Change in MRI in patients with spondyloarthritis treated with anti-TNF agents: systematic review of the literature and meta-analysis

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Abstract

Objective

Magnetic resonance imaging (MRI) is currently the most accurate imaging tool used in axial spondyloarthritis regarding its diagnostic approach. MRI of the spine and sacroiliac joints (SIJ) might be relevant in the follow-up of axial spondyloarthritis for difficult cases, provided that its validity and correlation with clinical, biological and functional outcomes is ascertained. The aim of this study was to assess the effect of TNF alpha inhibitors (TNFi) on MRI scoring of inflammation on spine and SIJ and to evaluate their correlation with the parameters used in daily practice.

Methods

A systematic review of the literature using PUBMED and the Cochrane library was performed until January 2016. All randomised controlled trials and controlled cohorts reporting the effect of TNFi on spine and SIJ MRI scores [Ankylosing Spondylitis spine MRI (ASspiMRI), Spondyloarthritis Research Consortium of Canada (SPARCC), and Berlin] were selected. The collected outcomes were: the change in scores between baseline and follow-up in TNFi and control groups, the correlation of these changes with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index/Functional Index (BASDAI/BASFI), Ankylosing Spondylitis Disease Activity Score (ASDAS), pain and morning stiffness. When appropriate, statistical analysis determined the pooled therapeutic effect of TNFi on MRI scores computed by meta-analysis.

Results

Of 39 screened references, 55 studies were included. In studies using ASspiMRI at 12-week and 2-year follow-up, and in those using SPARCC spine score at 12-week follow-up, a non-significant decrease in MRI score between the TNFi group and control group was reported ($p=0.36$; $p=0.73$; $p=0.12$, respectively). Only a significant decrease in the SPARCC SIJ score was reported at 12 weeks in the TNFi group versus control ($p<0.0001$). The correlation between MRI spine and SIJ scores on the one hand, and the clinical and biological data on the other was very heterogeneous across the different reports. However, an association was usually reported between the MRI scores and CRP, ESR and ASDAS.

Conclusion

There is not sufficient evidence to distinguish the difference between changes in MRI inflammatory lesions of the spine and SIJ in patients with axial SpA related to TNF alpha inhibitor effects and those due to the natural course of the disease activity (alternating periods of flares and remission in axial SpA).

Key words

axial spondyloarthritis, ankylosing spondylitis, TNF alpha inhibitors, ASspiMRI, SPARCC score, Berlin score, magnetic resonance imaging

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Introduction

Axial spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease mainly affecting the spine and sacroiliac joints (SIJ) of patients, which encompasses a wide spectrum of phenotypes, from painful but benign forms to severe and potentially disabling disease, such as ankylosing spondylitis/ radiographic axial SpA. Imaging has always had an important part in the diagnosis of axial SpA, even if the diagnostic and classification criteria have evolved over time. The New York criteria used standard x-rays of the pelvis to assess SIJ lesions, defining AS when definite changes are visualised (1). Recently, the use of Magnetic resonance imaging (MRI) has been developed, making the early detection of axial forms of the disease possible, even in the absence of structural lesions of the spine or SIJ. Indeed, the presence of suggestive bone marrow edema lesions of the SIJ is a major indicator of the disease in a patient with chronic back pain and symptom onset before 45 years of age according to the Assessment of Spondyloarthritis (ASAS) criteria for axial SpA (2). These radiological signs are mainly defined based on the study of MRI of the SIJ using short-tau-inversion- recovery (STIR) sequences (3). An inflammatory signal on two successive MRI slices of the sacroiliac joints, or two inflammatory signals on a single slice, is usually regarded as sufficiently suggestive of SpA, although the specificity of these abnormalities also depends on the location of the lesions, their extension as well as the context (aged, obese or intensively running patients). Spine inflammatory signals on MRI can also be evaluated on STIR sequences and appear as hypersignals of the vertebral corners, sometimes extending to a larger part of the vertebra itself (spondylitis), or depicting pseudo-spondylodiscitis images. In clinical practice, they are regarded as an additional argument for the diagnosis of axial SpA, but remain insufficiently specific to be included in the diagnostic criteria (4, 5).

Anti TNF-alpha agents are biological therapies whose efficacy has been demonstrated in radiographic and non-radiographic axial SpA (6-10). Presence of axial inflammatory lesions as detected by MRI are considered predictive of a good response to these agents (11, 12).

Although MRI of the spine and sacroiliac joints is often assessed in clinical trials designed to evaluate the efficacy of anti-TNF agents in SpA, its place in clinical practice for the disease monitoring has never been formally evaluated, and its correlation with clinical and biological parameters and functional or activity scores used in the disease monitoring remains uncertain.

The aim of this study was to assess the effect of TNF-alpha inhibitors on inflammation on spine and SIJ in patients with axial SpA as captured by MRI scoring systems, and to evaluate their correlation with the clinical and biological assessments of the disease used in daily practice.

Methods

This meta-analysis was conducted according to the Cochrane Collaboration guidelines.

Study selection

A systematic literature search was performed in Medline, Cochrane library databases as well as proceedings from recent major relevant congresses until January 2016 without limitation of years of publication or journal, using the followings key-words: (magnetic resonance imaging OR MRI OR Imaging, Magnetic Resonance) AND (spondyloarthritis OR spondylitis OR spondyl*) AND (anti-TNF OR tumor necrosis factor-alpha OR TNF OR etanercept OR adalimumab OR infliximab OR golimumab OR certolizumab). The limits were English or French language and randomised controlled trials and controlled cohorts. In addition, reference lists of the papers initially detected were hand searched to identify additional relevant reports.

