Rheumatol Ther (2019) 6:139–163
https://doi.org/10.1007/s40744-019-0141-y

REVIEW

A Review on the Effect of Tumor Necrosis Factor Inhibitors on Structural Progression in Early Axial Spondyloarthritis Using Magnetic Resonance Imaging

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Received: November 14, 2018 / Published online: February 20, 2019

ABSTRACT

Introduction: Considering the progressive nature of axial spondyloarthritis (axSpA), it is important to determine whether tumor necrosis factor alpha (TNFα) inhibitors have an effect on early inflammatory and structural lesions detected using magnetic resonance imaging (MRI).
Methods: A search of MEDLINE/PubMed for full-text, English-language articles on randomized controlled trials (RCTs) of adalimumab, certolizumab, etanercept, golimumab, or infliximab published since January 2007 was conducted in February 2018 and again in December 2018. The collected articles reported on inflammatory or fatty lesion progression in the spine or sacroiliac joint (SIJ), determined using MRI, in a population that included at least 40% of patients with early axSpA, defined as non-radiographic axSpA.
Results: Of the 105 articles retrieved, 19 were included in this review, of which the majority were on etanercept ($n = 11$). A majority of selected articles included information on inflammatory lesions (SIJ 15/19; spine 12/19). All five TNFα inhibitors showed benefits on inflammation, assessed by MRI, in patients with early axSpA for up to 204 weeks of treatment. Structural progression in SIJ and the spine was assessed in 6/19 and 3/19 articles, respectively, with mixed evidence on benefits of TNF-inhibitor treatment.
Conclusions: In conclusion, treatment with TNFα inhibitors reduces MRI-evident inflammatory lesions in the SIJ and spine of patients with early axSpA for up to 4 years. There is less evidence of benefits on structural lesions. Additional studies are required to determine whether TNFα-inhibitor therapy can limit or delay radiological progression in patients with early axSpA.
Funding: Pfizer.

Enhanced digital features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.7618604.

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Keywords: Adalimumab; Axial spondyloarthritis; Certolizumab; Etanercept; Golimumab; Infliximab; Lesions; Magnetic resonance imaging; Tumor necrosis factor inhibitor

INTRODUCTION

The term spondyloarthritis (SpA) refers to a group of inflammatory rheumatic disorders that can be broadly classified into axial SpA (axSpA), which primarily involves the spine and the sacroiliac joint (SIJ), and peripheral SpA, which primarily affects the extremities [1]. A recent revision of the classification criteria for axSpA by the Assessment of Spondyloarthritis International Society (ASAS) advocated for the further subdivision of axSpA into radiographic axSpA (r-axSpA; i.e., ankylosing spondylitis [AS]) and non-radiographic axSpA (nr-axSpA) [2]. Diagnosis of r-axSpA is based on the presence of definite sacroiliitis on X-ray imaging, in accordance with the modified New York criteria for AS [3]. Diagnosis of nr-axSpA is based on the presence of sacroiliitis on magnetic resonance imaging (MRI) or positivity for the human leukocyte antigen B27 (HLA-B27) [4], in addition to clinical and laboratory features associated with SpA [5].

MRI-evident sacroiliitis can precede the detection of sacroiliitis on radiographs by nearly a decade [6]; hence, early detection of axSpA may enable timely implementation of appropriate disease management strategies. Active inflammation in the SIJ and spine, as evidenced by inflammatory changes (bone marrow edema) that are followed by structural lesions (joint erosion, fat metaplasia) seen on MR images [7, 8], leads to bone repair and secondary bone formation, thus exacerbating disease progression in both early and established axSpA [9–12].

The management of patients with axSpA should be personalized according to their current disease state (e.g., axial, peripheral, and extra-articular manifestations), and any decision to initiate treatment with biological disease-modifying antirheumatic drugs (bDMARDs) should take into consideration C-reactive protein levels and MRI or radiographic findings [13]. Biological inhibitors of the proinflammatory cytokine tumor necrosis factor alpha (TNFα) have been shown to be an effective treatment in reducing SpA disease activity and improving patient function [14]. To date, four TNFα inhibitors—adalimumab, certolizumab, etanercept, and golimumab—have been approved by the European Medicines Agency for treatment of nr-axSpA. A fifth TNFα inhibitor, infliximab, has not been approved yet for use in patients with nr-axSpA, but its safety and efficacy in this patient population have been investigated in randomized controlled trials (RCTs). Considering the progressive nature of axSpA, it is important to determine whether TNFα inhibitors have an effect on early inflammatory and structural lesions detected on MR images.

The purpose of this literature review was to identify RCTs that evaluated the impact of TNFα-inhibitor therapy on inflammatory and structural lesions (particularly fatty lesions) in early axSpA, as assessed using MRI, and to summarize those findings.

METHODS

Literature Search Strategy

A search of the MEDLINE® and PubMed Central® databases was conducted in February 2018 and repeated in December 2018, using the PubMed® platform and the following search string: "(axial spondyloarthritis OR non-radiographic axial spondyloarthritis OR nonradiographic axSpA OR nr-axSpA OR non-radiographic axSpA) AND (MRI OR magnetic) AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab)." Individual searches were conducted for each TNFα inhibitor, in combination with the disease subtype and imaging modality search terms. The search was limited to full-text, English-language articles published since January 2007. Titles and abstracts of retrieved articles were screened manually to identify RCTs of TNFα inhibitors that assessed inflammatory or fatty lesion progression in the spine or SIJ using MRI in a population that included at least 40% of patients with early axSpA, defined as nr-axSpA (unless data analysis was stratified by radiographic vs. nr-axSpA). In this context, the adjective "early" refers to the extent of damage the SIJ and spine have sustained (and detectability of that damage using radiography), and not necessarily to the duration of symptoms.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. All procedures performed in studies involving human participants that were cited in this review were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, as reported in the primary reports.

RESULTS

Literature Search

A total of 106 articles were retrieved from the literature searches. Of these, 33 reported results from RCTs involving TNFα-inhibitor therapy and its effect on structural progression in early axSpA, with the majority of RCTs presenting data from trials on etanercept ($n = 20$). A detailed appraisal of these 33 papers identified the 19 which were ultimately included in this review (Table 1). Articles were excluded from further review if they did not report the outcome measure of interest, they included < 40% of patients with early axSpA, and they did not stratify results by radiographic versus nr-axSpA, or were reviews or available in abstract form only (e.g., conference proceedings).

