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Arends, Suzanne; Spoorenberg, Anneke; Brouwer, Elisabeth; van der Veer, Eveline

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Clinical studies on bone-related outcome and the effect of TNF-α blocking therapy in ankylosing spondylitis

Suzanne Arends[a,b], *Anneke Spoorenberg*[a,b], *Elisabeth Brouwer*[a], *and Eveline van der Veer*[c]

Purpose of review
To provide an overview of clinical trials and observational studies investigating the effect of tumor necrosis factor-alpha (TNF-α) blocking therapy on bone formation and bone loss in patients with ankylosing spondylitis (AS).

Recent findings
The effect of TNF-α blocking therapy on excessive bone formation or osteoproliferation remains inconclusive. Radiographic assessment of spinal osteoproliferation is complicated by the overall slow rate of progression and the high variability between individual AS patients. Multiple studies demonstrated that TNF-α blocking therapy results in a significant increase in bone mineral density (BMD) at the lumbar spine and hip. Based on bone turnover marker (BTM) analysis, this can mainly be explained by an increase in mineralization and decrease in bone resorption.

Summary
Both osteoproliferation (e.g. syndesmophytes and ankylosis of vertebrae) and excessive bone loss resulting in osteoporosis and vertebral fractures are frequently present in AS. Previous studies showed that BMD increases during TNF-α blocking therapy. Long-term follow-up in a large cohort of patients is needed to investigate whether TNF-α blockers can consolidate or stop spinal osteoproliferation and prevent vertebral fractures. Future studies should focus on the effect of these agents on bone-related outcome in AS patients with early vs. advanced disease.

Keywords
ankylosing spondylitis, osteoporosis, radiographic damage, TNF-α blocking therapy, vertebral fractures

INTRODUCTION

TNF-α blocking therapy has proven to be very effective in controlling systemic inflammation and improving clinical assessments such as pain, fatigue, physical function, and health-related quality of life in the majority of patients with ankylosing spondylitis (AS). As excessive bone formation and bone resorption are both well recognized features of AS, it is also important to have knowledge about the effect of TNF-α blocking agents on bone-related outcomes.

Radiographic outcome related to excessive bone formation, so-called osteoproliferation, comprises the formation of syndesmophytes and ankylosis of the axial skeleton. Eventually, complete fusion or ankylosing of vertebrae can result in a 'bamboo spine'. The modified Stoke AS Spinal Score (mSASSS) is most widely used in clinical research to assess chronic spinal changes. The lateral view of conventional radiographs of the cervical and lumbar spine are used to score the anterior corners of the vertebrae for the presence of erosions, sclerosis, and/or squaring (1 point per site), nonbridging syndesmophytes (2 points per site), and bridging syndesmophytes (3 points per site) [1].

[a]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, [b]Rheumatology, Medical Center Leeuwarden and [c]Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands

Correspondence to S. Arends, PhD, University Medical Center Groningen, Rheumatology and Clinical Immunology, P.O. Box 30001, 9700 RB Groningen, The Netherlands. Tel: +31 503613432; fax: +31 503619308; e-mail: s.arends@umcg.nl

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KEY POINTS

- The effect of TNF-α blocking therapy on radiographic outcome remains inconclusive.
- The radiographic assessment of spinal osteoproliferation in AS is complicated by the overall slow rate of progression and the high variability between individual patients.
- TNF-α blocking therapy results in a significant increase in BMD, accompanied by an increase in bone mineralization and decrease in bone resorption measured with BTM.
- Conventional radiographs of the spine with a minimum interval of 2 years should be considered during follow-up of AS patients in order to detect patients with rapid osteoproliferation and new vertebral fractures.
- Further research with long-term follow-up is needed to investigate whether TNF-α blocking therapy has effect on the development of spinal osteoproliferation and vertebral fractures in AS patients with early vs. advanced disease.

Outcome related to excessive bone loss includes osteoporosis and vertebral fractures. Bone mineral density (BMD) is usually monitored with dual-energy X-ray absorptiometry (DXA) at the hip and lumbar spine. According to the WHO classification, osteopenia is defined as T score between −1 and −2.5 and osteoporosis as T score −2.5 or less [2]. Bone turnover markers (BTMs) measured in serum or urine can be used to monitor more rapid changes in the bone metabolism. As BTM levels are influenced by age and sex, it is essential to use adequate healthy reference groups for the correct interpretation of results. Vertebral fractures are defined as height loss at the anterior, middle, or posterior part of the vertebral body on conventional radiographs of the thoracic and lumbar spine. According to the Genant classification, grade 1 fracture is defined as 20–25% reduction, grade 2 as 25–40% reduction, and grade 3 as more than 40% reduction [3].

