Rheumatol Int (2013) 33:2199–2213
DOI 10.1007/s00296-013-2772-6

REVIEW ARTICLE

Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis

Marina Amaral de Ávila Machado · Mariana Michel Barbosa · Alessandra Maciel Almeida · Vânia Eloisa de Araújo · Adriana Maria Kakehasi · Eli Iola Gurgel Andrade · Mariangela Leal Cherchiglia · Francisco de Assis Acurcio

Received: 4 February 2013 / Accepted: 30 April 2013 / Published online: 18 May 2013

Abstract Biological agents directed against tumor necrosis factor (TNF) represent therapeutic options for patients with ankylosing spondylitis with high disease activity despite use of non-steroidal anti-inflammatory drugs. To evaluate the efficacy and safety of the anti-TNF agents infliximab, etanercept, adalimumab, golimumab, and certolizumab for the treatment of ankylosing spondylitis, we performed a systematic review of randomized clinical trials on adult patients with ankylosing spondylitis using articles culled from the EMBASE, MEDLINE, Cochrane Controlled Trials Register and LILACS databases (September/2012), manual literature search, and the gray literature. Study selections and data collection were performed by two independent reviewers, with disagreements solved by a third reviewer. The following outcomes were evaluated: ASAS 20 response, disease activity, physical function, vertebral mobility, adverse events, and withdraws. The meta-analysis was performed using the Review Manager® 5.1 software by applying the random effects model. Eighteen studies were included in this review. No study of certolizumab was included. Patients treated with anti-TNF agents were more likely to display an ASAS 20 response after 12/14 weeks (RR 2.21; 95 % CI 1.91; 2.56) and 24 weeks (RR 2.68; 95 % CI 2.06; 3.48) compared with controls, which was also true for several other efficacy outcomes. Meta-analysis of safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks. Adalimumab, infliximab, etanercept, and golimumab can effectively reduce the signs and symptoms of the axial component of ankylosing spondylitis. Safety outcomes deserve further study, especially with respect to long-term follow-ups.

Keywords Ankylosing spondylitis · TNF blockers · Systematic review · Meta-analysis

Electronic supplementary material The online version of this article (doi:10.1007/s00296-013-2772-6) contains supplementary material, which is available to authorized users.

M. A. Á. Machado (✉)
College of Medicine, Federal University of Minas Gerais, Rua Daniel de Carvalho 1551 Apt 301 Gutierrez, Belo Horizonte, Minas Gerais 30441-152, Brazil
e-mail: avila110@yahoo.com.br

M. M. Barbosa
René Rachou Research Center, Oswaldo Cruz Foundation (FIOCRUZ), Av. Augusto de Lima 1715 Barro Preto, Belo Horizonte, Minas Gerais 30190-002, Brazil

A. M. Almeida
Faculty of Medical Sciences of Minas Gerais, Alameda Ezequiel Dias, 275, Belo Horizonte, Minas Gerais 30130-110, Brazil

V. E. de Araújo · F. A. Acurcio
College of Pharmacy, Federal University of Minas Gerais, Av. Presidente Antônio Carlos, 6627 Campus Pampulha, Belo Horizonte, Minas Gerais 31270-901, Brazil

A. M. Kakehasi · E. I. G. Andrade · M. L. Cherchiglia
College of Medicine, Federal University of Minas Gerais, Av. Prof. Alfredo Balena, 190, Belo Horizonte, Minas Gerais 30130-100, Brazil

Introduction

Ankylosing spondylitis (AS) is a rheumatic disease and its clinical manifestations include lumbar inflammation and enthesitis as well as increased spinal stiffness and loss of spinal mobility. Furthermore, 20–30 % of patients with AS are also affected by peripheral arthritis, which is characterized by asymmetric oligoarthritis of the lower extremities and generally signals a worsening of AS symptoms [1, 2].

In Europe, the prevalence of AS (which is more frequently observed in men than in women) varies from 0.1 to 1.4 %, with incidences reaching as high as 7 in every 100,000 adults in some areas. Approximately 80 % of patients develop their first symptoms before the age of 30, whereas <5 % develop initial symptoms after the age of 45 [1, 3]. Progression of the disease can cause physical incapacity, leading to lost work days, unemployment, or even early retirement due to disability. A study conducted in the Netherlands showed that among male patients with AS, only 69.5 % were employed, compared with 78.8 % of the general male population. As AS primarily affects young adults of working age, this disease can have significant socioeconomic impacts [4, 5].

An effective AS treatment would control symptoms and mitigate structural damage to maintain patient functionality and improve quality of life [6]. Non-steroidal anti-inflammatory drugs (NSAID) are the first line of pharmacological treatment. Disease-modifying antirheumatic drugs (DMARD) and intra-articular injections of glucocorticoids in patients with peripheral arthritis may also be considered, although there is no evidence to support the use of these medications in axial diseases. The use of biological agents directed against tumor necrosis factor (TNF) is another option for patients with elevated disease activity, despite conventional treatment [7].

Although results from a number of clinical trials support the use of anti-TNF agents in the treatment of AS, further meta-analysis of these studies could strengthen this evidence, as well as providing more robust information for physicians to determine the most appropriate therapies [8, 9]. The most recent systematic review published on this subject described the benefits of anti-TNF agents, although the search of studies was completed in 2009 [8]. Continuous updates can aggregate data from new studies. Therefore, we performed a systematic review including meta-analysis of randomized clinical trials on adult patients with active AS to evaluate the efficacy and safety of treatment with five TNF blockers: infliximab, etanercept, adalimumab, golimumab, and certolizumab.

Methods

This systematic review was carried out according to the recommendations of the Cochrane Collaboration Handbook and is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [9, 10].

Eligibility criteria

Only randomized clinical trials (RCT) with adult patients diagnosed with active AS, as defined by the modified New York criteria, were included in this analysis [11]. We considered studies comparing treatment with infliximab, etanercept, adalimumab, golimumab, and certolizumab either alone or in combination with other medications, against control groups. These studies were published in Portuguese, English, and Spanish.

Studies search

Several article searches were performed in EMBASE, MEDLINE, Cochrane Controlled Trials Register, and LILACS (September/2012). Various combinations of terms were used to search these electronic databases, including terms referring to the disease, to interventions, and to the type of study. Appropriate MESH (Medical Subject Headings) terms were used to carry out a sensitive search for clinical trials in the MEDLINE database. The complete search strategies are provided in ESM Appendix 1. We also performed manual search of references included in the identified studies as well as in systematic reviews.

In addition, we performed gray literature search, including the following sources: congress abstracts from the American College of Rheumatology (2010 and 2011) and the European League Against Rheumatism (2010, 2011 and 2012); clinical trials registered at ClinicalTrials.gov, Pharmaceutical Industry Clinical Trials database, Center Watch Clinical Trials Listing Service, Community Research & Development Information Service, International Clinical Trials Registry Platform Search Portal and Brazilian Clinical Trials Registry; theses and dissertations archived in the Brazilian Digital Library of Theses and Dissertations, the Digital Library of Theses and Dissertations of USP (University of São Paulo), and ProQuest Dissertation & Theses Database.

Study selection and data collection processes

The study selection process was performed in three phases by two independent reviewers (MAAM, MMB) and included analyses of titles, abstracts, and whole texts. Dissimilar results were analyzed by a third reviewer (AMA). Data collection was performed by two independent researchers (MAAM, MMB). A standardized form was used to compile information regarding study design, populations, disease duration, prior or concomitant use of DMARD, NSAID, and/or glucorticoids, as well as interventions and outcomes. When necessary, the authors were contacted for additional information.

The primary outcome was the ASAS 20 response, which is defined by the Assessment of SpondyloArthritis international Society (ASAS) as a reduction by at least 20 % and 10 units (visual analog scale from 0 to 100) in at least three of the following domains: patient global assessment,

lumbar pain, physical function, and inflammation (without a worsening of >20 % and 10 units in the remaining fourth domain). The secondary outcomes were the ASAS 40 response, which is defined as an improvement of at least 40 % and 20 units in three of the above domains (without a worsening in the fourth), and the ASAS 5/6 response, which is defined as an improvement >20 % in five of the six following domains: patient global assessment, lumbar pain, physical function, inflammation, C-reactive protein (or erythrocyte sedimentation rate), and vertebral mobility [12]. The other secondary outcomes were partial remission according to ASAS criteria (reductions of at least 20 units in the above four domains), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the BASDAI 50 response (a 50 % improvement on the BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Metrology Index (BASMI), withdraws and safety outcomes.