The trials were initially selected on the basis of their titles and abstracts, then on the full texts. The inclusion criteria were all randomised controlled trials and controlled cohorts reporting the effect of TNF-alpha inhibitors on spine and SIJ MRI scores, and/or evaluating the correlation of these imaging modi-

fications with the visual analogue score of pain, the duration of morning stiffness, the CRP (C-reactive protein), the ESR (erythrocyte sedimentation rate), the BASDAI score, the BASFI score and the ASDAS score. Articles reporting not interpretable results (lacking of MRI follow-up, lacking of data needed included mean and standard deviation (SD) at baseline and at the moment of follow-up) were not analysed.

MRI scoring methods

In order to evaluate inflammatory signals on spine and sacroiliac joints, MRI scores have been developed. These validated and reproductible scoring methods are usually used in clinical trials. Our research identified five major scores.

For the assessment of spinal inflammation on MRI, three different scores have been performed: the Ankylosing Spondylitis spine Magnetic Resonance Imaging activity (ASspiMRI-a), the Berlin score and the Spondyloarthritis Research Consortium of Canada (SPARCC) score.

The ASspiMRI-a score assesses the spinal inflammatory lesions. It is based on the analysis of 23 vertebral units from C2 to S1. Each vertebral unit is defined between two virtual lines. Each line runs through the middle of a vertebra. Every vertebral unit is then scored from 0 to 6 considering the bone marrow edema (grades 0 to 3) visualised in STIR sequence, and erosions (grades 4 to 6). The ASspiMRI-a score can range from 0-138 (13). The Berlin scoring method for spine (Berlin/spine) is a variation of the AsspiMRI-a score which evaluates only the bone marrow edema for the same 23 vertebral units. Each vertebral unit is then graded from 0 to 3, and the score can thus range from 0 to 69. The SPARCC spine scoring method (SPARCC/spine) is a dichotomous score evaluating the six most abnormal discovertebral units of the spine on the STIR MRI sequences. Each vertebral unit is divided into four quadrants, which are each evaluated on three slices. The total score of each level is graded from 0 to 12. A high intensity signal, comparable to cerebrospinal fluid or a "deep" lesion (extending signal ≥1 cm) dive an additional sore of 1. The SPARCC spinal score can range from 0 to 108 (14).

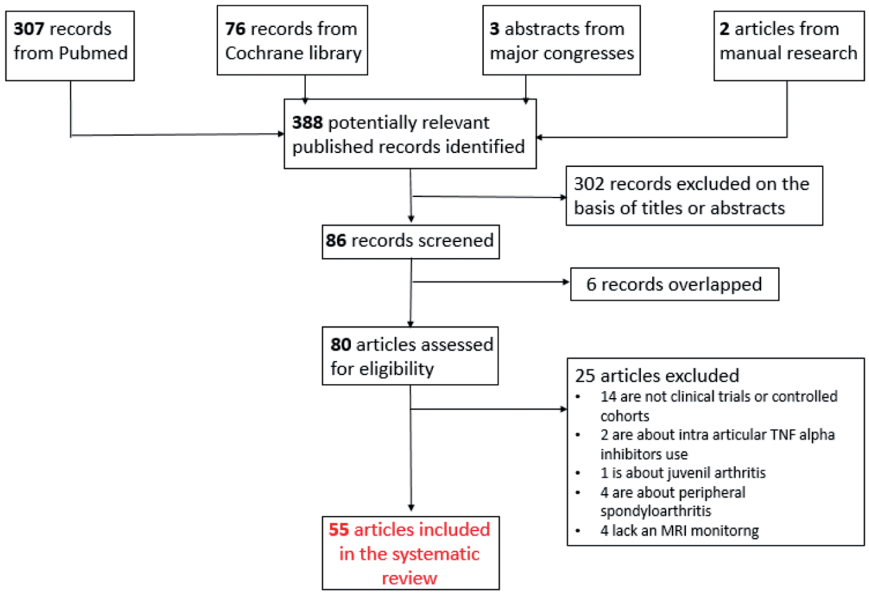

Fig. 1. Flow chart of the literature review selection.

For the assessment of SIJ inflammation on MRI, two different scores have been developed: the Berlin score and the SPARCC score for SIJ. The SPARCC sacroiliac joints score (SPARCC/SIJ) is a dichotomous score evaluating both SIJ in STIR sequences. Each sacroiliac joint is divided into four quadrants, each evaluated on six consecutive slices, giving a maximum score of 48. A high intensity signal or a "deep" lesion (extending signal ≥1cm) give an additional score of 1. The SPARCC/SIJ score can range from 0 to 72 (15). The Berlin sacroiliac joints score (Berlin/SIJ) assesses the volume of the bone marrow oedema (BME) in each of the 4 quadrants of the sacroiliac joints: 0 for no BME, 1 when the BME <33%, 2 when the BME volume is between 33% and 66%, and 3 when the BME volume >66%. This score can range from 0 to 24 (16).

Data collection

One investigator selected the articles and collected data using a predetermined form. For each clinical trial, the selected outcomes were: the diagnostic criteria of SpA used, the radiographic/non-radiographic form of the SpA, the TNF-alpha inhibitor(s) used, the therapy (or placebo) used in the control group, the number of patients included and the number of those receiving the TNF-alpha inhibitor treatment, the axial involvement studied (spine, SIJ or both), the epidemiological characteristics of patients (age, gender, HLA B27 status and disease duration), the MRI follow-up times, the MRI score used for assessment (ASspiMRI, SPARCC, Berlin or other score). Whether the MRI score had been validated or not was checked, and only data based on validated scores were potentially used for pooled analyses. For every article, if mentioned, the correlation between changes in MRI score and clinical outcomes (visual analogic scale of pain, morning stiffness duration), between MRI scores and scores evaluating the disease activity (ASDAS, BASDAI, BASFI) and between MRI scores and biological outcomes (CRP, ESR) was collected. Finally articles using the same MRI scores and evaluating them at the same time intervals were pooled.