Patient Populations

The articles identified in this analysis reported either on trials that enrolled patients with nr-axSpA only (9 of 19 articles) or presented subgroup data for patients with nr-axSpA (10 of 19 articles) (Table 1). Key baseline characteristics of the patients included in the studies are shown in Table 1. Consistent with a high proportion of patients with early axSpA, participants in the selected studies had a mean age range of 28–-39 years, disease duration of 1–10 years, and Bath Ankylosing Spondylitis Functional Index (BASFI) scores of 3.6–5.5 (Table 1).

Effect of TNFα Inhibitors on Inflammatory Lesions

The majority of selected articles included information on the effect of TNFα-inhibitor therapy on MRI-evident inflammatory lesions in the SIJ (15/19 articles) or spine (12/19) (Tables 2–6). All four TNFα inhibitors approved for treatment of nr-axSpA demonstrated significant improvements versus comparator therapies in MRI scores for inflammation. Infliximab, although not indicated for nr-axSpA, also showed a positive effect on MRI-assessed inflammation in this patient population.

Adalimumab

Evidence for an effect of adalimumab on inflammatory lesions in the SIJ and spine comes primarily from the ABILITY-1 trial, a randomized, placebo-controlled, phase III study in which patients with active nr-axSpA ($n = 185$) received adalimumab 40 mg or placebo every 2 weeks (Q2W) for 12 weeks, followed by an open-label extension to week 114 [15]. At week 12, adalimumab therapy was associated with significant reductions in MRI scores for inflammation compared with placebo in both the SIJ (mean change from baseline: − 3.2 vs. − 0.6, $P = 0.003$) and spine (− 1.8 vs. − 0.2, $P = 0.001$) (Table 2) [15].

A post hoc analysis of data from two phase II/III clinical trials of adalimumab (D2E7-Early AS, conducted in patients with nr-axSpA only, $n = 46$) and etanercept (ESTHER, conducted in patients with nr-axSpA or r-axSpA, $n = 76$) revealed that both TNFα inhibitors were associated with improvements in SIJ inflammation and that adalimumab was particularly effective in patients with early disease (mean improvement score change from baseline: 7.0 [symptom duration < 4 years] vs. 2.7 [symptom duration ≥ 4 years]; $P = 0.04$) (Table 2) [16].

Certolizumab

In the randomized, placebo-controlled, phase III RAPID-axSpA study, patients with axSpA (imaging set, $n = 163$; $n = 68$ with nr-axSpA) received certolizumab (200 mg Q2W or 400 mg Q4W) or placebo for 24 weeks [17]; active

Table 1 Studies identified in the literature review and selection of patient baseline characteristics

Agent and study	Study population	Study duration	Treatment groups	Baseline characteristics			
				Age (years)	Disease duration (years)	BASDAI	BASFI
Adalimumab							
Sieper et al. (2013) [15]	nr-axSpA	12 weeks	ADL n = 91	37.6 (11.3)	10.1 (9.0)	6.4 (1.5)	4.5 (1.9)
ABILITY-1 trial			PBO n = 94	38.4 (10.4)	10.1 (8.8)	6.5 (1.6)	4.9 (2.3)
ClinicalTrials.gov Identifier: NCT00939003							
Weiß et al. (2014) [16]	nr-axSpA (ADL)	1 year	ADL n = 46				
D2E7-Early AS (ADL) trial			< 4 years[b] n = 16	31.8 (8.1)	1.9 (1)	4.7 (2.4)	3.6 (2.8)
ClinicalTrials.gov Identifier: NCT00235105			≥ 4 years[b] n = 30	38.5 (9.1)	9.7 (5.9)	6.3 (1.5)	5.4 (1.9)
ESTHER (ETN)	r-axSpA (~ 50%) and nr-axSpA		ETN n = 66				
D2E7-Early AS (ADL) trial trialNCT00844142	(ETN)		< 4 years[b] n = 42	31.6 (8.2)	2 (1.1)	5 (1.7)	3.9 (2.2)
			≥ 4 years[b] n = 24	37 (7.7)	5.2 (0.9)	5.5 (2)	4.4 (2.3)
Certolizumab							
Braun et al. (2017) [18]	r-axSpA and nr-axSpA[a]	12 weeks	CZP n = 46[c]	36.7 (12.8)	5.4 (0.3–31.4)	6.5 (1.5)	4.8 (2.3)
RAPID-axSpA		48 weeks					
ClinicalTrials.gov Identifier: NCT01087762		96 weeks	PBO n = 22[c]	36.2 (13.5)	5.0 (0.5–39.6)	6.4 (1.4)	4.7 (2.0)
van der Heijde et al. (2018) [19]	r-axSpA and nr-axSpA[a]	204 weeks	CZP n = 141[d]	37.5 (11.9)	5.8 (0.3–41.5)	6.5 (1.5)	4.9 (2.3) (n = 140)
RAPID-axSpA							

Table 1 continued

Agent and study	Study population	Study duration	Treatment groups	Baseline characteristics			
				Age (years)	Disease duration (years)	BASDAI	BASFI
Etanercept							
Song et al. (2011) [20]	r-axSpA (~ 50%) and nr-axSpA	24 weeks	ETN n = 40	34.5 (8.6)	2.6 (1.7)	5.5 (1.3)	4.3 (2.3)
ESTHER 48-week data		48 weeks	SSZ n = 36	32.8 (8.4)	3.0 (1.8)	6.0 (1.2)	4.3 (1.8)
Inflammatory Lesions							
ClinicalTrials.gov Identifier: NCT00844142							
Song et al. (2011) [33]	r-axSpA (~ 50%) and nr-axSpA	24 weeks	ETN n = 35	33.5 (8.7)	2.5 (1.6)	–	–
ESTHER trial 48-week data		48 weeks	SSZ n = 30	32.4 (8.4)	3.0 (1.8)	–	–
Fatty Lesions							
ClinicalTrials.gov Identifier: NCT00844142							
Song et al. (2014) [22]	r-axSpA (~ 50%) and nr-axSpA[a]	3 years	ETN n = 30	33.2 (8.2) (incl. AS pts; n = 61)	2.2 (NR)	5.7 (1.2)	4.3 (2.0)
ESTHER trial 3-year data							
LOCF							
ClinicalTrials.gov Identifier: NCT00844142							
Song et al. (2015) [23]	r-axSpA (~ 40%) and nr-axSpA	3 years	ETN n = 41	32.8 (8.1)	2.6 (1.6)	5.5 (1.2)	4.0 (2.0)
ESTHER trial 3-year data							
Completers							
Inflammatory Lesions							
ClinicalTrials.gov Identifier: NCT00844142							