The purpose of this review is to provide an overview of randomized controlled trials (RCTs) and observational studies that investigated the effect of TNF-α blocking therapy on bone formation and bone loss in patients with AS.

BACKGROUND ON BONE-RELATED OUTCOME IN ANKYLOSING SPONDYLITIS

Cohort studies using data from daily clinical practice are important and helpful to obtain information on the natural course of bone-related outcome in AS. Identifying AS patients who are at risk to develop severe disease outcome can help physicians in the process of decision-making on the management of AS, aiming at healthy aging with this chronic autoinflammatory disease.

Long-term follow-up (up to 12 years) of 186 AS patients from the Outcome in AS International Study (OASIS) cohort demonstrated that spinal radiographic progression is linear at group level, with a mean progression rate of 0.98 mSASSS units per year (on a scale of 0–72). However, the individual variation within this population was very large. The mean 2-year progression rate was 2.0 (SD 3.5) mSASSS units. After a mean follow-up time of 7.9 years, at least one new syndesmophyte was found in 55–63% of patients, whereas 24% showed no radiographic progression [4▪▪].

This high variability between individuals is in line with a retrospective study of 146 patients with advanced AS (defined as long disease duration and extensive radiographic damage), which were hospitalized for different reasons, for example, pain, disease activity, and functional decline. In this Herne cohort, the mean radiographic progression was 1.3 (SD 2.5) mSASSS units per year. Of all patients, 43% showed a progression rate that was four-fold higher than the mean change in mSASSS, and 23% had no radiographic progression after a mean follow-up time of 3.8 years [5].

A recent analysis of the German Spondyloarthritis Inception Cohort (GESPIC) cohort showed that definite radiographic progression, defined as 2 mSASSS units after 2 years, occurred in 20% of the 115 AS patients with symptom duration 10 years or less compared with 7% of the 95 nonradiographic axial spondyloarthritis (SpA) patients with symptom duration 5 years or less ($P = 0.01$). Mean 2-year progression rate was 0.95 (SD 2.78) and 0.46 (SD 1.63) mSASSS units, respectively ($P = 0.23$) [6].

The most important prognostic factor for the development of more extensive radiographic damage is the presence of syndesmophytes at study entry [5,7,8]. Other characteristics that may play a role include male sex, longer disease duration, smoking, HLA-B27 positivity, and increased inflammatory markers [4▪▪,6,9▪].

The prevalence of osteoporosis varies largely between studies in AS, ranging from 16 to 62% [10]. Based on more recent prospective studies [11–13], the prevalence rate of osteoporosis can be estimated at approximately 25%. Recently, a systematic review in 'early' AS, defined as less than 10 years after diagnosis, reported that osteoporosis at the lumbar spine and femoral neck occurred in 16% (range 8–29) and 13% (range 3–25) of the patients, respectively [14▪]. Osteoporosis can thus

already be observed at early stages of the disease. The anterior–posterior view of the lumbar spine DXA is very useful in early AS. However, physicians should be aware that this measurement can be overestimated by the presence of syndesmophytes and fusion of facet joints in patients with more advanced disease [15,16]. Furthermore, it is important to exclude fractured vertebrae from BMD analysis.

Until now, conflicting results on BTM were reported in AS, which may partly be explained by differences in disease activity, disease duration, age and sex, comorbidity such as inflammatory bowel disease, use of medication, and BTM assays. This variability can be reduced by the standardization of measurements and the implementation of international reference standards [17]. In the majority of studies, markers of bone resorption (deoxypyridinoline; DPD, type I collagen N-telopeptide; NTX, or type I collagen C-telopeptide; CTX) were increased in AS, although no differences were found in the markers of bone formation (bone-specific alkaline phosphatase; BALP, procollagen type 1 N-terminal peptide; PINP, or osteocalcin) between AS patients and healthy controls [18]. Multiple studies [16,19,20] found a significant association between high levels of bone resorption and low hip BMD. Inflammatory processes, low serum levels of vitamin D, use of medication, and decreased mobility related to pain, stiffness, and the presence of radiographic damage may also contribute to the development of osteoporosis in AS patients [11,16,21,22].