Statistical analysis

For the meta-analysis, the mean difference between treatment groups was estimated with 95% confidence interval (CI) in anti-TNF *versus* control population by generic inverse variance method, with a random effect model when appropriate, *i.e.* when resulting heterogeneity was found relevant. The primary objective was the comparison of MRI change scores in patients treated under blinded conditions by either anti-

Table I. Randomised controlled trials evaluating the MRI monitoring in axial spondyloarthritis.

Article	TNF alpha inhibitor used	TNF alpha inhibitor group (n)	region	Mean age (years)	HLA B27 status n (%)	Disease mean duration (years)	MRI scoring method	MRI follow-up
Brandt, 2000 (17)	IFX	10	spine/SIJ	36	10 (100)	5	NV	week 2- week 6
Marzo-Ortega, 2001 (18)	ETA	10	spine/SIJ	37	8 (80)	12	NV	week 24
Stone, 2001 (19)	IFX	21	spine/SIJ	37.9	21 (100)	8.7	NV	day 2- week 2
Maksymowych, 2002 (20)	IFX	22	SIJ	42.5	20 (95.2)	13.8	NV	week 14
Marzo-Ortega, 2002 (21)	ETA	10	spine/SIJ	NA	8 (80)	12	NV	week 24
Haibel, 2006 (22)	ADA	15	spine/SIJ	40	35 (87)	11	Berlin	week 12- week 52
Treves, 2006 (23)	IFX	34	SIJ	40.4	22 (64.7)	8.2	NV	week 14
Maksymowych, 2007 (24)	ADA, IFX	29	spine	NA	NA	NA	ASspiMRI-a, SPARCC	month 18
Rudwaleit, 2008 (11)	ETA, IFX	99	spine/SIJ	NA	NA	NA	Berlin	NA
Bonel, 2010 (25)	IFX	28	spine	38.5	17 (60.7)	10.4	ASspiMRI-a	week 12
Pedersen, 2010 (26)	ADA, IFX, ETA	60	spine/SIJ	40	49 (82)	12	Berlin	week 22, week 46
Pedersen, 2011 (27)	ADA, IFX, ETA	23	spine	40.4	NA	18.2	NV	month 19- month 27
Pedersen, 2011 (28)	ADA, IFX, ETA	60	spine/SIJ	40	49 (82)	12	Berlin	week 22- week 46
Wang, 2012 (29)	IFX	39	spine	35.3	NA	NA	ASspiMRI-a	week 30
Song, 2013 (30)	ETA	40	spine	NA	NA	2.6	Berlin	week 48
Karpitschka, 2013 (31)	ETA	10	spine/SIJ	40	10 (100)	NA	NV	week 26- week 52
Baraliakos, 2013 (32)	NA	22	spine	38	NA	13.9	ASspiMRI-a, Berlin	year 2
Pedersen, 2014 (33)	NA	79	SIJ	40.36	NA	16.53	SPARCC	year 2
WeiB, 2014 (34)	ADA, ETA	112	SIJ	34.75	86 (76.7)	4.7	Berlin	week 48
Baraliakos, 2014 (35)	IFX	73	spine	40.5	61 (83.5)	10	NV	year2
Song, 2015 (36)	ETA	41	spine/SIJ	32.8	33 (80.5)	2.6	Berlin	year 2- year 3
Cantarini, 2015 (37)	ADA	37	SIJ	49.4	22 (60.6)	4.5	SPARCC	month 18
Griffith, 2015 (38)	IFX	32	spine	35.5	NA	NA	Berlin	week 30

**ETA: etanercept; IFX: infliximab; ADA: adalimumab; NA: not available; NV: non validated score.

TNF or control (usually placebo), *i.e.* at 12 weeks as it is the usually applied delay before rescue therapy is offered to clinically non-responding patients. Indeed, within this period of time, patients, investigators and radiologists are all blinded for the treatment received.
The risk of publication bias was assessed by the means of funnel plots.

Results

Literature search results

Figure 1 shows the selection process. Among 388 potentially relevant hits, 55 were included in the systemic review after careful review of title, abstract and full text when appropriate. Thirty two were randomised controlled trials Table I) and 23 were longitudinal cohorts (Table II). Forty six articles studied spine MRI changes and 34 articles SIJ MRI changes. Fifteen records used ASspiMRI, 15 used SPARCC, 15 the Berlin score and 15 records used non validated scores. In total, this systematic review included 2624 patients treated with TNF-alpha inhibitors and 1352 controls. The mean ages varied between 27.8 and 49.4 years, the disease duration between 2.5 and 18.2 years and 60.6 to 100% of patients were HLA B27 positive (Tables I and II). Periods of MRI follow-up were very heterogeneous, and ranged from 2 weeks to 3 years.