Table 1 continued

Agent and study	Study population	Study duration	Treatment groups	Baseline characteristics			
				Age (years)	Disease duration (years)	BASDAI	BASFI
Song et al. (2016) [34]	r-axSpA (~ 40%) and nr-axSpA	3 years	ETN *n* = 41	32.8 (8.1)	2.6 (1.6)	5.5 (1.2)	4.0 (2.0)
ESTHER trial 3-year data							
Completers							
Fatty Lesions							
ClinicalTrials.gov Identifier: NCT00844142							
Dougados et al. (2014) [21]	nr-axSpA	12 weeks	ETN *n* = 106	31.9 (7.8)	2.4 (1.9)	6.0 (1.8)	4.2 (2.5)
EMBARK trial 12-week data			PBO *n* = 109	32.0 (7.8)	2.5 (1.8)	6.0 (1.9)	3.9 (2.5)
ClinicalTrials.gov Identifier: NCT01258738							
Maksymowych et al. (2016) [24]	nr-axSpA	12 weeks	ETN/ETN *n* = 102	31.6 (7.8)	2.4 (2.0)	6.0 (1.8)	4.2 (2.4)
EMBARK trial 48-week data							
ClinicalTrials.gov Identifier: NCT01258738		48 weeks	PBO/ETN *n* = 106	32.1 (7.7)	2.5 (1.8)	6.0 (1.9)	3.8 (2.5)
Dougados et al. (2017) [25]	nr-axSpA	12 weeks	ETN (ETN) *n* = 106	31.9 (7.8)	2.4 (1.9)	6.0 (1.8)	4.2 (2.5)
EMBARK trial 104-week data							
ClinicalTrials.gov Identifier: NCT01258738		104 weeks	PBO (ETN) *n* = 109	32.0 (7.8)	2.5 (1.8)	6.0 (1.9)	3.9 (2.5)
Maksymowych et al. (2017) [35]	nr-axSpA	12 weeks	ETN *n* = 88	31.7 (7.8)	2.5 (2.0)	5.9 (1.8)	4.2 (2.5)
EMBARK trial 12-week data			PBO *n* = 97	32.2 (7.9)	2.4 (1.5)	6.0 (1.9)	3.8 (2.5)
ClinicalTrials.gov Identifier: NCT01258738							

Table 1 continued

Agent and study	Study population	Study duration	Treatment groups	Baseline characteristics			
				Age (years)	Disease duration (years)	BASDAI	BASFI
Wei et al. (2016) [26]	nr-axSpA	12 weeks	ETN n = 54	32.0 (6.8)	2.3 (1.5)	5.9 (1.9)	4.2 (2.5)
EMBARK trial 12-week data			PBO n = 57	32.2 (8.7)	2.4 (1.6)	6.3 (1.7)	4.1 (2.5)
Latin America/Europe/Asia							
ClinicalTrials.gov Identifier: NCT01258738							
Dougados et al. (2017) [37]	nr-axSpA	104 weeks	ETN (EMBARK): N = 162	31.8 (7.7)	2.4 (1.8)	5.9 (1.8)	4.0 (2.4)
EMBARK trial 104-week data							
vs.			No treatment (DESIR): N = 193	32.2 (7.0)	1.7 (1.0)	3.6 (1.9)	2.2 (2.0)
DESIR 104-week data							
ClinicalTrials.gov Identifier: NCT01258738 (EMBARK)							
ClinicalTrials.gov Identifier: NCT01648907 (DESIR)							
Golimumab							
Sieper et al. (2015) [27]	nr-axSpA	16 weeks	GLM n = 98	30.7 (7.1)	1: 68.4%[e]	6.6 (1.6)	5.3 (2.4)
GO-AHEAD study					1–2: 20.4%[e]		
ClinicalTrials.gov Identifier: NCT01453725					3–5: 11.2%[e]		
			PBO n = 100	31.7 (7.2)	1: 65.0%[c]	6.4 (1.5)	4.8 (2.5)
					1–2: 19.0%[c]		
					3–5: 16.0%[c]		

Table 1 continued

Agent and study	Study population	Study duration	Treatment groups	Baseline characteristics			
				Age (years)	Disease duration (years)	BASDAI	BASFI
Infliximab							
Barkham et al. (2009) [28] Leeds Early SI EudraCT number: 2004-001880-23	r-axSpA (12%) and nr-axSpA (88%)	16 weeks	INF n = 20	29.5 (NR)	1.43 (NR)	5.85 (NR)	4.42 (NR)
			PBO n = 20	28.2 (NR)	1.12 (NR)	5.76 (NR)	4.11 (NR)
Poddubnyy et al. (2016) [30] INFAST Part 1 MRI ClinicalTrials.gov Identifier: NCT00844805	r-axSpA (60%) and nr-axSpA (40%)	28 weeks	INF + NAP n = 105	31.7 (8.51)	1.76 (0.896)	6.4 (NR)	5.3 (NR)
			PBO + NAP n = 51	30.7 (7.34)	1.91 (1.439)	6.3 (NR)	5.4 (NR)
Sieper et al. (2016) [31] INFAST Part 1 nr-axSpA ClinicalTrials.gov Identifier: NCT00844805	r-axSpA and nr-axSpA[a]	28 weeks	INF + NAP n = 40	31.8 (8.89)	1.44 (0.855)	6.41 (1.634)	5.54 (2.085)
			PBO + NAP n = 16	30.9 (7.28)	1.54 (0.898)	6.13 (1.389)	4.52 (2.101)