Assessing for methodological quality and risk of bias

Evaluations of methodological quality and risk of bias were performed independently by two reviewers (MAAM, VEA), and disagreements between the two were solved by consensus. Methodological quality was assessed using the modified Jadad scale, in which a study is given a score ranging from 0 to 6, with 6 representing trials of the highest quality. Risk of bias was assessed according to the recommendations of the Cochrane Collaboration, with each domain classified as having either a low, high or unclear risk of bias (i.e., the information in the report was insufficient to classify it as either high or low risk). These two metrics evaluate methodological aspects such as randomization, blinding, and withdraws [13, 14]. Inter-examiner concordances were found to be substantial, with $\kappa = 0.73$ (SD = 0.70) and $\kappa = 0.77$ (SD = 0.65) for the modified Jadad scale and risk of bias, respectively [15].

Meta-analysis

The meta-analysis was carried out using Review Manager® 5.1 software. Continuous data were analyzed as a mean difference and dichotomous data were reported as relative risk, with both 95 % confidence intervals.

We analyzed the reasons of possible clinical heterogeneity according to differences in methodological quality, characteristics of participants, and intervention. Therefore, we assumed that the clinical heterogeneity was present among the included studies because of the differences related to type of anti-TNF, disease duration, medications allowed during the study and quality scores. A random effects model was chosen for the analysis due to the fact it yields a more conservative estimation of the results. Statistical heterogeneity was considered to exist if the Chi-square test yielded a value of $p < 0.10$ and/or the I^2 statistic was >40 %. In positive cases, factors that could potentially influence heterogeneity were investigated [16].

Meta-analysis was performed at the time of 12 and 30 weeks of follow-up, with subgroups for each anti-TNF agent. Sensitivity analysis was performed to determine the influence of the following variables on our results: conflicts of interest, a modified Jadad score of <5, a high or unclear risk of bias related to random sequence generation and allocation concealment, disease duration, concomitant use of other medications, and patients with prior failed NSAID treatments. The existence of a publication bias for the meta-analysis was examined using a funnel plot.

Quality of evidence

The quality of evidence from this systematic review was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for the primary outcome (considering only the studies included in the meta-analysis). The GRADE contains evaluation of the risk of bias in the included studies, the precision and consistency of the results, the presence of indirect evidence, and the presence of publication bias [17, 18].

Results

A total of 1,382 articles were retrieved from various electronic databases as well as two additional articles from manual search. Following the elimination of duplicates and analysis by the reviewers, 27 articles were included in this analysis, representing 18 randomized clinical trials (Fig. 1). Two trials compared the effects of adalimumab with placebo [19–25]. Seven compared the effects of etanercept with placebo and one trial compared the effects of etanercept to sulfasalazine [26–35]. Five studies evaluated the effects of infliximab with placebo and one study evaluated the effects of infliximab and methotrexate versus methotrexate and placebo [36–43]. One trial studied the effects of golimumab versus placebo [44]. Finally, one study assessed the effects of infliximab versus etanercept (Table 1) [45]. No study about certolizumab was found.

All of the included studies were randomized and double-blind, with the exception of the study by Giardina et al. [45]. Disease duration for the patients varied from 7 to 20 years; these data were not available in the study by Barkham et al. [40] in which it was only reported that the patients had approximately 1 year of lumbar pain prior to the study. The study by Giardina et al. [45] reported data from the longest follow-up period (104 weeks), whereas the other trials varied between 6 and 30 weeks. The use of

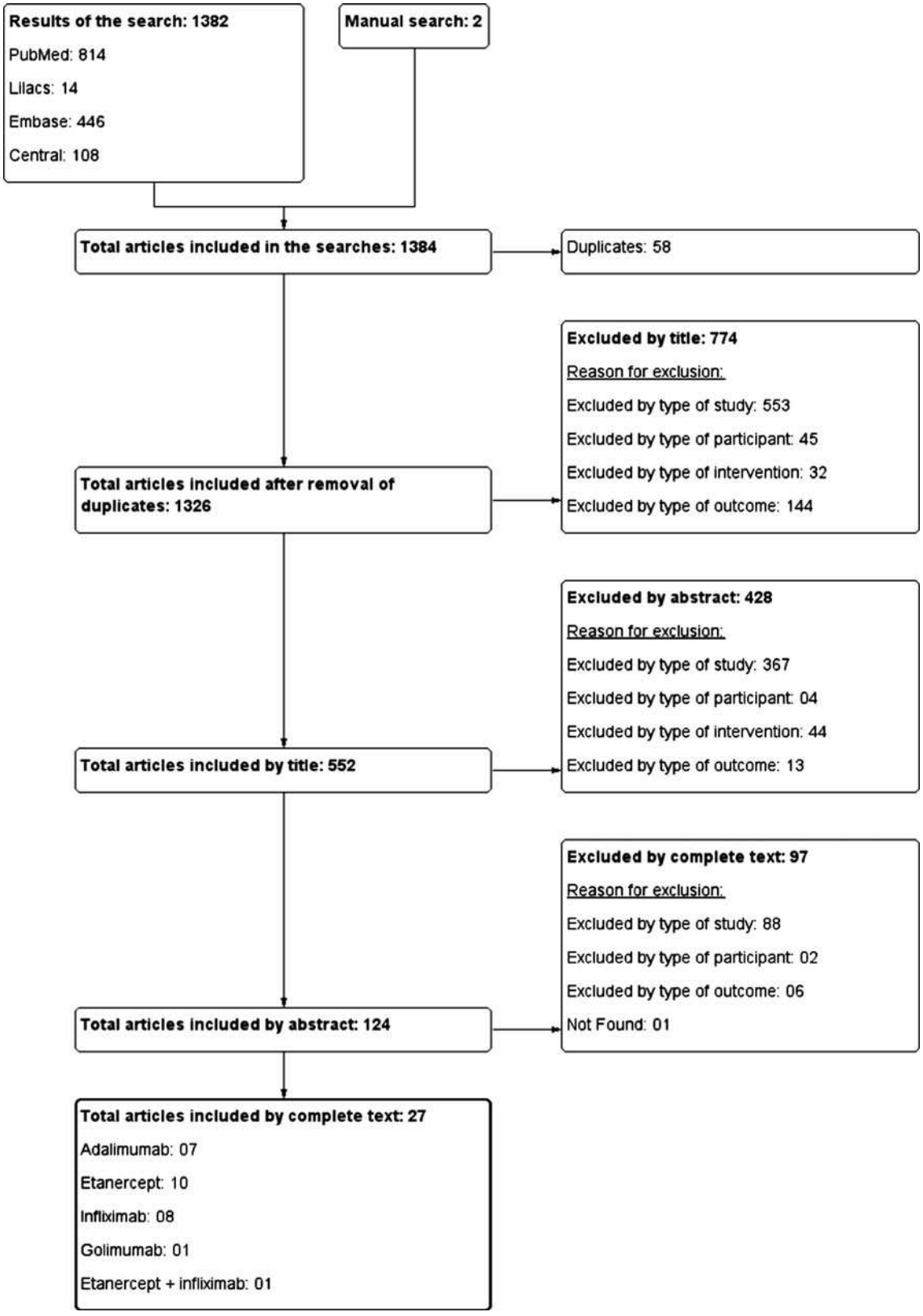

Fig. 1 A diagram showing the selection process for articles used in this systematic review. Reasons for exclusion are also indicated