Large population-based studies [23,24] showed that AS patients have a 3.3–7.6-fold increased risk on clinical vertebral fractures, with a prevalence rate of 10–17%. Diagnosing vertebral fractures is complicated by the facts that no typical symptoms of acute fracture occur in two-thirds of the cases, acute and chronic back pain is common in AS, and fractures of the vertebral body are often overlooked on radiographs [25]. The total prevalence of vertebral fractures, defined as more than 20% reduction in vertebral height, reported in different studies [11,13,16,26] varies from 12 to 43%.

Male sex, older age, longer disease duration, low body weight, high disease activity, low hip BMD, radiographic damage, worse spinal mobility, and peripheral joint involvement have been identified as risk factors for the occurrence of vertebral fractures in AS [25].

In summary, both osteoproliferation (e.g. syndesmophytes and ankylosis) and excessive bone loss resulting in osteoporosis and vertebral fractures occur frequently in AS. The natural course of the disease can vary from mild to severe axial involvement and from slow to rapid radiographic progression. The presence of syndesmophytes at study entry is the most important predictor for the development of more extensive radiographic damage. Physicians should be aware that osteoproliferation could cause overestimation of anterior–posterior lumbar spine DXA in patients with advanced AS. Furthermore, vertebral fractures are easily missed due to the lack of symptoms or poor recognition. Conventional radiographs of the spine with a minimum interval of 2 years should be considered to timely recognize AS patients with rapid radiographic progression and the development of vertebral fractures in daily clinical practice. BTM can be useful to monitor rapid changes in the bone metabolism. However, standardization of measurements and the use of reference values are essential to reduce variability. Longitudinal studies are needed to assess the value of BTM as biomarkers for bone-related outcome in AS.

EFFECT OF TNF-α BLOCKING THERAPY ON OSTEOPROLIFERATION

Although TNF-α blocking therapy results in a clear improvement of clinical outcome in AS patients who do not respond to conventional treatment, there is an ongoing scientific debate whether these agents can consolidate or prevent spinal osteoproliferation. It has been argued that after the inhibition of present and advanced inflammation by TNF-α blocking therapy, repair processes and bone formation will persist because these pathways were already triggered. This mechanism, known as the 'TNF brake hypothesis', may result in further progression of radiographic damage. However, if early inflammatory lesions resolve by TNF-α blocking therapy before the development of such repair processes and the development of new lesions can be prevented, long-term treatment may be able to inhibit radiographic progression over time. A recent MRI study [27▪] showed that new syndesmophytes developed significantly more often from vertebral corners that had fat lesions and/or advanced (type B) vertebral corner inflammatory lesions compared with acute (type A) or no vertebral corner inflammatory lesions in 76 AS patients during 2 years of adalimumab treatmen.

Previous studies [4▪▪,9▪,29–35,36▪] have reported inconsistent results regarding the effect of TNF-α blocking therapy on spinal osteoproliferation in AS patients fulfilling the modified New York criteria [28] (Table 1). In line with the TNF brake hypothesis, data from multiple RCTs showed that radiographic progression could not be inhibited during 2–4 years of treatment with various TNF-α blockers [29–34]. A tendency for decrease in the number of new syndesmophytes over time was

Table 1. Overview of studies investigating the effect of TNF-α blocking therapy on spinal osteoproliferation in ankylosing spondylitis patients fulfilling the modified New York criteria