Values are presented as the mean with the standard deviation in parenthesis or as the median with the minimum–maximum in parenthesis, unless otherwise stated *ADL* adalimumab, *AS* ankylosing spondylitis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *CZP* certolizumab, *ETN* etanercept, *GLM* golimumab, *LOCF* last observation carried forward *INF* infliximab, *NAP* naproxen, *NR* not reported, *nr-axSpA* non-radiographic axial spondyloarthritis, *PBO* placebo, *r-axSpA* radiographic axial spondyloarthritis, *SSZ* sulfasalazine, *TNF* tumor necrosis factor

[a] Data presented for nr-axSpA subgroup only

[b] Stratified by disease duration: < 4 years or ≥ 4 years

[c] Imaging subset only

[d] Imaging and non-imaging subsets

[e] Proportion of patients with disease duration since diagnosis of 1, 1–2, or 3–5 years

Table 2 Adalimumab studies: measures of inflammatory lesions by magnetic resonance imaging

Study	Study population	Study duration	Treatment groups	Inflammatory lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS
Sieper et al. (2013) [15] ABILITY-1 trial ClinicalTrials.gov Identifier: NCT00939003	nr-axSpA	12 weeks	ADL $n = 91$	5.1 (9.5)[b]	Mean Δ: − 3.2	4.1 (5.3)[b]	Mean Δ: − 1.8
			PBO $n = 94$	4.7 (9.9)[b]	Mean Δ: − 0.6 ($P = 0.003$)	4.6 (6.3)[b]	Mean Δ: − 0.2 ($P = 0.001$)
Weiß et al. (2014) [16] D2E7-Early AS (ADL) trial ClinicalTrials.gov Identifier: NCT00235105 ESTHER (ETN) trial ClinicalTrials.gov Identifier: NCT00844142	nr-axSpA (ADL)	1 year	ADL $n = 46$	5.4 (7)[c] 3.2 (3.4)[c]	Mean ↑: 7.0 (3.8, 10.1)	–	–
			< 4 years[a] $n = 16$		Mean ↑: 2.7 (0.7, 4.7)		
			≥ 4 years[a] $n = 30$		($P = 0.04$)		
	r-axSpA (∼ 50%) and nr-axSpA (ETN)		ETN $n = 66$	6.4 (6)[c] 5 (5.7)[c]	Mean ↑: 3.9 (3.3, 4.6)		
			< 4 years[a] $n = 42$		Mean ↑: 3.7 (2.8, 4.6)		
			≥ 4 years[a] $n = 24$		($P = 0.71$)		

Values are presented as the mean with the SD in parenthesis or as the mean with the 95% confidence interval (CI) in parenthesis, unless otherwise stated. Δ, change from BL; ↑, improvement from BL

BL Baseline, *CI* confidence interval, *EOS* end of study, *PBO* placebo, *SIJ* sacroiliac joint, *SPARCC* Spondyloarthritis Research Consortium of Canada

[a] Stratified by disease duration: < 4 years or ≥ 4 years

[b] SPARCC MRI score

[c] Berlin magnetic resonance imaging (MRI) score

Table 3 Certolizumab study: measures of inflammatory lesions by magnetic resonance imaging

Study	Study population	Study duration	Treatment groups	Inflammatory lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS
Braun et al. (2017) [18] Van der Heijde et al. (2018) [19] RAPID-axSpA ClinicalTrials.gov Identifier: NCT01087762	r-axSpA and nr-axSpA[a]	12 weeks 48 weeks 96 weeks 204 weeks	CZP *n* = 46	12 weeks: 7.4 (9.9)[b] 48 weeks: 8.3 (11.3)[b] 96 weeks: 8.8 (11.4)[b] 204 weeks: 7.5 (1.5)[b,c]	Mean Δ: 12 weeks: − 4.4 (7.9) 48 weeks: − 4.8 (12.2) 96 weeks: − 5.6 (12.4) Mean score: 204 weeks: 2.4 (0.8)[b,c]	12 weeks: 2.9 (4.2)[d] 48 weeks: 2.9 (5.7)[d] 96 weeks: 3.3 (5.9)[d] 204 weeks: 4.4 (1.0)[c,d]	Mean Δ: 12 weeks: − 2.0 (3.2) 48 weeks: − 1.9 (4.7) 96 weeks: − 2.3 (5.0) Mean score: 204 weeks: 1.9 (0.4)[c,d]
			PBO *n* = 22	12 weeks: 12.2 (14.5)[b]	Mean Δ: 12 weeks: + 1.2 (4.6) ($P < 0.001$)	12 weeks: 3.7 (8.3)[d]	Mean Δ: 12 weeks: + 0.3 (1.6) ($P = 0.006$)

Values are presented as the mean with the SD in parenthesis, unless otherwise stated. Δ, Change from BL
Results from weeks 48 and 96 include patients originally randomized to placebo at baseline but who received CZP from weeks 16 or 24
SEM Standard error of the mean
[a] Data presented for nr-axSpA subgroup only
[b] SPARCC MRI score
[c] Data presented as mean with the SEM in parenthesis
[d] Berlin MRI score

Table 4 Etanercept studies: measures of inflammatory and structural lesions by magnetic resonance imaging

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Song et al. (2011) [20] ESTHER trial 48-week data Inflammatory Lesions ClinicalTrials.gov Identifier: NCT00844142	r-axSpA (~ 50%) and nr-axSpA	24 weeks 48 weeks	ETN n = 40	7.8 (6.3)[d]	24 weeks: 3.1 (3.6)[d] Mean Δ: − 4.7[f] 48 weeks: 2.4 (3.2)[d] Mean Δ: − 5.4[f]	2.3 (3.5)[d]	24 weeks: 1.4 (3.1)[d] Mean Δ: − 0.9[f] 48 wks: 1.0 (2.1)[d] Mean Δ: − 1.3[f]	–	–	–	–
			SSZ n = 36	5.4 (5.1)[d]	24 weeks: 3.7 (3.2)[d] Mean Δ: − 1.7[f] (P = 0.006) 48 weeks: 3.5 (3.8)[d] Mean Δ: − 1.9[f] (P = 0.02)	1.4 (3.1)[d]	24 weeks: 1.5 (3.1)[d] Mean Δ: + 0.1[f] (P = 0.03) 48 weeks: 1.3 (2.9)[d] Mean Δ: − 0.1[f] (P = 0.01)				