Table 1 Characteristics of the studies included in the systematic review

Study	Number of patients	Age (years)	Male patients *N* (%)	Disease duration (years)	Time of follow-up (weeks)	Medications allowed during the study	Modified Jadad score	Random sequence generation	Allocation concealment
Adalimumab (ADA)									
ATLAS [19–23]	315				24	DMARD, glucocorticoids, NSAID	5	Unclear	Unclear
ADA 40 mg every 2 weeks	208	41.7 (11.69)	157 (75.5)	11.3 (9.99)					
Placebo	107	43.4 (11.32)	79 (73.8)	10.0 (8.34)					
Canadian AS Study [24, 25]	82				24	DMARD, glucocorticoids, NSAID	5	Unclear	Unclear
ADA 40 mg every 2 weeks	38	41.9 (11.1)	29 (76.3)	14.5 (9.0)					
Placebo	44	40.0 (10.9)	36 (81.8)	12.1 (8.7)					
Etanercept (ETA)									
Gormam et al. [26]	40				16	DMARD, glucocorticoids, NSAID	6	Low risk	Low risk
ETA 25 mg 2 × weekly	20	38 (10)[a]	13 (65)	15 (10)[a]					
Placebo	20	39 (10)[a]	18 (90)	12 (9)[a]					
Davis et al. [27]	277				24	DMARD, glucocorticoids, NSAID	5	Unclear	Unclear
ETA 25 mg 2 × weekly	138	42.1 (24–70)[b]	105 (76)	10.1 (0–30.7)[b]					
Placebo	139	41.9 (18–65)[b]	105 (76)	10.5 (0–35.3)[b]					
Brandt et al. [28]	30				6	NSAID	5	Unclear	Low risk
ETA 25 mg 2 × weekly	14	39.8 (9.1)	10 (71.43)	14.9 (8.3)					
Placebo	16	32.0 (7.5)	12 (75)	11.4 (8.8)					
Calin et al. [29]	84				12	DMARD, glucocorticoids, NSAID	5	Unclear	Unclear
ETA 25 mg 2 × weekly	45	45.3 (9.5)	36 (80)	15.0 (8.8)					
Placebo	39	40.7 (11.4)	30 (77)	9.7 (8.2)					
van der Heijde et al. [30], Braun et al. [31]	356				12	DMARD, glucocorticoids, NSAID	4	Unclear	Unclear
ETA 25 mg 2 × weekly	150	39.8 (10.7)	114 (76)	10.0 (9.1)					
ETA 50 mg 1 × weekly	155	41.5 (11.0)	109 (70)	9.0 (8.7)					
Placebo	51	40.1 (10.9)	40 (78)	8.5 (6.8)					
Barkham et al. 32]	40				12	NSAID and DMARD	5	Unclear	Unclear
ETA 25 mg 2 × weekly	20	40.8 (9.7)	15 (75.0)	11 (2–45)[c]					
Placebo	20	39.4 (10.1)	17 (85.0)	20 (0.6–30)[c]					
SPINE [33]	82				12	NSAID and DMARD	5	Unclear	Unclear
ETA 50 mg 1 × weekly	39	46 (11)	37 (95)	19 (10)					

Table 1 continued

Study	Number of patients	Age (years)	Male patients *N* (%)	Disease duration (years)	Time of follow-up (weeks)	Medications allowed during the study	Modified Jadad score	Random sequence generation	Allocation concealment
Placebo	43	48 (10)	39 (91)	23 (11)					
ASCEND [34, 35]	566				16	NSAID, paracetamol and tramadol	6	Low risk	Unclear
ETA 50 mg 1 × weekly	379	40.7 (11.7)	279 (73.6)	7.5 (9.5)					
Sulfasalazine	187	40.9 (12.2)	140 (74.9)	8.0 (8.9)					
Infliximab (IFX)									
Braun et al. [36]	69				12	NSAID	6	Low risk	Low risk
IFX 5 mg/Kg	34	40.6 (8.0)	23 (68)	16.4 (8.3)					
Placebo	35	39 (9.1)	22 (63)	14.9 (9.3)					
ASSERT [37–39]	279				24	NSAID, paracetamol and tramadol	5	Unclear	Unclear
IFX 5 mg/Kg	201	40.0 (32.0; 47.0)[d]	157 (78.1)	7.7 (3.3; 14.9)[d]					
Placebo	78	41.0 (34.0; 47.0)[d]	68 (87.2)	13.2 (3.7; 17.9)[d]					
Barkham et al. [40]	40				16	NSAID	5	Unclear	Unclear
IFX 5 mg/Kg IV	20	29.5	15 (75)	1.4[e]					
Placebo	20	28.2	15 (75)	1.1[e]					
Inman et al. [41]	76				12	NSAID, DMARD, analgesics and glucocorticoids	5	Unclear	Unclear
IFX 3 mg/kg	39	42.9 (10.4)	32 (82)	11.7 (10.6)					
Placebo	37	39.3 (9.0)	29 (78)	11.1 (10.3)					
Maksymowych et al. [42]	36				12	DMARD, glucocorticoids or NSAID	3	Unclear	Unclear
IFX 3 mg/kg	18	43.6 (11.8)	14 (77.8)	12.0 (11.2)					
Placebo	18	41.7 (9.3)	14 (77.8)	14.3 (12.0)					
Marzo-Ortega et al. [43]	42				30	NSAIDs and glucocorticoids	6	Low risk	Low risk
IFX 5 mg/Kg + methotrexate	28	41 (28–74)[b]	23 (82.14)	8 (0–41)[c]					
Placebo + methotrexate	14	39 (30–56)[b]	11 (78.57)	10 (0–35)[c]					
Golimumab (GOL)									
GO-RAISE [44]	356				24	NSAID, MTX, SSA, HCQ, corticosteroids	6	Low risk	Low risk
GOL 50 mg	138	38.0	102 (73.9)	5.15 (1.60; 11.60)					
GOL 100 mg	140	38.0	98 (70.0)	5.20 (1.50; 13.25)					
Placebo	78	41.0	55 (70.5)	7.25 (2.80; 18.60)					

Table 1 continued

Study	Number of patients	Age (years)	Male patients *N* (%)	Disease duration (years)	Time of follow-up (weeks)	Medications allowed during the study	Modified Jadad score	Random sequence generation	Allocation concealment
Infliximab versus etanercept									
Giardina et al. [45]	50				104	NI	3	Unclear	Unclear
ETA 50 mg 1 × weekly	25	32.6 (6.8)	20 (80)	15.7 (6.5)					
IFX 5 mg/Kg	25	31.9 (9.2)	19 (76)	15.4 (10.6)					

Average (standard deviation) values for age and disease duration are shown, except when otherwise indicated

NSAID non-steroidal anti-inflammatories, *DMARD* disease-modifying antirheumatic drugs, *NI* no information, *MTX* methotrexate, *SSA* sulfasalazine, *HCQ* hydroxychloroquine

[a] Median value (standard deviation)

[b] Average (amplitude)

[c] Median (amplitude)

[d] Median (interquartile interval)

[e] indicates the time of lumbar pain

other medications in addition to the anti-TNF agents was allowed for patients who had been using them prior to the study, and stable doses were generally maintained. Variations existed in the types of medications used during these studies as well as among the patients in each trial (Table 1). The Canadian AS, ASCEND, and Maksymowych et al. studies included patients who had failed treatment with NSAID [24, 25, 34, 35, 42]. The GO-RAISE study included subjects with inadequate response to NSAID or DMARD, whereas the other studies did not report this criterion [44]. None of the studies considered patients who had prior failed treatment with anti-TNF agents.

The average modified Jadad score was 5.0, with the majority of studies having high-quality scores (i.e., 5 or 6) [19–29, 32–41, 43, 44]. The studies by Giardina et al. [45] and Maksymowych et al. [42] each received a score of 3, the former for not being double-blind, and the latter for not describing the reasons for withdraws (Table 1).

Five studies showed low risks of bias related to random sequence generation and allocation concealment (Table 1) [26, 28, 34–36, 43, 44]. All of the studies were identified as randomized but thirteen trials did not describe the method of randomization nor how the allocation sequence was protected from the researchers, and therefore, they were classified as having an unclear risk of bias. All of the studies showed a low risk of bias with respect to the blinding of participants and personnel and blinding of outcome assessment, with the exception of the study by Giardina et al. [45]. No study showed a high or unclear risk of bias with respect to the criteria of incomplete outcome data; Maksymowych et al. [42] reported equal withdraws among the two groups (11.1 %), and therefore, despite the lack of an explanation for these losses, this study was classified as low risk. The ASSERT, ATLAS, Canadian AS, ASCEND, SPINE, and GO-RAISE studies showed low risks of bias with respect to selective reporting of outcomes, whereas the other studies showed unclear risks of bias [19–25, 33–35, 37–39, 44].

