteria [23] or who met criteria for axial spondyloarthritis through the imaging arm of the ASAS criteria [24]. Interventions included any available TNFi agents or secukinumab with follow-up of at least 48 weeks. We performed three separate searches.

1. Effect of TNFi on BMD
2. Effect of secukinumab on BMD
3. Effect of secukinumab on radiographic disease progression

Our primary outcome was bone density by DXA and secondary outcome for bone metabolism was vertebral fractures. Radiographic disease progression was assessed with modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). High quality randomized controlled trials or prospective observational cohort studies were sought.

Search Strategy and Study Selection

PubMed, Embase, and Cochrane databases were searched from the inception of each database to October 17, 2017, using the following retrieval languages for both subject headings and keywords (spondyloarthritis, ankylosing spondylitis, TNF, IL-17, x-rays, osteoporosis). In addition, Clinicaltrials.gov and Conference proceedings were screened for search 2. Publication language was restricted to English. Two of the three reviewers selected studies independently based on prespecified inclusion and exclusion criteria. Conflicts of opinion between investigators were resolved by the third reviewer.

Results

For search 1, we identified 283 studies, 53 duplicates were eliminated and 230 underwent full review. For search 2, we identified 317 studies in the three databases and an additional 100 searching Clinic.trials.gov and Conference proceedings; 34 duplicates were removed for a total of 383 which underwent full review. Our search identified 102 studies for search 3; 10 duplicates were eliminated and 92 underwent full review. In all, 802 titles were screened by title and abstract, 97 duplicates were removed for a total of 705 that underwent full review. Studies in which disease progression was investigated

Table 1 Characteristics of Eligible Studies

Author design	Subjects	Study	Intervention	Duration	Outcome	Findings
Li et al.; 2015 [26]	89 patients with active AS meeting modified NY criteria and low bone density	Open label prospective observational study	ETN/ADA in 42 patients vs Sulfasalazine in 47	1 year	DXA at LS and FN, serum CTX and serum PINP	Significant increase in LS and FN BMD in TNFi group (14.9% ± 15.6% and 4.7% ± 7.9%, respectively). Significant decrease in control group (− 8.6 ± 9.7 in LS and − 9.8 ± 11.5 in FN). sCTX significantly decreased in study group (− 40%). BSalkphos and PINP increased (45% and 30.8%, respectively.
Venceviciene et al.; 2015 [27]	41 patients fulfilling Euopean Spondyloarthropathy Study Group criteria for SpA.	Open label prospective observational study	TNFi in 9 patients vs variety of DMARDs in 32 patients	4 years	DXA at TH	27% of SpA patients experienced significant proximal femoral bone loss defined as 4% or greater. TNFi treatment made BMD loss unlikely.
Briot et al.; 2016 [28]	265 patients with early inflammatory back pain and symptoms suggestive of SpA. 79.6% fulfilled ASAS criteria for axSpA. (DESIR cohort)	Longitudinal prospective cohort study	TNFi in 89 patients ± NSAIDs; 176 without TNFi	2 years	DXA at LS and TH	LS BMD increased from baseline significantly (3.2% ± 8) and TH BMD did not change (0.6% ± 4.1) in TNFi-treated patients. LS BMD did not change (0.3% ± 5.3) and TH BMD decreased significantly (−0.8% ± 3.9) in patients without TNFi. Baseline use of NSAIDs had a protective effect on hip bone loss.
Van der Weijden et al.; 2016 [29•]	49 patients with AS meeting modified NY criteria	Open label prospective study	ETN	2 years	DXA at LS and TH; lateral radiographs of thoracic and LS	LS BMD increased significantly (7% ± 9.5). Hip BMD increased significantly (2.2% ± 5.7).
Maas et al.; 2016 [30]	105 patients with active AS meeting modified NY criteria. (GLAS cohort)	Prospective, longitudinal, observational cohort study	IFN, ETN or ADA	4 years	DXA at LS and TH; lateral radiographs of thoracic and LS	LS BMD Z scores increased significantly from baseline (− 0.52 ± 1.49) after 4 years of TNFi treatment (0.7 ± 1.7). Hip BMD also increased from baseline (− 0.4 ± 1) at 4 years (0.1 ± 1.2) although less so.

by mSASSS in patients treated with secukinumab or in which bone loss was investigated by using DXA in patients treated with either TNFi or secukinumab were eligible.