Reference	Treatment groups, number of patients	Patient characteristics[b]	Study design, radiological scoring method	Follow-up	Baseline mSASSS (mean ± SD, median)	Follow-up mSASSS (mean ± SD, median)	Change in mSASSS (mean ± SD, median)
Baraliakos *et al.* [29]	Infliximab: $n=41$	Age: 39 (21–53)[c]; Male: 63%; DD: 16 (3–35); HLA-B27+: 90%; BASDAI: 6.3 (3.8–8.8)	Prospective, RCT vs. observational cohort; Radiographs: randomized, blinded for clinical data, time; Observers: 1	2 years	12.1 ± 16.9	12.5 ± 17.0	Δ0–2 yr: 0.4 ± 2.7[a]
	Standard (GESPIC): $n=41$	Age: 35 (22–76); Male: 71%; DD: 6 (1–10); HLA-B27+: 85%; BASDAI: 3.2 (0.2–7.0)			5.9 ± 13.4	6.6 ± 14.8	Δ0–2 yr: 0.7 ± 2.8
Van der Heijde *et al.* [30]	Infliximab: $n=201$ (mSASSS 0–2: 190–156)	Age: 40 ± 11; Male: 78%; DD: 10 ± 9; HLA-B27+: 87%; BASDAI: 6.5 ± 1.5	Prospective, RCT vs. observational cohort; Radiographs: randomized, blinded for clinical data, time; Observers: 2	2 years	17.7 ± 17.9 (10.8)	18.1 ± 17.5 (11.5)	Δ0–2 yr: 0.9 ± 2.6 (0.0)[a]
	Standard (OASIS, all): $n=192$ (mSASSS 0–2: 176–165)	Age: 44 ± 13; Male: 67%; DD: 11 ± 9; HLA-B27+: 84%; BASDAI: 3.5 ± 2.1			15.8 ± 18.1 (8.8)	16.6 ± 18.4 (9.0)	Δ0–2 yr: 1.0 ± 3.2 (0.0)
	Standard (OASIS, matched): $n=70$ (mSASSS 0–2: 65–61)	Age: 44 ± 13; Male: 67%; DD: 10 ± 9; HLA-B27+: 84%; BASDAI: 5.7 ± 1.3			17.5 ± 19.1 (9.7)	18.4 ± 19.0 (10.1)	Δ0–2 yr: 1.2 ± 3.9 (0.0)
Van der Heijde *et al.* [31]	Etanercept: $n=257$	Age: 41 ± 10; Male: 76%; DD: 10 ± 9; HLA-B27+: 78%; BASDAI: 6.3 ± 2.1	Prospective, RCT vs. observational cohort; Radiographs: randomized, blinded for clinical data, time; Observers: 2	2 years	16 ± 18.3		Δ0–2 yr: 0.9 ± 2.5[a]
	Standard (OASIS, all): $n=175$	Age: 44 ± 13; Male: 69%; DD: 11 ± 9; HLA-B27+: 81%; BASDAI: 3.5 ± 2.1			14 ± 17.6		Δ0–2 yr: 1.0 ± 3.2
	Standard (OASIS, matched): $n=76$	Age: 48 ± 12; Male: 71%; DD: 12 ± 10; HLA-B27+: 84%; BASDAI: 4.7 ± 2.0			19 ± 20.8		Δ0–2 yr: 1.3 ± 3.6
Van der Heijde *et al.* [32]	Adalimumab: $n=307$	Age: 42 ± 12; Male: 77%; DD: 11 ± 9; BASDAI: 6.2 ± 1.7	Prospective, RCT vs. observational cohort; Radiographs: randomized, blinded for clinical data, time Observers: 2	2 years	19.8 ± 19.3		Δ0–2 yr: 0.8 ± 2.6[a]
	Standard (OASIS, all): $n=169$	Age: 44±13; Male: 69%; DD: 11 ± 9; BASDAI: 3.4 ± 2.1			15.8 ± 17.6		Δ0–2 yr: 0.9 ± 3.3
	Standard (OASIS, matched): $n=77$	-					Δ0–2 yr: 0.9 ± 4.1