The majority of studies had sponsorship from the pharmaceutical industry and/or their authors had conflicts of interest within this sector. Braun et al. [36] declared no conflict of interest, and Giardina et al. [45] did not present this information.

Patients who used anti-TNF agents were more likely to achieve ASAS 20 responses compared with patients from control groups (Fig. 2). The relative risk (RR), with a 95 % confidence interval (95 % CI), of reaching this outcome after 12/14 weeks was 2.21 (1.91; 2.56) without significant heterogeneity ($I^2 = 0$ % and $p = 0.78$) [19, 24, 27–30, 33, 41, 42, 44]. After 24 weeks, the RR was 1.83 (95 % CI 1.15; 2.90) with high heterogeneity ($I^2 = 84$ % and $p < 0.0001$). After excluding the ASCEND [34, 35] and Marzo-Ortega et al. [43] studies, the heterogeneity became non-significant

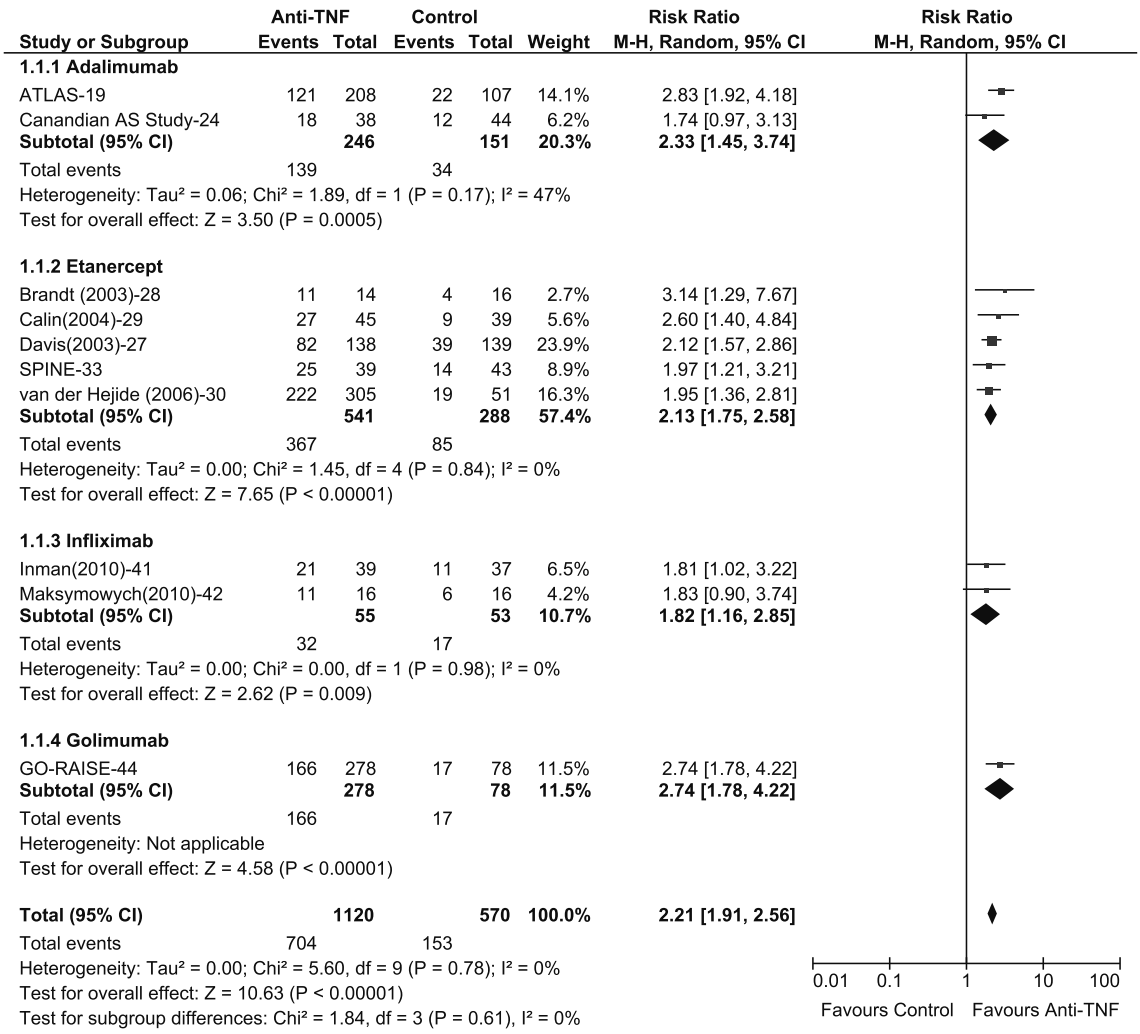

Fig. 2 Meta-analysis of ASAS 20 responses after 12 weeks of follow-up

($I^2 = 0$ % and $p = 0.63$), whereas the effects of the anti-TNF agents remained significant (RR = 2.68; 95 % CI 2.06; 3.48) (Fig. 3) [24, 27, 34, 37, 43].

The golimumab presented the highest RR for ASAS 20 response (2.74, 95 % CI 1.78; 4.22), followed by adalimumab (RR 2.33, 95 % CI 1.45; 3.74), etanercept (RR 2.13, 95 % CI 1.75; 2.58), and infliximab (RR 1.82, 95 % CI 1.16; 2.58). However, these values are similar with each other and the GO-RAISE study [44] estimated this outcome at week 14, whereas the others valued it at week 12. After 24 weeks, only one study of each medicine remained in the meta-analysis and the highest RR was related to infliximab (RR 3.18 95 % CI 1.99; 5.08), followed by etanercept (RR 2.53 95 % CI 1.80; 3.57) and adalimumab (RR 2.15 95 % CI 0.96; 4.83).[1] The infliximab and etanercept results are alike, while the 95 % CI for adalimumab is not significant.

The same trend was observed with respect to the ASAS 40 response, the ASAS 5/6 response, and partial remission during the 12/14- and 24-week periods. The ASCEND [34, 35] study was removed from the 24-week meta-analysis due to high heterogeneity, although no changes in the direction or significance of the results were observed after its removal (Table 2). Patients who received treatment with anti-TNF agents showed favorable responses on the disease activity (BASDAI). After 12 weeks, the average difference between the treatment and control groups was −1.64 (95 % CI −2.06; −1.22) [19, 32, 33, 42], and after 30 weeks, the mean difference was −1.79 (95 % CI −2.27; 1.31) without significant heterogeneity [19, 37, 40, 43]. The meta-analysis showed benefits for the anti-TNF group with respect to other metrics, physical function as determined by the BASFI and vertebral mobility as determined by the BASMI (Tables 2, 3). The RR to achieve BASDAI 50 response was 2.87 (95 % CI 2.23; 3.69) at 12/14 weeks and 3.39 (95 % CI 2.46; 4.67) at 24 weeks, both with no significant

[1] The GO-RAISE study presented the ASAS 20 response at week 24 only graphically and the exact value was unable to be obtained. We contacted the authors to get more information.