Of the 705 studies that underwent full review, 676 were eliminated as not meeting pre-specified criteria for study population, study design, follow up, intervention, or outcomes.

We included 29 studies for full-text review; 27 regarding the effect of TNFi on BMD, 2 of which also studied the effect of TNFi on vertebral fracture. Of these, we excluded studies previously reported in the seminal SLR and meta-analysis published by Haroon et al. in 2014, leaving 5 full-text papers which fulfilled the inclusion and exclusion criteria for search 1 (Table 1). Two studies (one paper and one abstract) addressed x-ray progression in the setting of IL-17 blockers; both from the Measure 1 investigators. There were 0 studies examining the effect of secukinumab on bone density. An independent review by DA and SG of the abstracts from the 2018 American College of Rheumatology (ACR) meeting revealed one study addressing the effect of secukinumab on bone density. We were unable to perform a meta-analysis of the data due to methodologic differences and heterogeneity between studies.

Effect of TNFi on BMD

Haroon et al., publishing in 2014, report in a systematic literature review and meta-analysis that TNFi can increase BMD by DXA at the lumbar spine (LS) and total hip (TH) and maintain BMD at the femoral neck (FN) for up to 2 years in patients with AS. Included in this study are seven longitudinal studies and one randomized control trial, with a total of 568 AS patients. LS BMD increased by 5.1% after 1 year of treatment with TNFi and by 8.6% after 2 years. At the TH, BMD improved significantly by 1.8% after 1 year of treatment and 2.5% after 2 years. Compared with baseline, FN BMD remained stable after 1 year and there was not enough data to analyze results at 2 years. The effect of confounding factors that could influence the response of BMD (intake of Vitamin D, calcium, corticosteroids, NSAIDs) was not available in all the included studies [25].

Table 1 provides an overview of five studies published since 2014 [26–28, 29•, 30] examining the effect of TNFi on BMD. All are prospective cohort studies rendering these papers low for quality of evidence (QoE) using GRADE methodology [31].

Li et al. present data in a group limited to ankylosing spondylitis patients with active disease (BASDAI > 4). DXA studies in TNFi-treated patients showed a significant increase in LS and FN BMD as compared with Sulfasalazine-treated patients in whom significant decreases were observed at both sites. There was also a significant decrease in bone resorption markers and an increase in bone formation markers in the TNFi-treated group [26].

Briot et al. present 2-year data of BMD changes and their determinants in patients with early inflammatory back pain suggestive of axial spondyloarthritis, enrolled and followed prospectively in the DESIR cohort. Of 265 patients enrolled, 80% fulfilled the ASAS criteria for axSpa, 71% used NSAIDs at baseline, and 34% received TNFi therapy over 2 years. Similar to the prior studies, BMD significantly increased at the LS. However, there was no significant change at TH. Total hip BMD did decrease in patients without TNFi therapy (−0.8% + 3.9%) and this was significantly different than the group that received TNFi ($P = 0.003$). In multivariate analysis, baseline use of NSAIDs had a protective effect on hip bone loss [28]. The remaining three studies also report increases in BMD at the LS, hip, or both sites.

In summary, the eight studies reported on by Haroon et al. as well as the five additional studies published since 2014 all report a significant increase in the bone density of the LS with TNFi but benefits to bone density at the hip are less clear. In total, 11 of the 13 studies examined BMD at the TH and 8 of these reported a significant increase. Six out of 11 studies examined FN BMD; 2 reported a significant increase and 1 reported a trend towards an increase [7, 26, 32]. This discrepancy may relate in part to the decreased precision in FN measurements. Briot et al. in their initial study in 2013 report a positive effect of TNF blockade on total hip BMD but in their follow-up study in 2016, they report that in multivariate analysis, this improvement is ascribed to baseline use of NSAIDs rather than TNFi agents [28]. (Table 1).