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Song et al. (2011) [33] ESTHER trial 48-week data Fatty Lesions ClinicalTrials.gov Identifier: NCT00844142	r-axSpA (~ 50%) and nr-axSpA	24 weeks 48 weeks	ETN n = 35	–	–	–	–	4.0 (3.2)[g]	24 weeks: 4.6 (3.4)[g] Mean Δ: + 0.6[f] 48 weeks: 4.8 (3.2)[g] Mean Δ: + 0.8[f]	1.9 (5.0)[g]	24 weeks: 2.6 (5.6)[g] Mean Δ: + 0.7[f] 48 wks: 2.7 (5.8)[g] Mean Δ: + 0.8[f]
			SSZ *n* = 30					3.0 (2.8)[g]	24 weeks: 3.2 (2.9)[g] Mean Δ: + 0.2[f] (*P* = 0.018) 48 weeks: 3.2 (2.9)[g] Mean Δ: + 0.2[f] (*P* = 0.001)	1.1 (2.6)[g]	24 weeks: 0.9 (2.1)[g] Mean Δ: − 0.2[f] (*P* = 0.033) 48 weeks: 1.2 (2.7)[g] Mean Δ: + 0.1[f] (*P* = 0.020)

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Song et al. (2014) [22] ESTHER trial 3-year data LOCF ClinicalTrials.gov Identifier: NCT00844142	r-axSpA (~ 50%) and nr-axSpA[a]	3 years	ETN n = 30	6.2 (5.5)[d]	2 years: 1.4 (1.5)[d] Mean Δ: − 4.8[f] 3 yrs: 2 (2.3)[d] Mean Δ: − 4.2[f]	1.3 (2.5)[d]	2 years: 0.8 (1.7)[d] Mean Δ: − 0.5[f] 3 years: 1 (2.2)[d] Mean Δ: − 0.3[f]	–	–	–	–
Song et al. (2015) [23] ESTHER trial 3-year data Completers Inflammatory Lesions ClinicalTrials.gov Identifier: NCT00844142	r-axSpA (~ 40%) and nr-axSpA	3 years	ETN n = 41	7.1 (6.4)[d]	2 years: 2.0 (2.2)[d] Mean Δ: − 5.10 (− 7.21, − 2.98) 3 years: 2.2 (2.5)[d] Mean Δ: − 4.91 (− 7.06, − 2.77)	1.7 (3.4)[d]	2 years: 0.7 (1.4)[d] Mean Δ: −1.00 (−2.15, 0.14) 3 years: 0.9 (1.8)[d] Mean Δ: −0.77 (−1.97, 0.43)	–	–	–	–

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Song et al. (2016) [34] ESTHER trial 3-year data Completers Fatty Lesions ClinicalTrials.gov Identifier: NCT00844142	r-axSpA (~ 40%) and nr-axSpA	3 years	ETN n = 41	–	–	–	–	4.76 (6.34)[g]	2 years: 5.46 (6.54)[g] Mean Δ: + 0.7[f] 3 years: 4.74 (6.26)[g] Mean Δ: − 0.02[f]	1.13 (2.08)[g]	2 years: 1.40 (2.44)[g] Mean Δ: + 0.27[f] 3 years: 1.35 (2.34)[g] Mean Δ: + 0.22[f]
Dougados et al. (2014)[21] EMBARK trial 12-week data ClinicalTrials.gov Identifier: NCT01258738	nr-axSpA	12 weeks	ETN n = 106	8.0 (9.7)[e]	Mean (SEM) Δ: − 3.8 (0.7)	4.7 (7.1)[e]	Mean (SEM) Δ: − 2.1 (0.5)	–	–	–	–
			PBO n = 109	7.7 (10.1)[e]	Mean (SEM) Δ: − 0.8 (0.6) (P < 0.001)	3.5 (5.6)[e]	Mean (SEM) Δ: − 1.2 (0.5) (P = 0.041)				

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Maksymowych et al. (2016) [24] EMBARK trial 48-week data ClinicalTrials.gov Identifier: NCT01258738	nr-axSpA	12 weeks 48 weeks	ETN/ETN *n* = 102	7.9 (10.9)[e]	Mean Δ: 12 weeks: − 4.6 48 weeks: − 5.8 (10.3) ($P < 0.001$)	7.6 (11.4)[e]	Mean Δ: 12 weeks: −3.1 48 weeks: − 4.8 (11.3) ($P < 0.001$)	–	Mean Δ: + 0.46 (0.15, 0.77)	–	–
			PBO/ETN *n* = 106	7.0 (11.0)[e]	Mean Δ: 12 weeks: − 1.1 48 weeks: − 4.1 (8.3) ($P < 0.001$)	6.9 (9.2)[e]	Mean Δ: 12 weeks: −0.77 48 weeks: −4.2 (7.6) ($P < 0.001$)				
Dougados et al. (2017) [25] EMBARK trial 104-week data ClinicalTrials.gov Identifier: NCT01258738	nr-axSpA	12 weeks 104 weeks	ETN/ETN *n* = 106	8.0 (9.7)[e]	Mean (SEM) Δ: 12 weeks: − 4.0 (0.7) 104 weeks: − 6.0 (1.2)	4.7 (7.1)[e]	Mean (SEM) Δ: 12 weeks: − 1.9 (0.6) 104 weeks: − 2.1 (0.9)	–	–	–	–
			PBO/ETN *n* = 109	7.7 (10.1)[e]	Mean (SEM) Δ: 12 weeks: − 0.9 (0.4) 104 weeks: − 3.4 (0.8)	3.5 (5.6)[e]	Mean (SEM) Δ: 12 weeks: − 0.4 (0.2) 104 weeks: − 0.8 (0.5)				