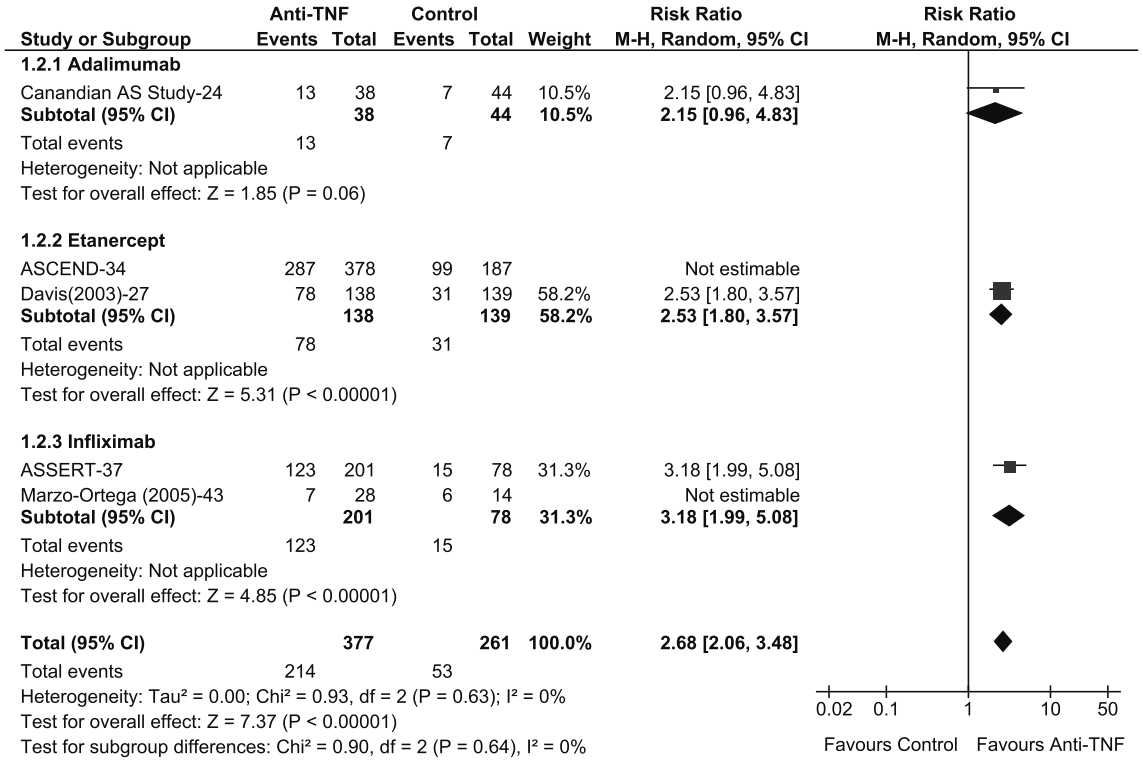

Fig. 3 Meta-analysis of ASAS 20 responses after 24 weeks of follow-up. The ASCEND [34, 35] and Marzo-Ortega et al. [42] studies have been excluded from the meta-analysis because of the statistical heterogeneity

Table 2 Meta-analysis of efficacy outcomes after 12/14 and 24 weeks

Outcome	Studies	Participants	Relative risk (CI 95 %)[a]	I^2 (%)[b]	p value[c]
Up to 12/14 weeks[d]					
ASAS 40 response	5 [19, 30, 33, 41, 42]	861	2.77 (2.05; 3.75)	0	0.45
ASAS 5/6 response	4 [19, 30, 33, 41]	829	3.52 (2.17; 5.71)	36	0.20
Partial remission	4 [19, 28, 30, 33]	783	4.79 (2.46; 9.34)	0	0.92
Up to 24 weeks					
ASAS 40 response	3 [19, 37, 40, 44]	629	3.32 (2.44; 4.51)	0	0.92
ASAS 5/6 response	3 [19, 37, 40]	627	4.25 (2.80; 6.46)	0	0.50
Partial remission	4 [19, 27, 37, 40]	905	4.43 (2.62; 7.49)	0	0.51

[a] CI 95 %: 95 % confidence interval

[b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies

[c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies

[d] Meta-analysis with the GO-RAISE study [44] after 14 weeks

heterogeneity [19, 28, 33, 36, 37, 41, 44]. The subgroup analysis shows that infliximab has the best response at weeks 12 and 24 (RR 4.02, 95 % CI 1.96; 8.26 and RR 4.90 95 % CI 2.51; 9.58) (Figs. 4, 5).

The meta-analysis of adverse events and withdraws due to adverse events did not show statistically significant outcomes and in fact showed reduced heterogeneity over the periods analyzed. Upper respiratory tract infection after 30 weeks showed a RR of 0.98 (95 % CI 0.93; 1.02) [26, 27, 34, 37, 43, 44]. After 12 weeks, the incidence of withdraws due to lack of efficacy was not significant, whereas after 30 weeks, in spite of the anti-TNF treatments showing significant positive benefits, this outcome resulted in a borderline 95 % confidence interval (Table 4).

Giardina et al. [45] reported that after 12 weeks, there were no statistically significant differences between the infliximab and etanercept groups with respect to either the ASAS 20 (76.0 vs. 60.0 %) or ASAS 40 (55.0 vs. 43.0 %) responses. This trend remained true up to 104 weeks and was also observed for other metrics, such as the BASDAI

Table 3 Meta-analysis of BASDAI, BASFI, and BSAMI outcomes after 12 and 24/30 weeks

Outcome	Studies	Participants	Mean difference (CI 95 %)[a]	I^2 (%)[b]	p value[c]
Up to 12 weeks					
BASDAI	4 [19, 32, 33, 42]	469	−1.64 (−2.06; −1.22)	0	0.69
BASFI	3 [19, 32, 33]	437	−1.39 (−1.59; −1.19)	0	0.85
BASMI	3 [19, 33, 41]	473	−0.53 (−0.72; −0.35)	9	0.32
Up to 24/30 weeks[d]					
BASDAI	4 [19, 37, 40, 43]	676	−1.79 (−2.27; −1.31)	0	0.49
BASFI	2 [19, 40]	355	−1.52 (−1.72; −1.31)	0	0.32
BASMI	1 [19]	82	−0.60 (−0.87; −0.33)	NA	NA

[a] CI 95 %: 95 % confidence interval

[b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies

[c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies

[d] Meta-analysis with the study by Marzo-Ortega et al. [43] after 30 weeks

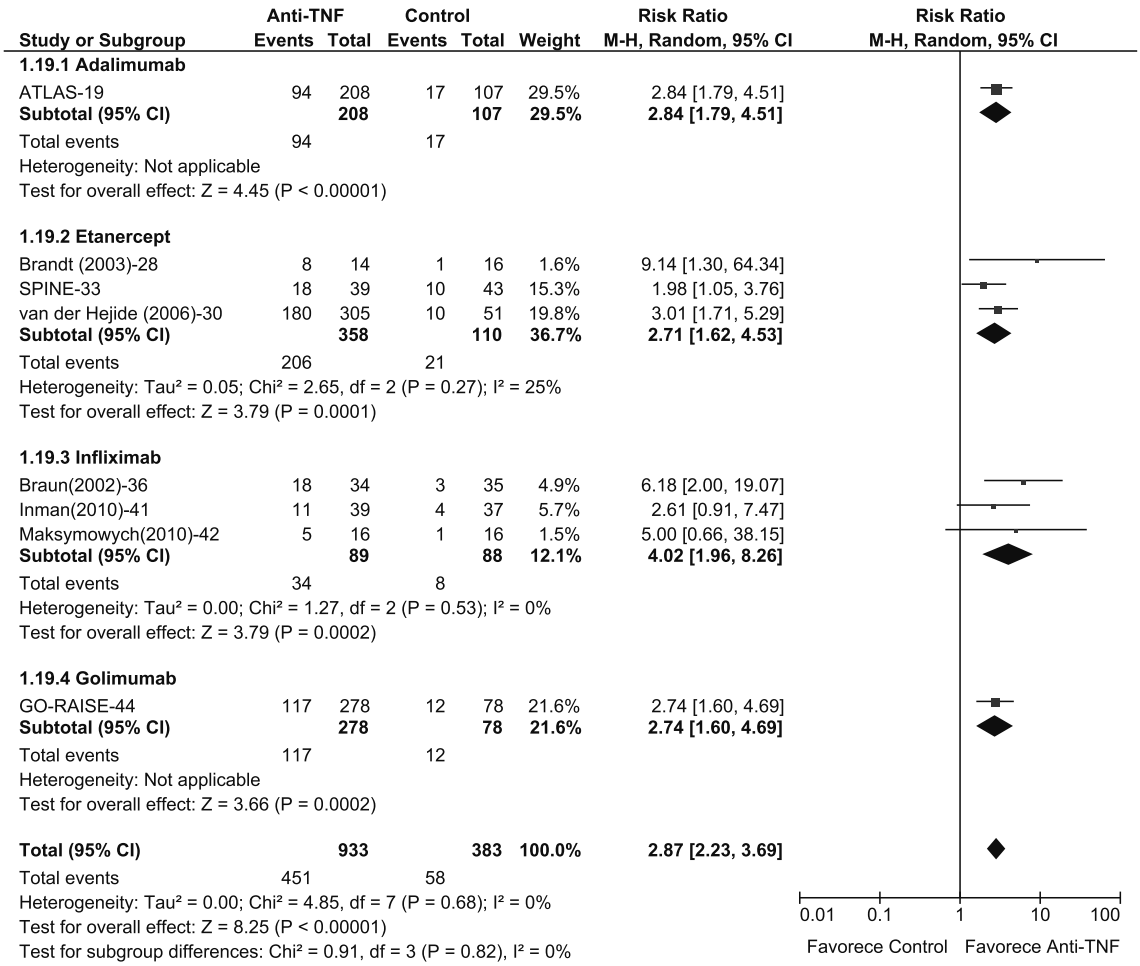

Fig. 4 Meta-analysis of BASDAI 50 responses after 12/14 weeks of follow-up

and BASFI. Reported adverse events were mild to moderate, no cases of opportunistic infections, tuberculosis, or cancer were recorded, and no patients failed to follow-up over the course of the 104-week study.