Effect of TNFi on Fracture

No RCT has been powered to investigate the effect of TNFi on fracture occurrence. In fact, the data on fractures in TNFi-treated patients comes from observational studies. For these reasons, whether these medications reduce risk of fracture is not clear. Van der Weijden et al. report that among the 49 patients treated with TNFi, the number of patients with vertebral fractures (VFx) increased from 6 patients at baseline to 15 patients at 2 years, as did the severity of the VFx. No variable was shown to be associated with these incident VFx (age, BMD, disease activity, radiological damage). Because BMD has been shown to be a limited predictor of fracture risk, the authors also studied bone turnover markers. The results, however, showed that change in markers of bone turnover (CTX, osteocalcin, RANKL or OPG) were not associated with fracture occurrences over 2 years of etanercept treatment [29•].

An extension study of this cohort, in which LS and TH BMD improved over 4 years of treatment, found that in 13 patients (12.1%), 14 VFx were observed at baseline. After 4 years of TNFI treatment, 26 VFx were observed in 21 patients. Of these 21 patients, 4 with > 1 VFx had a decreased BMD at hip and lumbar spine while the remaining 17 patients

had a normal BMD. The majority of VFx were in the mid or lower thoracic spine [33].

Maas et al. also studied rates of vertebral fractures in their cohort of 105 AS patients with active disease (BASDAI 6.0 ± 1.7). They reported that 27 of 105 AS patients (26%) had radiographic vertebral fractures at baseline. During 4 years of TNFi therapy, 21 (20%) of patients developed at least one new fracture. Most vertebral fractures were mild and were located in the lower thoracic spine. They reported, as did the prior study, that clinical disease activity and LSLS BMD improved during treatment. However, with both studies, it is not clear that DXA scans were reviewed and fractured vertebra omitted from analysis. If they were included, fractures of the LS could falsely elevate BMD. In contrast to the prior study by van der Weijden et al., Maas et al. did identify risk factors for presence of vertebral fractures at baseline which included older age, higher occiput to wall (OTW) at baseline, and a higher mSASSS. The development of new vertebral fractures was associated with low baseline LS BMD, older age, longer smoking duration, and worse function, measured as a higher score on the Bath Ankylosing Spondylitis Functional Index (BASFI) [30].

Effect of Secukinumab on Radiographic Progression and Bone Density

Interleukin-17A, a pro-inflammatory cytokine, has been shown to play a role in different features of spondyloarthritis, including inflammation as well as pathogenic bone remodeling. These initial findings led to the MEASURE1 study evaluating the effect of secukinumab, an IL-17A inhibitor, on clinical signs, symptoms, and radiographic changes in patients with ankylosing spondylitis. Radiographic progression was measured using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), with scores of 0–72 [34]. In the phase III MEASURE1 trial, Braun et al. present outcome data and conclude that at week 104, secukinumab improves AS signs and symptoms with minimal progression in mSASSS [20••].

Data from the MEASURE 1 extension trial out to 4 years (208 weeks) was presented in abstract form at the American College of Rheumatology 2017 meeting. Efficacy data at week 208 was reported for 78/87 patients originally assigned to 150 mg subcutaneous (sc) dosing who completed 208 weeks of follow up. The mean (± SD) change in mSASSS from BL to week 208 was lower with secukinumab 150 mg sq. (1.2 ± 3.91) vs 75 mg (1.7 ± 4.70). No radiographic progression was seen in 73% (mSASSS change < 0) and 79% showed minimal change (mSASSS change < 2) [21]. In addition, the MEASURE1 investigators have published MRI data in 10 subjects treated with secukinumab through 94 weeks, evaluating the effect of treatment on MRI inflammatory/non-inflammatory (fatty) changes at vertebral edges (VEs). These data demonstrated resolution of 79/91 (87%) inflammatory VEs present at baseline by week 94; suggesting regression of spinal inflammation [35].

Initial data of the effect of secukinumab on BMD from the MEASURE1 trial was presented in abstract form at the 2018 American College of Rheumatology meeting. In 104 AS patients treated for 2 years with 150 mg sc of secukinumab, an increase of 2.6% and 4.7% change from baseline was seen at the LS at 52 and 104 weeks, respectively, with small increases at the total hip (0.9% and 0.5%) and at the femoral neck (0.8% and 0.2%). There was no consistent pattern of change in bone turnover biomarkers at 2 years although levels of the bone resorption biomarker Type 1 collagen C-telopeptide remained stable [36].