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Maksymowych et al. (2017) [35]	nr-axSpA	12 weeks	ETN n = 88[b]	8.3 (10.1)[e]	–	5.5 (9.7)	–	0.50 (0.19)[h]	Mean (SEM) Δ:	–	–
EMBARK trial									0.06 (0.07)		
12-week data			PBO n = 97[b]	7.7 (10.1)[e]	–	3.9 (7.2)	–	0.27 (0.09)[h]	Mean (SEM) Δ:	–	–
ClinicalTrials.gov Identifier: NCT01258738									0.05 (0.07)		
Wei et al. (2016)[26]	nr-axSpA	12 weeks	ETN n = 54 [c]	7.4 (8.4)[e]	Mean (SEM) Δ:	5.0 (8.1)[e]	Mean (SEM) Δ:	–	–	–	–
EMBARK 12-week data					− 3.17 (0.85)		− 2.21 (0.69)				
Latin America/ Europe/Asia			PBO n = 57 [c]	6.3 (6.9)[e]	Mean (SEM) Δ:	3.4 (5.5)[e]	Mean (SEM) Δ:				
NCT01258738					− 0.38 (0.76)		− 1.37 (0.61)				
					(P = 0.0014)		(P = 0.2231)				

Table 4 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Dougados et al. (2017) [37] EMBARK trial 104-week data vs. DESIR truak 104-week data ClinicalTrials.gov Identifier: NCT01258738 (EMBARK) ClinicalTrials.gov Identifier: NCT01648907 (DESIR)	nr-axSpA	104 weeks	ETN (EMBARK) *n* = 162 No treatment (DESIR) *n* = 193	–	–	–	–	SIJ Total Score, mean (SD)[i]: 1.5 (1.2) SIJ Total Score, Mean (SD)[i]: 1.9 (1.6) *P* = 0.03 vs EMBARK	SIJ Total Score, LS Mean (95%CI) Δ[i]: − 0.14 (− 0.26, − 0.11) SIJ Total Score, LS Mean (95%CI) Δ[i]: 0.08 (− 0.04, 0.20) *P* = 0.008 vs .EMBARK (adjusted)		

Values are presented as the mean with the SD in parenthesis or as the mean with the 95% CI in parenthesis, unless otherwise stated. Δ, Change from BL

LS Least squares, *mITT* modified intent-to-treat

[a] Data presented for nr-axSpA subgroup only

[b] Data presented are for patients with MRI scans

[c] Data presented are for the mITT population

[d] Berlin MRI score

[e] SPARCC MRI score

[f] Calculated for this analysis

[g] Song et al. [33, 34] MRI score

[h] Mean with the SEM in parenthesis

[i] Score obtained by adding up values of both SIJs using the modified New York grading system

treatment continued as dose-blinded to week 48 and as open-label to week 204 [18].

A pre-specified subanalysis of pooled-dose MRI data over 96 weeks demonstrated that patients treated with certolizumab achieved greater mean reductions in MRI inflammation scores from baseline to week 12 than did placebo-treated patients in both the SIJ (− 4.4 vs. 1.2; $P < 0.001$) and spine (− 2.0 vs. 0.3; $P = 0.006$) (Table 3) [18]. These improvements in inflammation were maintained through weeks 48, 96, and 204 [19] for all patients who received certolizumab, including those originally randomized to placebo (Table 3).

Etanercept

Two major clinical trials of etanercept—the phase II ESTHER [20] and phase III EMBARK [21] trials—were conducted in patients with axSpA. ESTHER included both patients with r-axSpA (51% [39/76]) and those with nr-axSpA (49% [37/76]) [20], while EMBARK was conducted only in patients with nr-axSpA ($n = 215$) [21].

In ESTHER [20], patients with active axSpA refractory to non-steroidal anti-inflammatory drug (NSAID) treatment, symptom duration < 5 years, and MRI evidence of inflammatory lesions were randomized to twice-weekly etanercept 25 mg or daily sulfasalazine 2–3 g, both for 48 weeks, followed by a long-term, open-label treatment. The primary analysis of inflammatory lesions in the SIJ and spine demonstrated that etanercept treatment resulted in significant reductions in MRI inflammation scores at 24 and 48 weeks compared with sulfasalazine treatment (Table 4) [20]. For the primary endpoint at 48 weeks, the mean change in MRI inflammation scores in the SIJ was − 5.4 (etanercept) and − 1.9 (sulfasalazine) ($P = 0.02$); the mean changes for spinal inflammation were − 1.3 and − 0.1 ($P = 0.01$) (Table 4) [20]. Similar reductions in MRI inflammation scores in the SIJ and spine were observed over 3 years (156 weeks) of continuous etanercept treatment, in both a last observation carried forward (LOCF) analysis of patients with nr-axSpA ($n = 30$) [22] and an additional analysis of patients with axSpA ($n = 41$) (Table 4) [23].

In EMBARK, patients with active nr-axSpA who demonstrated an inadequate response to NSAID therapy and had symptom duration of between 3 months and 5 years were randomized to receive weekly doses of etanercept 50 mg or placebo on a background of NSAID treatment for 12 weeks, followed by a 92-week open-label period of etanercept therapy [21]. Etanercept treatment was associated with significant reductions in MRI-evident inflammation in the axial skeleton: mean changes in inflammation scores were − 3.8 (etanercept) and − 0.8 (placebo) ($P < 0.001$) for the SIJ and − 2.1 and − 1.2, respectively ($P = 0.041$) for the spine (Table 4) [21]. Notable improvements in inflammation scores in patients randomized to etanercept were sustained during open-label treatment to 48 and 104 weeks (Table 4) [24, 25]. An analysis of a subset of patients from Latin America, Central Europe, and Asia ($n = 117$) also found that etanercept therapy was associated with a significant improvement in the inflammation score versus placebo in the SIJ (− 3.2 vs. − 0.4; $P = 0.001$), but not in the spine, despite a numerical difference favoring active treatment (− 2.2 vs. − 1.4; $P = 0.223$) (Table 4) [26].

Golimumab

The effects of golimumab on MRI-evident inflammation in the SIJ of patients with nr-axSpA were assessed in a single phase III, randomized, placebo-controlled GO-AHEAD trial ($n = 198$); measures of spinal inflammation were not reported [27]. Treatment with golimumab 50 mg Q4W over 16 weeks was associated with significant reductions in SIJ inflammation versus placebo: − 5.3 vs. − 1.0, respectively ($P = 0.001$) (Table 5) [27]. The overall improvement in SIJ scores was largely driven by patients with evidence of sacroiliitis on MRI and/or an elevated CRP level at baseline [27].