The sensitivity analysis showed that the inclusion of studies with conflicts of interests, sponsorship from the pharmaceutical industry, modified Jadad scores of 3 or 4, and unclear risk (with respect to random sequence generation and

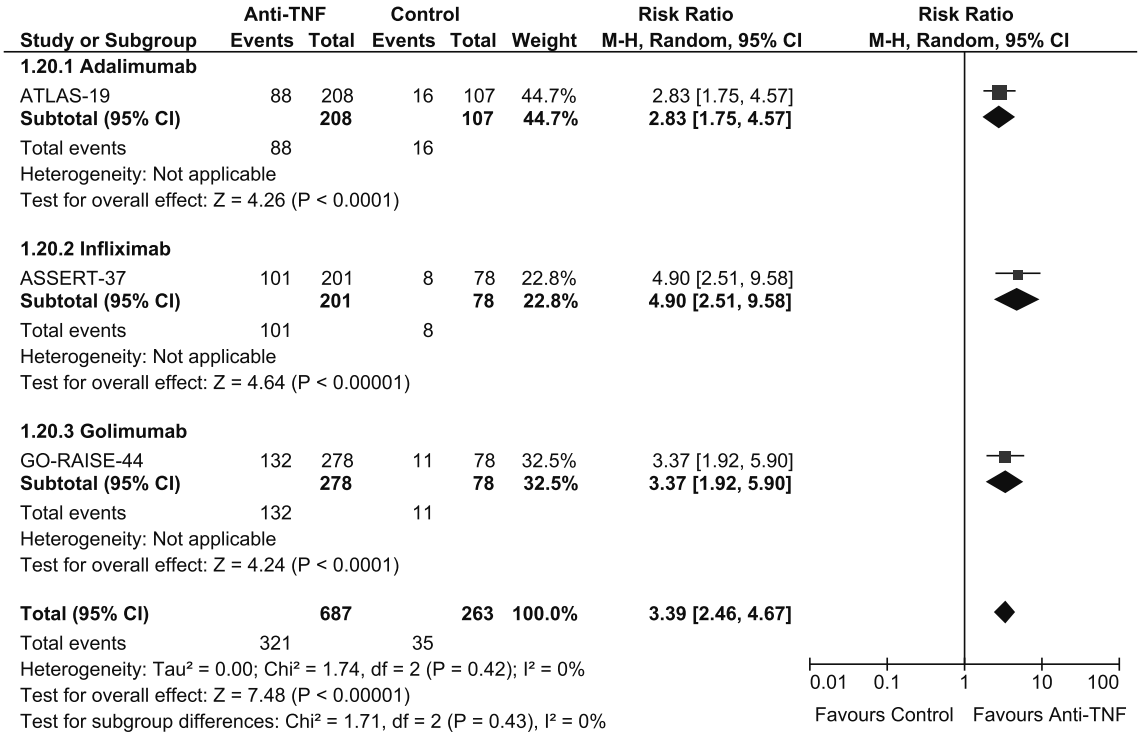

Fig. 5 Meta-analysis of BASDAI 50 responses after 24 weeks of follow-up

Table 4 Meta-analysis of safety outcomes and withdraw after 12 and 24/30 weeks

Outcome	Studies	Participants	Relative risk (CI 95 %)[a]	I^2 (%)[b]	p value[c]
Up to 12 weeks					
Serious adverse events	6 [26, 28–30, 33, 36]	661	0.98 (0.95; 1.01)	0	0.85
Serious infections	1 [28]	30	1.00 (0.88; 1.13)	NA	NA
Upper respiratory tract infections	2 [28, 30]	386	1.06 (0.95; 1.19)	0	0.59
Withdraw due to adverse reactions	6 [19, 28–30, 33, 36]	936	0.99 (0.96; 1.01)	25	0.24
Withdraw due to lack of efficacy	4 [29, 30, 33, 36]	591	1.01 (0.98; 1.04)	0	0.44
Up to 24/30 weeks[d]					
Serious adverse events	5 [19, 27, 34, 37, 43, 44]	1,833	1.00 (0.98; 1.02)	0	0.91
Serious infections	5 [19, 26, 34, 37, 43, 44]	1,596	1.00 (0.99; 1.01)	0	0.92
Upper respiratory tract infections	5 [26, 27, 34, 37, 43, 44]	1,558	0.98 (0.93; 1.02)	21	0.28
Withdraw due to adverse reactions	6 [19, 27, 34, 37, 40, 43, 44]	1,875	0.99 (0.98; 1.01)	13	0.33
Withdraw due to lack of efficacy	3 [26, 27, 43, 47]	359	1.11 (1,01; 1.22)	85	0.0002

[a] CI 95 %: 95 % confidence interval

[b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies

[c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies

[d] Meta-analysis with the study by Marzo-Ortega et al. [43] after 30 weeks

allocation concealment) did not modify the direction or significance of the results. Furthermore, studies involving patients with short disease times, multiple medications, and prior failed NSAID treatment did not influence the results.

Analysis of the funnel plot did not reveal asymmetry, suggesting that publication bias was not an important factor for these studies. Search of the gray literature did not yield new studies, although we did identify three in-progress studies evaluating the effects of etanercept [46–48].

In summary, the quality of the evidence of this review was considered to be high, as the studies did not have major limitations, the statistical heterogeneity was not significant, the findings were consistent, the results were precise, and publication bias was not found to be relevant.

Discussion

The results of this systematic review and meta-analysis indicate significant positive benefits for the anti-TNF agents infliximab, etanercept, adalimumab, and golimumab for the treatment of AS with respect to several metrics, including the ASAS response, disease activity, physical function, vertebral mobility after 12 and 30 weeks of treatment compared with control treatments. The incidence of adverse events was not significantly different between the groups. Any conclusion about certolizumab could not be done because the search did not retrieve RCT with only AS patients.

In summary, we can highlight the results of ASAS 20 response at week 24 and BASDAI 50 response at weeks 12 and 24 for infliximab. This medicine reached the highest measures, whereas the estimated RR presented large confidence intervals, and few studies were joined in the meta-analysis. On the other hand, the pooled result for all anti-TNF has a better robustness. The golimumab has a better result for ASAS 20 response at week 12, despite it did not significantly differ from others. The adalimumab and etanercept showed good results either. It remains a challenge to determine differences between the anti-TNF due the lack of studies comparing them.

Our findings are consistent with other systematic reviews, which also showed positive benefits for treatment with anti-TNF agents after 6–24 weeks with respect to pain, ASAS response, physical function, vertebral mobility; these reviews also did not find statistically significant differences between the groups related to safety outcomes [8, 49–52]. Baraliakos et al. [52] studied anti-TNF therapies in spondyloarthropathy (SpA) patients and showed similar results to our review and other studies that included only AS patients. We note that the present review includes new studies, reinforcing these conclusions.

Although the main objective of AS treatments is to improve the quality of life of the patient [6], it was not possible to conduct meta-analysis of this outcome, as there was great amount of variability between the studies with respect to measures of quality of life. However, we believe that the observed benefits, such as relief from pain and inflammation as well as improvements in physical function and vertebral mobility, positively influence quality of life for these patients.