Haroon *et al.* [9▪]	TNF-α blockers: $n=201$	Age: 39 ± 13; Male: 83%; DD: 16 ± 12; HLA-B27+: 82%; BASDAI: 4.6 ± 2.5	Prospective, observational cohort; Radiographs: blinded for clinical data, chronological time order; Observers: 1	Mean 2.9 ± 1.2 years (range 1.5–9)	10.6 ± 14.9		Less radiographic progression in patients receiving TNF-α blockers: OR 0.52 (0.30–0.88)
	Standard: $n=133$	Age: 43 ± 14; Male: 68%; DD: 16 ± 14; HLA-B27+: 85%; BASDAI: 3.6 ± 2.4			8.2 ± 13.8		Zero-inflated negative binomial model: less radiographic progression in patients receiving TNF-α blockers after >3.9 years
Baraliakos *et al.* [33]	Infliximab: $n=33$	Age: 44 ± 8; DD: 19 ± 9; BASDAI: 6.6 ± 1.4	Prospective, RCT; Radiographs: blinded; Observers: 1	4 years	11.6 ± 15.3	13.2 ± 16.7	Δ0–2 yr: 0.9 ± 2.3; Δ0–4 yr: 1.6 ± 2.6
Braun *et al.* [34]	Golimumab 50 mg: $n=138$ (mASSS 0 + 4 : 111)	Age: 38 (30–47)[d]; Male: 74%; DD: 11 (6–18); HLA-B27+: 82%; BASDAI: 6.6 (5.6–7.6)	Prospective, RCT; Radiographs: randomized, blinded for clinical data, time; Observers: 2	4 years	11.7 ± 16.4 (3.1)		Δ0–2 yr: 0.9 ± 2.7 (0.0)[a]; Δ0–4 yr: 1.3 ± 4.1 (0.0)[a]
	Golimumab 100 mg: $n=140$ (mASSS 0 + 4: 122)	Age: 38 (29–46); Male: 70%; DD: 10 (4–18); HLA-B27+: 84%; BASDAI; 7.0 (6.0–7.9)			13.5 ± 18.9 (3.5)		Δ0–2 yr: 0.9 ± 3.9 (0.0); Δ0–4 yr: 2.0 ± 5.6 (0.0)
	Placebo (24 wks), golimumab 50 mg: $n=78$ (mASSS 0 + 4: 66)	Age: 41 (31–50); Male: 71%; DD: 16 (6–25); HLA-B27+: 85%; BASDAI: 6.6 (5.7–7.7)			16.1 ± 18.7 (7.9)		Δ0–2 yr: 1.6 ± 4.6 (0.0); Δ0–4 yr: 2.1 ± 5.2 (0.0)
Baraliakos *et al.* [35]	Infliximab: $n=73$	Age: 41 ± 11; Male: 86%; DD: 10 ± 8; HLA-B27+: 84%; BASDAI: 6.5 ± 1.4	Prospective, extension trial; Radiographs: blinded for clinical data; Observers: 1	5 years			Δ0–2 yr: 35 new syndesmophytes; Δ2–5yr: 26 new syndesmophytes
Ramiro *et al.* [4▪▪]	Total group: $n=186$; 22% exposed to TNF-α blockers, 5% before 8 years of follow-up (mASSS 0 + 12: 64)	Age: 43 ± 12; Male: 70%; DD:20 ± 12; HLA-B27+: 83%; BASDAI: 3.4 ± 2.0	Prospective, observational cohort; Radiographs: blinded for clinical data, chronological time order; Observers: 2	Mean 7.9 ± 4.0 years (range 2–12)	11.6 ± 16.2	12 yr: 24.5 ± 21.7	Δ0–12 yr: 11.7 ± 11.5, progression rate 0.98 mSASSS units/year; Δ0–12 yr: higher in patients ever exposed to TNF-α blockers: 1.54 vs. 0.82 mSASSS units/year (interaction $P=0.041$)

(*Continued*)

Table 1 (*Continued*)

Reference	Treatment groups, number of patients	Patient characteristics[b]	Study design, radiological scoring method	Follow-up	Baseline mSASSS (mean ± SD, median)	Follow-up mSASSS (mean ± SD, median)	Change in mSASSS (mean ± SD, median)
Baraliakos *et al.* [36▪]	Infliximab: $n = 22$	Age: 39 ± 8; Male: 64%; DD: 16 ± 9; HLA-B27+: 91%; BASDAI: 6.2 ± 1.4	Retrospective, observational cohorts; Radiographs: blinded for clinical data, time; Observers: 2	8 years	13.2 ± 17.6	20.2 ± 21.4	Δ0–4 yr: similar between both groups; Δ4–8 yr: lower in patients receiving TNF-α blockers ($P = 0.03$)
	Standard (Herne): $n = 34$	Age: 50 ± 12; Male: 85%; DD: 21 ± 6; HLA-B27+: 65%; BASDAI: 4.3 ± 1.4			14.2 ± 13.8	25.9 ± 17.8	

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DD, disease duration; GESPIC, German Spondyloarthritis Inception Cohort; HLA-B27, human leukocyte antigen B27; mSASSS, modified Stoke AS Spinal Score; OASIS, Outcome in AS International Study; OR, odds ratio; RCT, randomized controlled trial; SD, standard deviation; TNF-α, tumor necrosis factor-alpha; yr, years.

[a]No significant difference in radiographic progression between treatment groups.
[b]Age and disease duration are given in years.
[c]Values are presented as median (range).
[d]Values are presented as median (interquartile range).

observed during 5 years of infliximab treatment in 73 AS patients of the European AS infliximab cohort (EASIC). Most new syndesmophytes were found in patients who already had syndesmophytes before the start of TNF-α blocking therapy ($P < 0.001$). Based on MRI analysis, vertebral edges with both inflammation and fatty degeneration at baseline had the highest risk (relative risk 3.3, $P = 0.009$) for syndesmophyte formation after a follow-up of 5 years. However, the majority of new syndesmophytes were not preceded by any MRI change at baseline [36▪].