Infliximab

Infliximab is not indicated for the treatment of nr-axSpA, but the available data show that it has a positive effect on MRI-evident inflammatory lesions, particularly in the SIJ (Table 6).

Table 5 Golimumab study: measures of inflammatory lesions by magnetic resonance imaging

Study	Study population	Study duration	Treatment groups	Inflammatory lesions	
				SIJ inflammation score BL	SIJ inflammation score EOS
Sieper et al. (2015) [27]	nr-axSpA	16 weeks	GLM $n = 98$	9.9 (11.82)[a]	4.6 (7.92)[a]
GO-AHEAD trial					Mean Δ: − 5.3[b]
ClinicalTrials.gov Identifier: NCT01453725			PBO $n = 100$	12.7 (15.62)[a]	11.71 (14.79)[a]
					Mean Δ: − 0.99[b]
					($P < 0.0001$)

Values are presented as the mean with the SD in parenthesis, unless otherwise stated. Δ, Change from BL
[a] SPARCC MRI score
[b] Calculated for this analysis

In a study by Barkham et al., in which patients with early sacroiliitis ($n = 40$; ~ 88% with nr-axSpA) were randomized to receive infliximab 5 mg/kg body weight or placebo over 16 weeks, infliximab-treated patients had a median change from baseline in the SIJ MRI score of − 2.00, compared with no change in the placebo group ($P = 0.033$) (Table 6) [28]. Moreover, significantly more lesions were resolved in patients who received infliximab ($P < 0.001$), whereas significantly more new lesions developed in placebo-treated patients ($P = 0.004$) [28].

The INFAST study was a randomized, double-blind, placebo-controlled trial of patients with MRI-evident r-axSpA (60%) or nr-axSpA (40%) and disease duration of ≤ 3 years [29]. Patients received intravenously administered infliximab 5 mg/kg body weight + naproxen 1000 mg/day ($n = 106$) or intravenously administered placebo + naproxen 1000 mg/day ($n = 52$) over 28 weeks; a total of 156 patients with available MRI data from at least one time point were included in the analysis (Table 6). Significant improvements in MRI inflammation scores were observed in the SIJ and spine in both treatment groups, but these were more notable in patients treated with infliximab (SIJ: − 4.3 vs. − 3.9, $P = 0.003$; spine: − 2.9 vs. − 2.0, $P < 0.001$) (Table 6) [30]. A post hoc analysis of INFAST data [31], with patients stratified on the basis of fulfilment of the modified New York criteria for AS [3], found that the effect of adding infliximab to NSAID therapy on MRI inflammation scores was greater in patients with AS than in those with nr-axSpA (data not shown). However, the latter also experienced reduction of active inflammation, most notably in the SIJ (Table 6). The apparent lack of treatment effect in the spine of patients with nr-axSpA was possibly due to low baseline levels of spinal inflammation in this subgroup.

EFFECT OF TNFα INHIBITORS ON STRUCTURAL LESIONS

Several articles identified in this analysis included information on the effect of TNFα-inhibitor therapy on MRI-evident structural lesions in the SIJ (6/19 articles) or spine (3/19 articles) (Tables 4, 6). These studies have provided mixed results regarding the benefit of TNFα-inhibitor therapy on structural progression in axSpA. A small ($n = 56$), single-center retrospective study suggests that long-term treatment with a TNFα inhibitor may slow progression of structural lesions in patients with AS [32].

Etanercept

In the ESTHER trial, treatment with etanercept was associated with a significantly higher increase in MRI fatty lesion scores compared with sulfasalazine therapy in both the SIJ and spine at 24 and 48 weeks (Table 4) [33].

Table 6 Infliximab studies: measures of inflammatory and structural lesions by magnetic resonance imaging

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Barkham et al. (2009) [28] Leeds Early SI EudraCT number: 2004-001880-23)	r-axSpA (12%) and nr-axSpA	16 weeks	INF $n = 20$	Median: 3.5 (IQR 2–8)[b]	Median Δ: − 2.00 (IQR − 6.25 to − 0.00)	–	–	–	–	–	–
			PBO $n = 20$		Median Δ: 0.00 (IQR − 2.00 to − 1.50) ($P = 0.033$)						
Poddubnyy et al. (2016) [30] INFAST Part 1 MRI ClinicalTrials.gov Identifier: NCT00844805	r-axSpA (~ 60%) and nr-axSpA	28 weeks	INF + NAP $n = 105$	5.3 (5.3)[c]	1.0 (1.9)[b] Mean Δ: − 4.3 (5.2)	3.7 (5.4)[c]	0.8 (1.9)[c] Mean Δ: − 2.9 (5.1)	9.2 (7.6)[c]	10.8 (7.3)[c] Mean Δ: + 1.7 (2.7)	4.9 (7.4)[c]	5.7 (8.2)[c] Mean Δ: + 0.8 (1.7)
			PBO + NAP $n = 51$	6.1 (4.0)[c]	2.2 (2.6)[c] Mean Δ: − 3.9 (3.7) ($P = 0.003$)	4.7 (5.7)[c]	2.7 (4.0)[c] Mean Δ: − 2.0 (4.2) ($P < 0.001$)	11.2 (8.6)[c]	12.5 (8.1)[c] Mean Δ: + 1.4 (2.6) ($P = 0.86$)	6.2 (8.0)[c]	7.2 (8.9)[c] Mean Δ: + 1.0 (1.8) ($P = 0.72$)

Table 6 continued

Study	Study population	Study duration	Treatment groups	Inflammatory lesions				Structural lesions			
				SIJ inflammation score BL	SIJ inflammation score EOS	Spine inflammation score BL	Spine inflammation score EOS	SIJ fatty lesion score BL	SIJ fatty lesion score EOS	Spine fatty lesion score BL	Spine fatty lesion score EOS
Sieper et al. (2016) [31] INFAST Part 1 nr-axSpA ClinicalTrials.gov Identifier: NCT00844805	r-axSpA and nr-axSpA[a]	28 weeks	INF + NAP *n* = 40	Median: 3.3[c]	Median: 0.5[c] Median Δ: − 2.0 % Δ: − 61.5	Median: 0.5[c]	Median: 0[c] Median Δ: 0 % Δ: 0	–	–	–	–
			PBO + NAP *n* = 16	Median: 6.5[c]	Median: 2.5[c] Median Δ: − 3.5 % Δ: − 53.8	Median: 0.5[c]	Median: 1.0[c] Median Δ: 0 % Δ: 0				