Changes in MRI scores in patients treated with anti-TNF vs. control group

All studies reported a significant decrease in mean MRI score on spine and SIJ compared to baseline value in the group of patients treated with TNF, regardless of the score used. Controls had variable changes in MRI scores, but most randomised controlled studies also showed a decrease in MRI scores even in patients who had not been treated with TNFi. Thus, randomised controlled studies were pooled considering MRI scores used and time of the follow-up to compare changes in TNFi treated patients and controls. Meta-analyses were performed when articles used the same MRI score, when MRI monitoring was done at the same time, and when data for TNFi and control groups were available.
Four meta-analyses could consequently be performed: 2 with 2 randomised controlled trials for the spine using ASspiMRI at 12 weeks (Table III) and 2 years of follow-up (Table IV), 1 with 3 randomised controlled trials for the spine using the SPARCC score at 12 weeks of follow-up (Table V) and 1 with 3 randomised controlled trials for the SIJ using the SPARCC score at 12 weeks of follow-up (Table VI). The first one showed a non-significant decrease in ASspiMRI score in TNFi group, compared with the control group at 12 weeks: mean difference= -1.67 (65.2; 1.87) p=0.36 (Fig. 2). The second did not show a statistically significant difference in ASspiMRI at 2 years between patients treated with TNFi and those having received the control treatment: mean difference = 1.34 (-6.30; 8.98) p=0.73 (Fig. 2). Regarding the SPARCC spine score, the difference was also not significant at 12 weeks, between TNF-alpha inhibitor- and control groups: mean difference= -4.85 (-10.99; 1.28) p=0.12 (Fig. 2). A significant decrease in the SPARCC SIJ score at 12 weeks in TNFi group *versus* control group was reported: mean difference = -3.19 (-4.80; -1.58), p<0.0001 (Fig. 2).

Table II. The review of the literature: cohort studies evaluating the MRI monitoring in axial spondyloarthritis.

Article	TNF Alpha inhibitor used	TNF alpha inhibitor group (n)	Control group (n)	Region	Mean age (years)	HLA B27 status n (%)	Disease mean duration (years)	MRI scoring method	MRI follow-up
Sieper, 2005 (40)*	IFX	9	11	spine	40.9	NA	16.5	ASspiMRI-a	week 12- week 104
Maksymowych, 2010 (54)*	IFX	18	18	spine	NA	27 (75)	NA	SPARCC	week 12
Hu, 2012 (41)*	ADA	26	20	spine/SIJ	27.8	37 (80.4)	7.5	SPARCC	week 12- week 24
Braun, 2012 (39)*	**GOL**	75	23	spine	NA	79 (80.6)	NA	ASspiMRI-a	week 14- week 104
Dougados, 2014 (42)*	ETA	106	109	spine/SIJ	32.0	154 (72)	NA	SPARCC	week 12
Pedersen, 2016 (43)*	ADA	25	27	SIJ	NA	43 (82.7)	NA	Berlin, SPARCC	week 12- week 24- week 48
Braun, 2003 (13)	IFX	9	11	spine	40.9	NA	NA	ASspiMRI-a	week 12
Rudwaleit, 2005 (55)	ETA	12	8	spine/SIJ	NA	NA	NA	ASspiMRI-a	week 6- week 24
Maksymowych, 2005 (56)	IFX	14	6	spine	NA	NA	NA	SPARCC	week 24
Marzo-Ortega, 2005 (57)	IFX	28	14	spine/SIJ	NA	38 (90.4)	NA	NV	week 30
Baraliakos, 2005 (58)	ETA	19	21	spine	NA	35 (88)	NA	ASspiMRI-a	week 12- week 24- week 48
Baraliakos, 2005 (59)	ETA	16	17	spine	37.1	23 (89)	13.7	ASspiMRI-a	week 6- week 24- week 102
Braun, 2006 (60)	IFX	194	72	spine	NA	NA	NA	ASspiMRI-a	week 24
Lambert, 2007 (49)	ADA	38	44	spine/SIJ	NA	NA	NA	SPARCC	week 12- week 52
Visvanathan, 2008 (61)	IFX	201	78	spine	NA	279 (86)	NA	ASspiMRI-a	week 24
Treitl, 2008 (62)	IFX	9	2	spine	37	10 (91)	10.3	AsspiMRI-a	Week 24- week 54- week 102
Gaspersic, 2008 (63)	IFX	10	20	spine/SIJ	38.4	NA	3.4	NV	week 8- week 52
Li, 2008 (64)	IFX	38	38	spine	NA	NA	NA	ASspiMRI-a	week 30
Maksymowych, 2009 (65)	ADA, IFX	36	44	spine	NA	NA	NA	NV	week 12 or 24- year 1 or year 2
Barkham, 2009 (66)	IFX	20	20	SIJ	NA	40 (100)	NA	NV	week 16
Song, 2011 (67)	ETA	35	30	spine/SIJ	33.0	54 (83.1)	2.7	NV	week 24- week 48
Song, 2011 (16)	ETA	40	36	spine/SIJ	33.7	62 (81.6)	2.9	Berlin	week 24- week 48
Machado, 2012 (68)	IFX	158	179	spine	NA	NA	NA	Berlin	week 24- week 102
Maksymowych, 2012 (44)	ADA	38	44	spine/SIJ	NA	NA	NA	SPARCC	week 12- week 52
Sieper, 2013 (69)	ADA	91	94	spine/SIJ	NA	145 (74.4)	NA	SPARCC	week 12
Maksymowych, 2013 (70)	ADA	38	44	spine	NA	NA	NA	NV	week 12- week 52
Krohn, 2014 (71)	ETA	40	35	SIJ	NA	NA	NA	Berlin	week 24- week 48
Maksymowych, 2015 (72)	ETA	102	106	spine/SIJ	31.9	148 (71.2)	2.5	SPARCC, ASspiMRI-a	week 12- week 48
Sieper, 2015 (73)	GOL	98	100	SIJ	NA	163 (82.3)	NA	SPARCC	
Abstracts									
Poddubnyy, 2014	infliximab	106	52	spine/SIJ	NA	NA	NA	Berlin	week 28
Van der Heijde, 2014	certolizumab	NA	NA	spine/SIJ	NA	NA	NA	SPARCC, Berlin	NA
Van der Heijde, 2014	adalimumab	69	73	spine/SIJ	NA	NA	NA	SPARCC	week 12- week 52- week 104

*ETA: etanercept; IFX:infliximab; ADA: adalimumab; GOL: golimumab; NA: not available; NV: non validated score.