Recently, a retrospective study [35] including a limited number of AS patients ($n = 22$) reported diminished radiographic progression during 4–8 years of infliximab compared with the historical Herne cohort. Furthermore, a significantly lower progression rate was found in patients with a short delay between their first symptoms and starting long-term TNF-α blocking therapy in an observational study of 334 AS patients. In their zero-inflated negative binomial model (used to correct for the relatively large proportion of patients with no change in mSASSS), the use of TNF-α blockers was significantly associated with reduced radiographic progression after monitoring for more than 3.9 years [9▪]. The importance of short delay in start of treatment in their study may suggest that less radiographic progression occurred in patients with early AS. Limitations include their definition of radiographic progression as an increase of at least 1 mSASSS unit/year assuming linearity in individual patients, the variable follow-up intervals (ranging from 1.5 to 9 years) without correction for treatment changes, and scoring of radiographs by only one of three different readers without blinding for the country of origin [37].

In contrast, a significantly higher radiographic progression rate over 12 years was found in a small group of AS patients who were ever exposed to TNF-α blocking therapy in the OASIS cohort. As the authors stated, this result is likely to be explained by 'confounding by indication'. Patients who started with TNF-α blocking therapy (22% of all patients; 5% before 8-year follow-up) were mainly those with most active and severe disease and subsequently higher progression rates [4▪▪].

In summary, previous studies investigating the effect of TNF-α blocking therapy on spinal osteoproliferation in AS showed inconsistent results. Less radiographic progression was observed in patients with limited signs of osteoproliferation before the start of treatment. The assessment of spinal osteoproliferation is complicated by the overall slow rate of progression and the high variability between individual AS patients. Therefore, long-term

Table 2. Overview of studies investigating the effect of TNF-α blocking therapy on bone mineral density in ankylosing spondylitis patients fulfilling the modified New York criteria

Reference	Treatment groups, number of patients	Patient characteristics[c]	Study design	Follow-up	Baseline BMD (mean ± SD)	Follow-up BMD (mean ± SD)	Change in BMD (mean ± SD)
Saad *et al.* [39]	TNF-α blockers: $n=30$	Age: 36 ± 11; Male: 80%; DD: 12 ± 9; BASDAI: 5.1 ± 2.1	Clinical practice; BMD spine and hip (total femur, femoral neck)	1 year	BMD LS 1.03 ± 0.18; TH 0.99 ± 0.17, FN 0.86 ± 0.16	1 yr: BMD LS 1.07 ± 0.17[b], TH 1.00 ± 0.17, FN 0.86 ± 0.16	
Briot *et al.* [40]	TNF-α blockers: $n=106$ (88% fulfill modified NY criteria)	Age: 38 ± 11; Male: 75%; DD: 17 ± 9; HLA-B27+: 89%; BASDAI: 6.1 ± 1.9	Prospective, clinical practice; BMD spine (L2–L4) and hip (total femur)	2 years	BMD LS 0.95 ± 0.16, TH 0.87 ± 0.13; T-score LS −1.3 ± 1.5, TH −1.2 ± 1.0	1 yr: BMD LS[b], TH[b]; 2 yr: BMD LS[b], TH[b]	Δ0–1 yr: LS BMD +3.9%, TH BMD +1.9%; Δ0–2 yr: LS BMD +5.8%, TH BMD +2.3%
Visvanathan *et al.* [38]	Infliximab: $n=201$	Age: 40 ± 11; Male: 78%; DD: 10 ± 9; HLA-B27+: 87%; BASDAI: 6.6 (5.3–7.6)[d]	Prospective, RCT; BMD spine (L1–L4) and hip	2 years	BMD LS 1.01 ± 0.18, hip 0.92 ± 0.14; T-score LS −0.96 ± 1.45, hip −0.75 ± 0.97	6 mo: BMD LS[b], hip[b]; Δ0–2 yr: BMD LS[b], hip[b]	Δ0–6 mo: BMD LS +2.5%[a], hip +0.5%[a]; Δ0–2 yr: BMD LS +6.8%, hip +1.8%
	Placebo (24 wks), infliximab: $n=78$	Age: 40 ± 9; Male: 87%; DD: 12 ± 8; HLA-B27+: 89%; BASDAI: 6.5 (5.2–7.1)			BMD LS 1.09 ± 0.25, hip 0.95 ± 0.14; T-score LS −0.28 ± 2.00, hip −0.62 ± 0.91		Δ0–6 mo: BMD LS +0.5%, hip +0.2%; Δ0–2 yr: BMD LS +4.1%, hip +0.9%
Kang *et al.* [41]	TNF-α blockers: $n=26$	Age: 37 ± 10; Male: 92%; DD: 10 ± 5; HLA-B27+: 83%	Clinical practice; BMD spine (L1–L4) and hip (total proximal femur, femoral neck)	2 years	BMD LS 1.09 ± 0.17, TH 0.87 ± 0.11, FN 0.86 ± 0.13	1 yr: BMD LS 1.15 ± 0.18[b], TH 0.89 ± 0.10[b], FN 0.86 ± 0.18; 2 yr: BMD LS 1.21 ± 0.19[b], TH 0.90 ± 0.10[b], FN 0.87 ± 0.12	Δ0–1 yr: BMD LS +6.8%, TH +2.0%; Δ1–2yr: BMD LS +3.7%, TH +1.5%; Δ0–2 yr: BMD LS[a], hip[a]
	Standard: $n=37$	Age: 39 ± 13; Male: 76%; DD: 8 ± 5; HLA-B27+: 90%			BMD LS 1.09 ± 0.20, TH 0.90 ± 0.13, FN 0.88 ± 0.16	1 yr: BMD LS 1.11 ± 0.19[b], TH 0.90 ± 0.13, FN 0.88 ± 0.16; 2 yr: BMD LS 1.12 ± 0.21[b], TH 0.90 ± 0.13, FN 0.88 ± 0.13	Δ0–1 yr: BMD LS +2.7%, TH −0.1%; Δ1–2 yr: BMD LS +0.3%