It is important to consider the limitations of these clinical trials, especially in regard to investigating rare adverse events that were not the primary outcome of any study. These limitations are mainly the result of three factors: small sample sizes, short follow-up periods, and selection criteria that exclude patients with recent infections, a history of neoplasms, and significant comorbidities. With this in mind, observational studies gain relevance with respect to the use of medications in situations similar to clinical practice. The Spanish record of adverse events after treatment of rheumatic diseases with biological agents followed approximately 7,000 patients, 13 % of which were diagnosed with AS, with an average exposure time to anti-TNF agents of 2.4 years. A total of 53.1 cases of infections were recorded per 1,000 patients/year and 472 cases of tuberculosis were recorded per 100,000 patients/year [53, 54].

A Cochrane Collaboration systematic review examining 160 clinical trials showed that the use of biological agents not restricted to anti-TNF was associated with increased likelihood of adverse events, withdraws due to adverse events, serious infections, opportunistic infections, and reactivation of tuberculosis compared with control groups. The median duration of these trials was 6 months, and the biological agents were targeted for inflammatory diseases, as rheumatoid arthritis, spondylitis ankylosing, inflammatory bowel disease, and others like cancer and neurological conditions [55]. This meta-analysis included a large number of studies, making them more powerful for demonstrating differences between groups—when they exist—compared with the meta-analysis performed in the present review.

AS was not very frequently observed in the populations of the studies described above. Although it is hoped that the safety profiles of medications are not dependent on the specific disease being treated, the physiopathology, clinical manifestations, and the use of DMARD set AS apart from other rheumatological diseases. Therefore, more data are necessary to confirm that the standard of safety for AS is the same as for rheumatoid arthritis.

The only head-to-head trial analyzed here indicates that etanercept and infliximab have similar efficacy and safety profiles. Using indirect comparisons, Migliore et al. [56] concluded that infliximab had a 72 % probability of being the best therapeutic option, followed by etanercept (15 %) and adalimumab (13 %). The outcome analyzed was the ASAS 20 response after 24 weeks of treatment in three double-blind clinical trials. This review did not include the Canadian AS study [24, 25] which found no difference between adalimumab and placebo for this outcome after 24 weeks, nor the study by Giardina et al. [45] which was not double-blind. The influence of these two studies on the direction of the results in the review by Migliore et al. [56] cannot be determined, and the limitations of the present study do not allow for a more robust comparison between anti-TNF agents.

The ASAS and the EULAR recommend the use of TNF blockers for patients with high disease activity despite conventional treatment, which usually includes non-steroidal anti-inflammatories, as glucocorticoids and DMARD such as methotrexate and sulfasalazine have limited uses in AS patients [7]. Using a randomized clinical trial, Li et al.

[57] showed that the addition of methotrexate to an infliximab regiment did not show clinical benefits with respect to the ASAS response, disease activity, physical function, lumbar flexion, and radiograph progression. The ASCEND [34, 35] study showed that etanercept was more effective than sulfasalazine, and Cochrane Collaboration systematic reviews indicate that methotrexate or sulfasalazine (compared with placebo or NSAID) is not effective in patients with AS [58, 59]. These guidelines do not contain recommendations in the case that anti-TNF therapies fail, and furthermore, this type of information is scarce, given that clinical trials do not include patients with this profile.

When the heterogeneity cannot be readily explained, one analytical approach is to incorporate it into a random effects model. A random effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical, but follow some distribution. The model represents the lack of knowledge about why real, or apparent, treatment effects differ by treating the differences as if they were random. It was possible to carry out meta-analysis with non-significant statistical heterogeneity despite the differences that existed among the populations of the included studies. For certain efficacy outcomes, it was necessary to remove the ASCEND [34, 35] and Marzo-Ortega et al. [43] studies to maintain low heterogeneity, although the direction and significance of the results were not altered by their removal. These were the only studies included in the meta-analysis that did not compare the effects of anti-TNF agents with placebo, which could explain the increased heterogeneity. The former study compared the effects of etanercept to sulfasalazine, and the latter study compared the effects of infliximab and methotrexate to methotrexate and placebo. The sensitivity analysis also revealed that differences between the studies did not affect the direction of the results.

The publication bias is inherent to any systematic review. However, the funnel plot did not indicate asymmetry, and to further minimize the interference of publication bias, we also performed an extensive search for pertinent studies in the gray literature. Therefore, we conclude that publication bias was probably not an important factor in this review.

With the exception of two studies [36, 45], all presented some connection with the pharmaceutical industry, including declared conflicts of interest and financing, which could be sources of bias. Systematic reviews have shown that studies connected to the pharmaceutical industry tend to report outcomes favorable to the medication produced by the sponsor [60–62]. However, the studies included in this review were chosen using detailed search of various databases and the gray literature, or in other words, from the total available body of scientific work. In addition, the sensitivity analysis did not indicate a correlation between the direction of the results and the existence of conflicts of interest. However, it is important to note that only one study included in the meta-analysis did not report a potential conflict of interest [36].

Out of the 18 RCTs evaluated, only one study results were not comparable to the others, so they were not used in the meta-analysis [45]. We included the other 17 RCTs in the meta-analysis, despite the maximum number of trials in the analysis was nine. The reason is that they had different outcomes and diverse ways to report them, especially those related to continuous data; some articles describe as median and interquartile interval, others as mean and standard deviation. However, this is a limitation and we should be aware that the meta-analysis results do not represent the summary of the 17 RCTs.

This systematic review presents high-quality evidence to reinforce the efficacy of the anti-TNF agents infliximab, etanercept, adalimumab, and golimumab for treatment of the axial components of AS. The safety profiles of these drugs do not significantly restrict their use, and therefore, treatment with these agents is recommended; however, rigorous follow-ups are needed due to the risk of infection. In addition, further studies will be needed to gather evidence of long-term safety. These results will be useful for evidence-based health care and proper decision making in health.

Conflict of interest Adriana Maria Kakehasi claims to have received an educational grant from Abbott. The other authors declare that they have no conflict of interest.

References

1. Braun J, Sieper J (2007) Ankylosing spondylitis. Lancet 369:1379–1390
2. Gensler L (2011) Clinical features of ankylosing spondylitis. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology (5th edn), pp 9–14
3. Rudwaleit M (2011) Classification and epidemiology of spondyloarthrits. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology (5th edn), pp 3–8
4. Boonen A, Chorus A, Miedema H, Van Der Heijde D, Van Der Tempel H, Van Der Linden S (2001) Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. Ann Rheum Dis 60:353–358. doi:10.1136/ard.60.4.353
5. Boonen A (2006) A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. Nat Clin Pract Rheumatol 2(10):546–553. doi:10.1038/ncprheum0297
6. Sieper J (2011) Management of ankylosing spondylitis. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology (5th edn), pp 37–57
7. Braun J, van den Berg R, Baraliakos X et al (2011) 2010 update of the ASAS/EULAR recommendations for the management of