Table III. Randomised controlled trials evaluating ASspiMRI-a score at 12-14 weeks, included in meta-analysis.

Article	TNF alpha inhibitor group (n)	Mean (SD) in TNF alpha inhibitor group at baseline	Mean (SD) in TNF alpha inhibitor group at 12-14 weeks	Mean difference (SD) in TNF alpha inhibitor group between baseline and 12-14 weeks	Control group (n)	Mean (SD) in control group at baseline	Mean (SD) in control group at 12-14 weeks	Mean difference (SD) in control group between baseline and 12-14 weeks
Braun, 2012 (39)	75	7.1 (6.9)	NA	-4.5 (6.1)	23	9.6 (9.5)	NA	-2.5 (8.9)
Sieper,2005 (40)	6	20.5 (16.6)	10.7 (9.4)	NA	11	11.9 (8.7)	10.8 (6.5)	NA

NA: Not available.

The heterogeneity across studies, as assessed by the meta-analyses performed, was substantial for ASsspiMRi at 2 years and for SPARCC/spine (I^2= 79% and I^2= 71%) and negligible for ASspiMRI at 12 weeks and for SPARCC/SIJ (I^2 = 0% in both analyses).

A general meta-analysis of the impact of TNFi on MRI scores of the spine after 12 weeks of treatment was also conducted by the means of the standardised mean difference method, that allows pooling of results obtained by different outcome measures, provided that they assess the same latent concept

Table IV. Randomised controlled trials evaluating ASspiMRI-a score at 2 years, included in meta-analysis.

Article	TNF alpha inhibitor group (n)	Mean (SD) in TNF alpha inhibitor group at baseline	Mean (SD) in TNF alpha inhibitor group at 2 years	Mean difference (SD) in TNF alpha inhibitor group between baseline and 2 years	Control group (n)	Mean (SD) in control group at baseline	Mean (SD) in control group at 2 years	Mean difference (SD) in control group between baseline and 2 years
Braun, 2012 (39)	75	7.1 (6.9)	NA	-5.3 (6.7)	23	9.6 (9.5)	NA	-10.4 (10.5)
Sieper, 2005 (40)	6	20.5 (16.6)	3.0 (4.6)	NA	11	11.9 (8.7)	5.7 (6.7)	NA

NA: not available.

Table V. Randomised controlled trials evaluating SPARCC spine score at 12 weeks, included in meta-analysis.

Article	TNF alpha inhibitor group (n)	Mean (SD) in TNF alpha inhibitor group at baseline	Mean (SD) TNF alpha inhibitor group at 12 12 weeks	Mean difference (SD) in TNF alpha inhibitor group between baseline and 12 weeks	control group (n)	Mean (SD) in control group at baseline	Mean (SD) in control group at 12 weeks	Mean difference (SD) in control group between baseline and 12 weeks
Hu, 2012 (41)	26	17.0 (12.2)	9.6(12.7)	NA	20	19.7(12.7)	16.1 (10.0)	NA
Maksymowych, 2010 (22)	16	18.94 (17.98)	7.0(9.89)	NA	16	19.0 (16.77)	18.88 (19.01)	NA
Dougados, 2014 (42)	106	4.7 (7.1)	NA	-2.1 (0.5)	109	3.5 (5.6)	NA	-1.2 (0.5)

NA: not available.

Table VI. Randomised controlled trials evaluating SPARCC SIJ score at 12 weeks, included in meta-analysis

Article	TNF alpha inhibitor group (n)	Mean (SD) in TNF alpha inhibitor group at baseline	Mean (SD) TNF alpha inhibitor group at 12 weeks	Mean difference (SD) in TNF alpha inhibitor group between baseline and 12 weeks	Control group (n)	Mean (SD) in control group at baseline	Mean (SD) in control group at 12 weeks	Mean difference (SD) in control group between baseline and 12 weeks
Hu, 2012 (41)	26	10.1 (9.5)	4.5(6.0)	NA	20	9.0 (9.1)	7.5(8.7)	NA
Dougados, 2014 (42)	106	8.0 (9.7)	NA	-3.8(0.7)	109	7.7 (10.1)	NA	-0.8 (0.6)
Pedersen, 2016 (43)	23	6.2 (8.9)	3.2 (7.6)	NA	23	11.1 (12.5)	8.6 (11.7)	NA

NA: not available.

(here the activity of SpA as depicted by MRI of the spine) (Fig. 3).

Funnel plots for each meta-analysis are available in the online supplementary data.

Correlation between MRI and clinical/biological outcomes

The correlation between changes in MRI scores on one side, and clinical, imaging and biological outcomes on the other side are shown in Table VII. These results were very heterogeneous across the different reports. Pain and morning stiffness were generally poorly correlated with changes in MRI in patients treated with TNFi in spine and SIJ, regardless of the score used and the time of evaluation (r ranging from -0.14 to 0.45, *i.e.* bad to moderate correlation). However, an association was usually reported between the MRI scores and acute phase reactants (CRP and ESR) especially between 14 and 54 weeks (r from 0.24 to 0.67), for BASDAI around the 24th to the 54th week (r from 0.32 to 0.831), for ASDAS (r from 0.22 to 0.58), and to a lesser extent for BASFI.