(*Continued*)

Table 2 (*Continued*)

Reference	Treatment groups, number of patients	Patient characteristics[c]	Study design	Follow-up	Baseline BMD (mean ± SD)	Follow-up BMD (mean ± SD)	Change in BMD (mean ± SD)
Arends *et al.* [42▪]	TNF-α blockers: $n=111$ (still using first agent after 3 years: 72)	Age: 42 ± 10; Male: 70%; DD: 16 (1–49)[e]; HLA-B27+: 81%; BASDAI: 6.1 ± 1.7	Prospective, observational cohort; BMD spine (L1–L4) and hip (total proximal femur)	3 years	T-score LS −0.58 ± 1.41, TH-0.53 ± 1.12; Z-score LS −0.36 ± 1.56, TH −0.40 ± 1.06	1 yr: Z-score LS 0.04 ± 1.42[b], TH −0.32 ± 0.91[b]; 2 yr: Z-score LS 0.20 ± 1.39[b], TH −0.24 ± 1.01[b]; 3 yr: Z-score LS 0.48 ± 1.61[b], TH −0.16 ± 1.03[b]	
Durnez *et al.* [43▪]	TNF-α blockers: $n=59$ (97% fulfill modified NY criteria)	Age: 40 ± 11; Male: 85%; DD: 13 ± 11; HLA-B27+: 88%; BASDAI: 5.2 ± 1.6	Retrospective, clinical practice vs. observational cohort; BMD spine (L2–L4) and hip (total femur, femoral neck, trochanter)	Mean 6.5 ± 1.6 years	BMD LS 0.99 ± 0.18, TH 0.91 ± 0.13, FN 0.78 ± 0.11; T-score LS −1.1 ± 1.6, TH −1.1 ± 1.0, FN −1.7 ± 1.1[a]	1 yr: BMD LS[b]; 6.5 yr: BMD LS[b], TH, FN, trochanter[b]	Δ0–1 yr: BMD LS +5.2%; Δ0–6.5 yr: BMD LS +11.8%[a], TH +0.9%, FN+1.1%[a], trochanter+3.6%[a]
	Standard (OASIS): $n=34$	Age: 40 ± 12; Male: 62%; DD: 10 ± 6; HLA-B27+: 88%; BASDAI: 2.8 ± 1.9		5 years	BMD LS 1.01 ± 0.15, TH 0.94 ± 0.11, FN 0.82 ± 0.11; T-score LS −1.0 ± 1.4, TH −0.8 ± 0.8, FN −1.1 ± 1.0	5 yr: BMD LS, TH, FN[b]	Δ0–5 yr: BMD LS +1.9%, TH −1.0%, FN −4.2%

AS, ankylosingspondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMD, bone mineral density; DD, disease duration; FN, femoral neck; HLA-B27, human leukocyte antigen B27; LS, lumbar spine; mo, months; NY, New York; OASIS,Outcome in AS International Study; RCT, randomized controlled trial; SD, standard deviation; TH, total hip; TNF-α, tumor necrosis factor-alpha; wks, weeks; yr, years.
[a]Significant difference in BMD between treatment groups.
[b]Significant difference in BMD compared with baseline values.
[c]Age and disease duration are given in years.
[d]Values are presented as median (interquartile range).
[e]Values are presented as median (range).

follow-up in a large cohort of patients is essential to be able to investigate differences in radiographic progression between treatment groups. Recently, TNF-α blocking therapy has been registered for non-radiographic axial SpA, which makes it possible to investigate the effect on spinal osteoproliferationin patients with early disease.