ankylosing spondylitis. Ann Rheum Dis 70:896–904. doi:10.1136/ard.2011.151027
8. Escalas C, Trijau S, Dougados M (2010) Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis. Rheumatology (Oxford) 49(7):1317–1325. doi:10.1093/rheumatology/keq078
9. Green S, Higgins JPT, Alderson P et al (2011). In: Higgins JPT, Green S (eds) Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The cochrane collaboration. Available from www.cochrane-handbook.org
10. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6(7). doi:10.1136/bmj.b2700
11. Van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 27:361–368. doi:10.1002/art.1780270401
12. Sieper J (2011) Management of ankylosing spondylitis. Section 9 Spondyloarthropathies. In: Hochberg MC (ed) Rheumatology, 5th edn. Philadelphia, Elsevier
13. Woodroffe R, Yao GL, Meads C et al (2005) Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess 9(21)
14. Higgins JPT, Altman DG, Sterne JAC (2011) Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S (eds) Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The cochrane collaboration. Available from www.cochrane-handbook.org
15. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33(1):159–174
16. Deeks JJ, Higgins JPT, Altman DG (2011) Chapter 9: analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (eds) Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The cochrane collaboration. Available from www.cochrane-handbook.org
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-ytter Y, Schünemann HJ (2008) GRADE: what is "quality of evidence" and why is it important to clinicians? BMJ 336:995–998. doi:10.1136/bmj.39490.551019.BE
18. Guyatt GH, Oxman AD, Vist GE et al (2008) GRADE: going from evidence to recommendations. BMJ 336:1049–1051. doi:10.1136/bmj.39493.646875.AE
19. van der Heijde D, Kivitz A, Schiff MH et al (2006) Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 54(7):2136–2146
20. Davis JC Jr, Revicki D, van der Heijde DM et al (2007) Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Arthritis Rheum 57(6):1050–1057. doi:10.1002/art.21913
21. Dougados M, Luo MP, Maksymowych WP et al (2008) Evaluation of the patient acceptable symptom state as an outcome measure in patients with ankylosing spondylitis: data from a randomized controlled trial. Arthritis Rheum 59(4):553–560. doi:10.1002/art.23527
22. Revicki DA, Luo MP, Wordsworth P et al (2008) Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS). J Rheumatol 35(7):1346–1353 (Epub 2008 May 15). Erratum in: J Rheumatol. 2011 Apr; 38(4):788
23. van der Heijde D, Schiff MH, Sieper J et al (2009) Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 68(6):922–929. doi:10.1136/ard.2007.087270 (Epub 2008 Aug 13)
24. Maksymowych WP, Rahman P, Keystone E, Wong R, Inman R (2005) Efficacy of adalimumab in active ankylosing spondylitis (AS)—results of the Canadian AS study. Arthritis Rheum 52:505
25. Lambert RG, Salonen D, Rahman P et al (2007) Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 56(12):4005–4014. doi:10.1002/art.23044
26. Gorman JD, Sack KE, Davis JC Jr (2002) Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 346(18):1349–1356
27. Davis JC Jr, van der Heijde D, Braun J et al (2003) Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis. Arthritis Rheum 48(11):3230–3236. doi:10.1002/art.11325
28. Brandt J, Khariouzov A, Listing J et al (2003) Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 48(6):1667–1675. doi:10.1002/art.11017
29. Calin A, Dijkmans BA, Emery P et al (2004) Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 63(12):1594–1600. doi:10.1136/ard.2004.020875
30. van der Heijde D, Da Silva JC, Dougados M et al (2006) Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis 65(12):1572–1577. doi:10.1136/ard.2006.056747
31. Braun J, McHugh N, Singh A, Wajdula JS, Sato R (2007) Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford) 46(6):999–1004. doi:10.1093/rheumatology/kem069
32. Barkham N, Coates LC, Keen H et al (2010) Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. Ann Rheum Dis 69(11):1926–1928. doi:10.1136/ard.2009.121327 Erratum in: Ann Rheum Dis. 2011 Aug; 70(8):1519
33. Dougados M, Braun J, Szanto S et al (2011) Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 70(5):799–804. doi:10.1136/ard.2010.139261. (Erratum in: Ann Rheum Dis. 2011 Jul; 70(7):1349)
34. Braun J, van der Horst-Bruinsma IE, Huang F et al (2011) Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum 63(6):1543–1551. doi:10.1002/art.30223
35. Braun J, Pavelka K, Ramos-Remus C et al (2012) Clinical efficacy of etanercept versus sulfasalazine in ankylosing spondylitis subjects with peripheral joint involvement. J Rheumatol 39(4):836–840. doi:10.1002/art.30223 (Epub 2012 Feb 15)
36. Braun J, Brandt J, Listing J et al (2002) Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 359(9313):1187–1193. doi:10.1016/S0140-6736(02)08215-6
37. van der Heijde D, Dijkmans B, Geusens P et al (2005) Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 52(2):582–591. doi:10.1002/art.24001
38. van der Heijde D, Han C, DeVlam K et al (2006) Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial. Arthritis Rheum 55(4):569–574. doi:10.1002/art.22097

39. Braun J, Landewé R, Hermann KG et al (2006) Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum 54(5):1646–1652. doi:10.1002/art.21790
40. Barkham N, Keen HI, Coates LC et al (2009) Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 60(4):946–954. doi:10.1002/art.24408 Erratum in: Arthritis Rheum. 2010 Oct; 62(10):3005
41. Inman RD, Maksymowych WP (2010) CANDLE study group. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol 37(6):1203–1210. doi:10.3899/jrheum.091042 (Epub 2010 Mar 15)
42. Maksymowych WP, Salonen D, Inman RD, Rahman P, Lambert RG (2010) CANDLE study group. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol 37(8):1728–1734. doi:10.3899/jrheum.091043 (Epub 2010 May 1)
43. Marzo-Ortega H, McGonagle D, Jarrett S et al (2005) Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 64(11):1568–1575. doi:10.1136/ard.2004.022582 (Epub 2005 Apr 13)
44. Inman RD, Davis JC Jr, Heijde Dv et al (2008) Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 58(11):3402–3412
45. Giardina AR, Ferrante A, Ciccia F et al (2010) A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 30:1437–1440. doi:10.1007/s00296-009-1157-3 (Epub 2009 Oct 23)
46. EU Clinical Trials Register. Prevention of the progression of very early symptoms into ankylosing spondylitis: a placebo controlled trial with etanercept. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-015515-40. Accessed 11 Jan 2013
47. EU Clinical Trials Register. Estudio piloto randomizado, doble ciego, multicéntrico a 12 semanas para evaluar el efecto de etanercept 100 mg y 50 mg semanales en sujetos con espondilitis anquilosante. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002349-35. Accessed 11 Jan 2013
48. EU Clinical Trials Register. A multicentre, double-blind, placebo-controlled, randomised study of etanercept in the treatment of adult patients with active, severe and advanced axial ankylosing spondylitis. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002748-27. Accessed 11 Jan 2013
49. McLeod C, Bagust A, Boland A, et al (2007) Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess 11(28)
50. Montilla Salas J, Muñoz Gomáriz E, Collantes E (2007) Meta-analysis of efficacy of anti-TNF alpha therapy in ankylosing spondylitis patients. Reumatol Clin 3(5):204–212. doi:10.1016/S1699-258X(07)73688-4 (Epub 2008 Dec 29)
51. Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L (2010) Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. Ann Rheum Dis 69(10):1756–1761. doi:10.1136/ard.2008.098822 (Epub 2009 Jul 28)
52. Baraliakos X, van den Berg R, Braun J, van der Heijde D (2012) Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. Rheumatology (Oxford) 51(8):1378–1387
53. Pérez-Sola MJ, Torre-Cisneros J, Pérez-Zafrilla B et al (2011) Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry. Med Clin (Barc). 137(12):533–540. doi:10.1016/j.medcli.2010.11.032 (Epub 2011 Apr 22)
54. Gómez-Reino JJ, Carmona L, Descalzo MA (2007) Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 57(5):756–761. doi:10.1002/art.22768
55. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev, Issue 2. Art. No.: CD008794. doi:10.1002/14651858.CD008794.pub2
56. Migliore A, Broccoli S, Bizzi E, Laganà B (2012) Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials. J Med Econ 15(3):473–480. doi:10(3111/13696998).2012.660255 (Epub 2012 Feb 16)
57. Li EK, Griffith JF, Lee VW et al (2008) Short-term efficacy of combination methotrexate and infliximab in patients with ankylosing spondylitis: a clinical and magnetic resonance imaging correlation. Rheumatology (Oxford) 47(9):1358–1363. doi:10.1093/rheumatology/ken207 (Epub 2008 Jun 23). Erratum in: Rheumatology (Oxford). 2010 Jul; 49(7):1423
58. Chen J, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev 2006, Issue 4. Art. No.: CD004524. doi:10.1002/14651858.CD004524.pub3
59. Chen J, Liu C (2006) Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol 33(4):722–731
60. Bero L, Oostvogel F, Bacchetti P, Lee K (2007) Factors associated with findings of published trials of drug–drug comparisons: why some statins appear more efficacious than others. PLoS Med. 4(6):e184. doi:10.1371/journal.pmed.0040184
61. Lexchin J, Bero LA, Djulbegovic B, Clark O (2003) Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 326:1167. doi:10.1136/bmj.326.7400.1167
62. Kjaergard LL, Als-Nielsen B (2002) Association between competing interests and authors'conclusions: epidemiological study of randomised clinical trials published in the BMJ. BMJ 325:249. doi:10.1136/bmj.325.7358.249