Discussion

This study aimed at evaluating the potential performance of MRI of spine and SIJ in the monitoring of axial SpA treated with TNFi and to compare its evolution with the changes of clinical and biological outcomes commonly used in the clinical follow-up of patients. The systematic review of the literature and the meta-analysis showed the following results: the MRI scoring of the spine of patients treated with TNFi for an axial SpA was not significantly improved in comparison with control treatments after 12 weeks and 2 years of follow-up. However, there was an early improvement in MRI of the SIJ in the TNF-alpha inhibitors group. MRI changes were not significantly correlated with most clinical patient-reported outcomes used in the monitoring of axial SpA, while activity scores and acute phase reactants showed a fair association with the inflammatory lesions of the spine and SIJ as captured by MRI.

This study is to our knowledge the first systematic literature review and meta-analysis having studied the effect of TNF-alpha inhibitors on axial MRI in comparison to control treatments. It has included patients from randomised

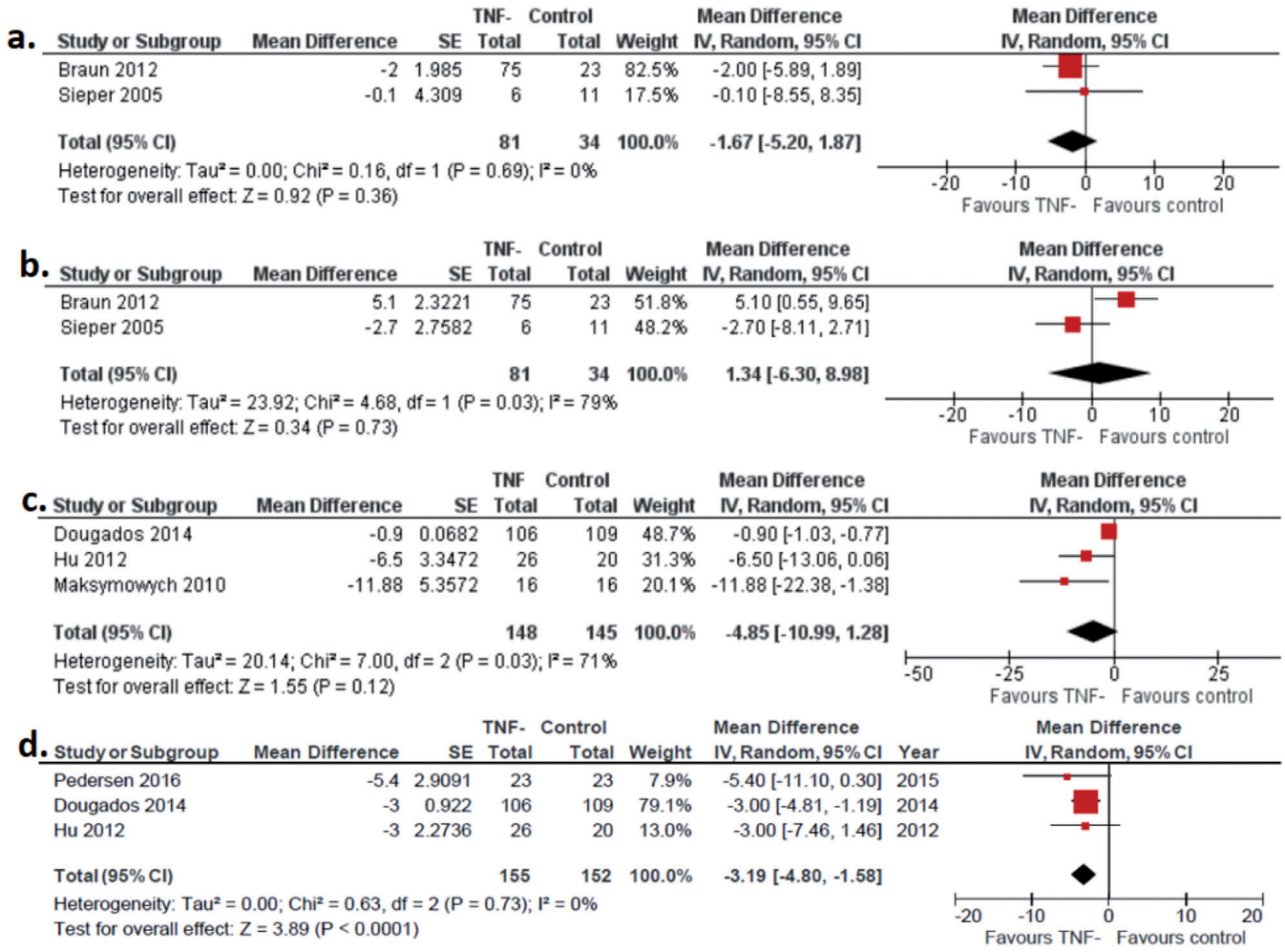

Fig. 2. MRI scores changes in TNF- group compared to the control group after different periods of follow-up.
a: ASspiMRI-a changes in TNF- group compared to the control group after 12-14 weeks of follow-up;
b: ASspiMRI-a changes in TNF- group compared to the control group after 2 years of follow-up;
c: SPARCC spine score changes in TNF- group compared to the control group after 12 weeks;
d: SPARCC SIJ score changes in TNF- group compared to the control group after 12 weeks.