EFFECT OF TNF-α BLOCKING THERAPY ON BONE MINERAL DENSITY AND VERTEBRAL FRACTURES

The effect of TNF-α blocking therapy on BMD has been investigated in one RCT and several observational studies [38–41,42▪,43▪] including patients with established AS (Table 2). So far, data about the effect of TNF-α blocking therapy on the occurrence of new vertebral fractures are scarce in AS.

In the RCT, consisting of 279 AS patients, a significant increase in BMD at the lumbar spine and hip was found after 6 months of infliximab compared with placebo. A further improvement in BMD (lumbar spine 6.8% and hip 1.8%) was found after 2 years of infliximab [40]. In line with these results, multiple observational studies reported a continuous improvement in lumbar spine BMD after 1–3 years of TNF-α blocking therapy. In most studies [38,39,41,42▪,43▪], also a significant increase in hip BMD was found, although this improvement was less impressive than at the lumbar spine.

A very recent retrospective analysis of 59 AS patients showed a clear improvement in BMD at the lumbar spine (11.8%) and trochanter (3.6%) after 6.5 years of TNF-α blocking therapy, whereas the increase in BMD at the femoral neck and total hip was not statistically significant. In comparison, lumbar spine, total hip, and trochanter BMD remained stable and femoral neck BMD (−4.2%) decreased significantly during 5-year follow-up in 34 AS patients of the historical OASIS cohort. The BMD changes at the lumbar spine, trochanter, and femoral neck were significantly different between both groups. During follow-up, five vertebral fractures diagnosed by vertebral fracture assessments (VFAs) technology using DXA were observed in the anti-TNF group. No data on vertebral fractures were available in the control group [43▪].

In the prospective observational Groningen Leeuwarden AS (GLAS) cohort, BTM levels of individual AS patients were corrected for the normal influence that age and sex have on bone turnover (using Z-scores; similar to the international interpretation of BMD). In total, 72 AS patients were analyzed during 3 years of treatment with their first TNF-α blocking agent. Apart from the increase in BMD, a significant increase in bone mineralization marker BALP and decrease in bone resorption marker sCTX were found after 3 months, which persisted up to 3 years. The increase in bone formation marker PINP was less pronounced [42▪].

These results are in line with previous findings. In the earlier described RCT, the increase in BMD after 2 years of infliximab was accompanied by a significant increase in bone mineralization marker BALP and decrease in bone resorption marker sCTX, whereas bone formation marker osteocalcin was comparable with baseline values [40]. Another analysis in 34 axial SpA patients also reported a significant increase in BALP after 36–52 weeks of adalimumab treatment, whereas no significant changes were found in 71 TNF-α blocker naïve AS patients from the GESPIC cohort [44].

In summary, multiple studies demonstrated that TNF-α blocking therapy results in a significant increase in lumbar spine and hip BMD. Based on BTM analysis, this improvement can mainly be explained by an increase in bone mineralization and decrease in bone resorption. No longitudinal data are available about the effect of TNF-α blocking therapy on the occurrence of new vertebral fractures in AS.

CONCLUSION

Spinal osteoproliferation, osteoporosis, and vertebral fractures are well known complications of AS. So far, the results regarding the effect of TNF-α blocking therapy on spinal osteoproliferation have been inconclusive. Multiple studies have shown that these agents give a significant increase in lumbar spine and hip BMD, accompanied by an increase in bone mineralization and decrease in bone resorption measured with BTM. Long-term follow-up in a large cohort of AS patients is needed to investigate whether TNF-α blocking therapy can consolidate or stop osteoproliferation and prevent vertebral fractures. Future studies should focus on the effect of TNF-α blocking therapy in AS patients with no or limited vs. more extensive spinal osteoproliferation, with as ultimate goal the development of personalized intervention strategies to promote healthy aging with AS.

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Conflicts of interest

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