Values are presented as the mean with the SD in parenthesis, unless otherwise stated. Δ, Change from BL

IQR Interquartile range, *SI* sacroiliitis

[a] Data presented for nr-axSpA subgroup only

[b] Leeds MRI score

[c] Berlin MRI score

Increases in fatty lesion scores at 48 weeks were 0.8 and 0.2, respectively, in the SIJ ($P = 0.001$), and 0.8 and 0.1 in the spine ($P = 0.020$) (Table 4). After 1 year, active suppression of inflammation was strongly associated with the appearance of fatty lesions, which may be the first sign of chronic damage in the bone after prior inflammation [33]. Analysis of the long-term ESTHER data found a small increase in fatty lesion scores from baseline to month 24 (which was significant only for the spine; $P = 0.025$), but no further increases in fatty lesion scores were observed during the third year of etanercept therapy (Table 4) [34]. New fatty lesion formation was primarily observed in those areas where active inflammation was present at baseline [34]. Notably, no changes in erosion or ankylosis scores—indicative of more chronic structural changes—were observed during the entire follow-up period [33, 34].

Similar observations of an increase in fatty lesion formation were noted in the EMBARK trial, but not before week 48 [24]. At week 12, there were significant differences between etanercept- and placebo-treated patients in the reduction of erosion (− 0.57 vs. − 0.08, respectively; $P = 0.017$) and increase in backfill (0.36 vs. 0.06; $P = 0.022$) at the SIJ, but not in the changes in fat metaplasia (0.06 vs. 0.05) (Table 4) [35]. In addition, changes in fat metaplasia at week 12 did not correlate significantly with the changes in SIJ inflammation (data not shown). At week 48, the mean SIJ structural lesion scores for fat metaplasia and backfill increased by 0.46 and 0.89, respectively (Table 4); the ankylosis score increased by 0.04, and the erosion score decreased by − 1.29 [24].

Finally, radiographic changes on the SIJ after 104 weeks of etanercept treatment in the EMBARK trial were compared with those from participants in a contemporary control cohort (DESIR) [36] who met the ASAS criteria for axSpA and who did not receive any biologic treatment for the first 2 years of follow-up [37]. At week 104, patients from EMBARK ($n = 154$) had an adjusted least-squares mean total SIJ score improvement of − 0.14, while their DESIR counterparts ($n = 182$) experienced an overall worsening of 0.08 ($P = 0.008$) (Table 4). (The total SIJ score was calculated by adding up structural damage scores for both SIJs, using the modified New York grading system [5]). In addition, the net difference in the proportion of patients who experienced improvement versus worsening significantly favored etanercept-treated (EMBARK) over biologic-naïve (DESIR) patients on two out of three radiographic assessment criteria (Table 4) [37].

Infliximab

The effect of infliximab therapy on fatty lesion formation was also investigated in the INFAST trial [30]. As observed with short-term etanercept therapy, increases in fatty lesion MRI scores in the SIJ and spine were observed in both the infliximab + NSAID group and the placebo + NSAID group after 28 weeks, with no significant difference in treatment effect at either site (Table 6).

DISCUSSION AND CONCLUSIONS

A number of RCTs have shown that TNFα inhibitors reduce MRI-evident inflammatory lesions in the SIJ and spine of patients with early axSpA. Although studies reported improvements in MRI-evident inflammation primarily over the short to medium term (12 weeks to 1 year), reductions in inflammation were maintained for up to 4 years (204 weeks) with certolizumab therapy and for up to 3 years (156 weeks) with etanercept therapy. Little data are available on the effect of TNFα inhibitors on structural lesions, but the EMBARK etanercept trial indicates an improvement with up to 2 years of treatment, compared with a no-treatment cohort from another trial. In addition, increased fatty lesion formation following the resolution of inflammatory lesions with etanercept therapy appears to be transient in nature, with no associated change in joint erosion or ankylosis over the longer term.

Effective anti-inflammatory treatment of axSpA may be associated with an apparent increase in fatty lesion scores, irrespective of the presence or absence of concomitant therapy with a TNFα inhibitor. Fatty lesion formation

may represent an important long-term parameter for assessing the effect of early suppression of joint inflammation on more chronic, structural bone changes, such as erosion and ankylosis. However, the specificity of fatty lesions in patients with axSpA needs to be investigated further. A 2012 ASAS/OMERACT (Outcome Measures in Rheumatology) consensus statement based on a systematic literature review suggested that the presence of several corner fatty lesions may indicate axSpA, especially in younger patients, but the authors cautioned that prospective studies in patients aged < 45 years would be needed to strengthen the evidence [8]. In one such study, conducted at two clinical centers, the presence of ≥ 3 corner inflammatory lesions and ≥ 6 corner fatty lesions did not help distinguish between patients with axSpA and those with nonspecific back pain, despite the mean age of all cohorts being < 40 years [38]. In conclusion, additional studies are required to determine the exact role of fatty lesions in axSpA progression and whether TNFα-inhibitor therapy can limit or delay radiological progression in patients with early axSpA.

ACKNOWLEDGMENTS

Funding. This literature review and the article processing charges were funded by Pfizer. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing. Medical writing support was provided by Shirley Smith and Vojislav Pejović of Engage Scientific Solutions and was funded by Pfizer.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Ko-Jen Li was a speaker for AbbVie, Johnson & Johnson, Lilly, Novartis, Pfizer, and Roche. Ramesh Jois has nothing to disclose. Juan Javier Lichauco is an advisor to Pfizer. Paul Santos Estrella is an employee of Pfizer and may own Pfizer stock. Lyndon John Llamado is an employee of Pfizer and may own Pfizer stock. Amit Vilas Thorat is an employee of Pfizer and may own Pfizer stock. Ehab Mahgoub is an employee of Pfizer and may own Pfizer stock.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. All procedures performed in studies involving human participants that were cited in this review were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, as reported in the primary reports.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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