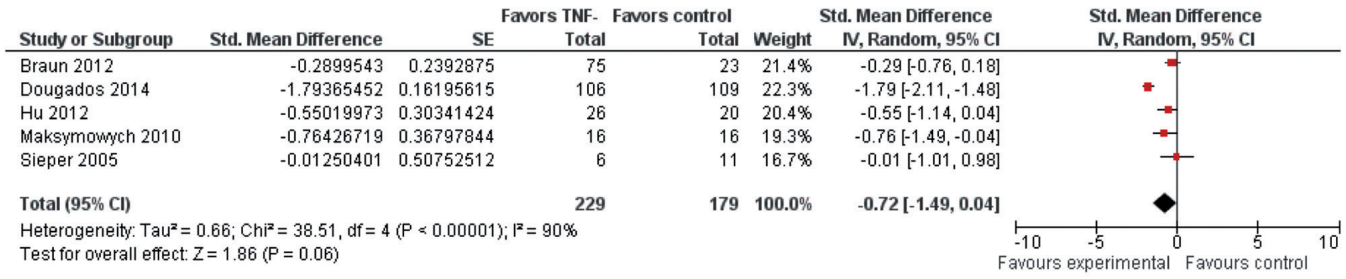

Fig. 3. ASspiMRI and SPARCC scores changes in TNF- group compared to the control group after 12 weeks of follow-up.

controlled trials, and the population from the different studies that were pooled is globally fairly homogenous. It allowed to assess the evolution of spine and SIJ MRI at different times of the disease monitoring. And although different scores were used in this evaluation, resulting data appeared to be very consistent.

However, this study has also several limitations. The systematic review of the literature allowed us to include an important number of records, but finally, few studies only could be pooled and meta-analysed. This was due to the different scores used to evaluate the -supposed- same outcomes, sometimes by non-standardised or non-validated scores, and secondly to the variability of times of follow-up applied across the different studies. Furthermore, patients in this review come from randomised controlled trials, and might therefore be different from those encountered in daily practice. Finally, the assessment of MRI changes was often not the main objective of the included studies, but

a secondary outcome, where the main aim was the demonstration of the efficacy of TNFi in axial SpA.

Our results noticed a difference in the observed changes captured by MRI between spine and SIJ. With regards to diagnostic issues, it is usually considered that the SIJ of patients with axial SpA is the most appropriate site to explore, with the highest likelihood to detect inflammation (4, 5), while the detection of inflammatory lesions is more inconstant on the spine, therefore the decrease of inflammatory signal on SIJ under efficient treatment might be easier to highlight. Indeed, the minimally important change in SPARCC scoring system is estimated at 5 for spine and at 2.5 for SIJ to be associated with sufficiently high levels of sensitivity and specificity (about 80% both for SPARCC/ spine and 90% both for SPARCC/SIJ). Furthermore, interreader agreement seems higher, and scores variations lower in SPARCC/SIJ than SPARCC/spine (44). Another hypothesis for the lack of difference found between the placebo groups and the TNF alpha inhibitors treated groups is that SpA is a chronic inflammatory rheumatic disease with usually alternating periods of flares and remission, and patients are mandated to be in an active disease state at the time of their inclusion in a clinical trial, which was the case for a large majority of subjects included in this review. This may have resulted in a decreased discriminatory ability of MRI inflammatory scoring systems, because of the spontaneously resolving disease and placebo effect in patients of the control groups, and consequently a more limited difference between compared groups of treatments (anti-TNF *vs*. control).

Furthermore, other confounding factors can impact on inflammatory signal changes. The presence of HLA B27 is usually considered a predictor of good response to TNFi (45), and the follow-up of SIJ MRI in axial SpA without TNF-alpha has shown a significant reduction of the inflammatory signal on SIJ in positive HLA B27 patients only (46). Here the presence of a higher percentage of HLA B27 positive patients in studies evaluating the SPARCC scoring system of the SIJ (41-43) com-

Table VII. Correlation between MRI changes and clinical, biological outcomes used in the monitoring of axial spondyloarthritis.