Discussion

Bone metabolism is mediated by a balance of osteoblast and osteoclast function. During inflammation, immune cells release multiple cytokines including TNF, IL-6, IL-1, and IL-17 that participate in shifting the balance in favor of osteoclast function and bone resorption. Use of TNFi has been shown to decrease inflammatory bone loss. Given the preliminary data, it is reasonable to hypothesize that use of IL-17 blockers may also inhibit inflammatory bone loss.

Our aim in this review was to examine the literature for evidence of the effect of TNFi and IL-17 inhibitors on bone metabolism in axial spondyloarthritis patients. We limited our literature search to RCTs and prospective observational cohort studies. While there were numerous studies which examined the effects of TNFi on bone metabolism in these patients; no published studies were identified that evaluated the effects of secukinumab on BMD in this group. We were also unable to find studies of bone metabolism in secukinumab-treated patients with psoriasis or psoriatic arthritis, although this population was not included in our formal search.

In studies of patients with AS/SpA, TNFi were associated with increases in both lumbar spine and hip BMD. The presence of syndesmophytes may falsely elevate the spine BMD however this should not be the case in the evaluation of the hip. The effect of TNFi on the osteoproliferation that characterizes structural damage in axSpA is not clear, although recent publications suggest some improvement after 8 years of treatment in those started on TNFi therapy early in the course of disease who have remained on therapy. The MEASURE1 trial has demonstrated a low mean progression of spinal radiographic change at weeks 104 and 208 with secukinumab; earlier time points than seen with TNFi, although they were not directly compared. Concomitant data showing that evidence of inflammation on LS MRI in vertebral edges is significantly decreased lends further credence to the possibility that a decrease in vertebral inflammation may lead to inhibition of bone loss in axSpA patients treated with secukinumab. This

evidence for early decrease in inflammation at vertebral edges increases the likelihood that treatment with secukinumab may decrease the number and severity of vertebral fractures with treatment, an effect not seen with treatment with TNFi.

This review is limited by the differences in reported outcomes that prevented us from pooling data to increase the power of our analysis. In addition, no studies compared TNFi and Il-17 inhibitors directly. Nonetheless, this paper has gathered the available evidence regarding these therapies to try and better understand the effects of treatment on bone density in axSpA.

The studies presented in this review suggest the possibility that treatment with IL-17 antagonists, in addition to improving clinical symptoms and disease progression, may prevent the bone loss and osteoporosis associated with axSpA. Further studies evaluating the effects of secukinumab on bone loss and fractures as well as direct head to head comparisons of the effects of TNFi and IL17 blockers remain important questions. More research is required to study the mechanisms of bone loss and bone formation in relation to bone density in AS and the influence of biologic treatments on fracture risk.

Conclusions

Patients with axSpA are at increased risk for osteoporosis and fractures. Clinicians should be mindful of this risk and monitor patients appropriately. TNFi is widely used in treatment of axSpA and also improve bone density at the lumbar spine and to a lesser degree at the hip. Thus far, a decrease in vertebral fractures has not been demonstrated. Secukinumab has more recently been introduced in treatment for axSpA and ongoing investigations suggest that this treatment may be efficacious in preventing disease progression Additional studies are needed to determine whether IL-17 inhibition by secukinumab translates into improved bone density and lower risk of fractures. The answers to these as yet unanswered questions will have important clinical relevance in choosing therapy for patients with spondyloarthritis.

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Authors' Contributions DA, EMS, and SMG contributed to the conception and design of the review and assessed all papers, data extraction, and quality assessment. DA, EMG, RG, and SMG performed the literature search. DA drafted the paper; EMS and SMG revised the article for important intellectual content. All authors gave final approval of the version to be published.

Compliance with Ethical Standards

Conflict of Interest Dr. Goodman reports grants from Novartis, personal fees from Novartis, personal fees from Pfizer, personal fees from UCB, grants from Horizon, outside the submitted work.

Dr. Ashany reports grants from Novartis, outside the submitted work.

Emily M. Stein and Rie Goto declare that they have no conflict of interest.

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

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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- •• Of major importance

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