Article	MRI score	Time (weeks)	Correlation coefficient (r)	*p*-value
Pain				
Maksymowych, 2007 (24)	ASspiMRI	24	0.26	NS
	SPARCC spine	24	0.26	NS
Braun, 2012 (39)	ASspiMRI-a	24	0.15	NS
		104	0.002	NS
Maksymowych, 2015 (72)	SPARCC SIJ	12	0.28	<0.01
		4	0.45	<0.001
Morning Stiffness				
Braun, 2012 (39)	ASspiMRI-a	14	-0.14	NS
		104	0.06	NS
CRP				
Baraliakos, 2005 (58)	ASspiMRI-a	14	0.005	NS
Maksymowych, 2005 (56)	SPARCC spine	24	0.79	0.001
Maksymowych, 2007 (24)	ASspiMRI	24	0.068	<0.0001
	SPARCC spine	24	0.068	<0.0001
Lambert, 2007 (49)	SPARCC SIJ	12	NA	0.590
	SPARCC spine	12	NA	0.018
Visvanathan, 2008 (61)	AsspiMRI-a	24	0.243	0.001
Treitl, 2008 (62)	ASspiMRI-a	24	0.675	<0.023
		54	0.636	<0.036
Bonel, 2010 (25)	ASspiMRI-a	14	0.41	NA
Maksymowych, 2010 (54)	SPARCC spine	12	0.045	0.0012
			0.34	NS
Braun, 2012 (39)	ASspiMRI-a	14	0.45	<0.001
		104	0.38	<0.01
Machado, 2012 (68)	Berlin spine	24	0.25	0.002
		52	0.32	<0.001
WeiB, 2014 (34)	Berlin SIJ	48	0.4	0.02
Pedersen, 2014 (33)	SPARCC SIJ	104	-0.40	0.001
Maksymowych, 2015 (72)	SPARCC SIJ	12	0.31	<0.01
		48	0.37	<0.001
ESR				
Baraliakos, 2005 (58)	ASspiMRI-a	14	0.016	NS
Maksymowych, 2010 (54)	SPARCC spine	12	0.57	0.001
		12	0.43	0.02
BASDAI				
Braun, 2003 (14)	ASspiMRI-a	12	0.6	0.005
Baraliakos, 2005 (58)	ASspiMRI-a	14	0.11	NS
Sieper, 2005 (40)	ASspiMRI-a	12	0.50	0.05
		104	NA	NS
Maksymowych, 2005 (56)	SPARCC spine	24	0.32	NS
Lambert, 2007 (49)	SPARCC spine	12	NA	NS
	SPARCC SIJ	12	NA	NS
Maksymowych, 2007 (24)	ASspiMRI	24	0.36	NS
	SPARCC spine	24	0.36	NS
Treitl, 2008 (62)	ASspiMRI-a	24	0.831	<0.001
		54	0.369	<0.001
Maksymowych, 2010 (54)	SPARCC spine	12	0.25	NS
		12	0.14	NS
Machado, 2012 (68)	Berlin spine	24	0.14	0.090
		52	0.14	0.057
Braun, 2012 (39)	ASspiMRI-a	14	0.26	<0.05
		104	0.11	NS
WeiB, 2014 (34)	Berlin SIJ	48	0.2	0.1
Maksymowych, 2015 (72)	SPARCC SIJ	12	0.27	<0.1
		48	0.42	<0.001
BASFI				
Sieper, 2005 (40)	ASspiMRI-a	12	0.62	0.01
		104	NA	NS
Lambert, 2007 (49)	SPARCC spine	12	NA	NS
	SPARCC SIJ	12	NA	NS

Article	MRI score	Time (weeks)	Correlation coefficient (r)	*p*-value
Maksymowych, 2010 (54)	SPARCC spine	12	0.16	NS
		12	0.007	NS
Braun, 2012 (39)	ASspiMRI-a	14	0.19	NS
		104	0.005	NS
WeiB, 2014 (34)	Berlin, SIJ	48	0.1	0.3
Maksymowych, 2015 (72)	SPARCC SIJ	12	0.17	NS
		48	0.35	<0.001
ASDAS				
Braun, 2012 (39)	ASspiMRI-a	14	0.35	<0.01
		104	0.22	NS
Machado, 2012 (68)	Berlin spine	24	0.22	0.06
		52	0.23	0.02
Maksymowych, 2015 (72)	SPARCC SIJ	12	0.35	<0.001
		48	0.58	<0.001

NA: not available; NS: not significant.

pared with studies having applied the spinal MRI scores may partly explain the observed difference.

In our meta analyses, MRI changes were assessed at 12–14 weeks and 2 years for the spine and at 12 weeks for the SIJ. It is actually difficult to judge the appropriateness of the timing of evaluations of MRI scores performed during the follow-up. MRI scores were initially validated on the finding of a good inter-readers correlation and a significant decrease of these scores in patients treated with TNFi, assessed at 2–3 months and 1–2 years on average (24, 40, 47-49). It might consequently be considered a methodological nonsense to evaluate its performance under the same conditions, although our aim in this work was predominantly to focus on the appreciation of the discriminatory ability of MRI, which indeed was finally found quite limited.

Available data in the systematic review of the literature show that the changes in MRI scores are not always consistent with the changes in clinical and biological parameters used in the monitoring of axial SpA. Outcomes that were reported to be correlated with the MRI scores changes are objective ones as: ASDAS, ESR and CRP, and this finding was consistent across different studies. On the other hand, subjective data used in practice in the disease monitoring like assessments of pain, morning stiffness or functional status (BASFI) were not found to be significantly correlated with MRI inflammatory lesions as assessed by most scoring systems. The lack of correlation between MRI scores and BASFI can be explained by the fact that the functional impairment reported by patients with axial SpA is caused by an association of inflammatory/active lesions and chronic/structural damages (”sequelae”, including syndesmophytes) while the MRI scoring systems that were evaluated in this review aim at capturing the inflammatory aspect of the disease only. And the lack of correlation between MRI scores and BASDAI can also be explained by the impact of other sites of disease activity like peripheral joints or entheses on the total BASDAI score (50).

This might also be explained by the interference of other spine diseases, and in this case MRI could be useful to rule out other causes of back pain (51). Degenerative discovertebral diseases could cause inflammatory back pain and are common in men and patients aged 30–40 years (52). MRI discriminate type 1 Modic degenerative changes which are hypersignals of vertebral plates and intervertebral discs on STIR and T2 MRI sequences from active inflammatory lesions of spondyloarthritis like bone marrow oedema on vertebral corners (53).

Conclusions

In summary, and considering our findings, it seems difficult to distinguish the difference between changes in MRI inflammatory lesions of the spine and SIJ if patients with axial SpA related to TNF-alpha inhibitor effects and those due to the natural course of the disease activity (alternating periods of flares and remission in axial SpA). MRI (especially MRI of the spine) does not sufficiently reflect the axial activity of SpA to recommend its use in individual follow-up or assessment of the disease, which should remain a clinical and global evaluation of each individual patient, with other additional tests (biologic or radiologic) remaining supplementary and most often optional.

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