Clinic Rev Allerg Immunol (2018) 54:234–243
DOI 10.1007/s12016-017-8623-6

The Comparative Safety of TNF Inhibitors in Ankylosing Spondylitis—a Meta-Analysis Update of 14 Randomized Controlled Trials

Li-qiong Hou[1] · **Ga-xue Jiang**[2] · **Yan-fei Chen**[1] · **Xi-Mei Yang**[1] · **Lei Meng**[1] · **Miao Xue**[1] · **Xiao-guang Liu**[1] · **Xi-chao Chen**[1] · **Xiao Li**[3]

Published online: 17 July 2017

Abstract TNF inhibitors have been used in ankylosing spondylitis (AS). The efficacy of TNF inhibitors was already evaluated by meta-analysis of randomized controlled trials (RCTs). However, the safety of TNF inhibitors is still unclear. Therefore, we aimed to evaluate and update the safety data from RCTs of TNF inhibitors in patients treated for AS. A systematic literature search was conducted from 1990 through May 31, 2016. All studies included were randomized, double-blind, controlled trials of patients with ankylosing spondylitis that evaluated adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab treatment. The overall serious adverse events, the risk of serious infection events, and the risk of malignancy and discontinuation rates were abstracted, and risk estimates were calculated by Peto odds ratios (ORs). Fourteen randomized controlled trials involving 2032 subjects receiving TNF inhibitors and 1030 subjects receiving placebo and/or traditional disease-modifying anti-rheumatic drugs (DMARDs) were included. The overall serious adverse events (OR, 1.34; 95% CI, 0.87–2.05), the risk of serious infection events (OR, 1.59; 95% CI, 0.63–4.01), the risk of malignancy (OR, 0.98; 95% CI, 0.25–3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95–2.54) in patients treated with TNF inhibitors as a group were not significantly different from those treated with placebo in the control group. TNF inhibitors were generally safe for treatment of ankylosing spondylitis. These data may help guide clinical comparative decision making in the management of AS.

Keywords Ankylosing spondylitis · TNF inhibitors · Safety · Adverse events · Meta-analysis

Introduction

Ankylosing spondylitis (AS), a disease characterized by inflammation of the axial skeleton, peripheral joints, and entheses can cause considerable disability and pain. After approval of the first tumor necrosis factor (TNF) inhibitor infliximab, for the treatment of patients with AS, the treatment of this chronic inflammatory disease has changed remarkably. Recent meta-analyses of randomized controlled trials (RCTs) [1, 2] demonstrate that the efficacy of TNF inhibitors show no detectable difference in AS. So, their safety profile is likely to be an important determinant for decision making in AS care. Since a meta-analysis published on this subject described the safety of anti-TNF agents, this study shows the safety outcomes and withdrawals did not indicate statistically significant differences between treatment and control groups, but the search of studies was completed in 2012 [3]. The most recent meta-analysis [4] shows that serious adverse events and all-cause withdrawals did not indicate statistically significant differences between treatment and control groups, but the meta-analysis did not report the risk of malignancy and the risk of serious infection events. Recently, more and more RCTs [5–7] focused on malignancy risk and serious infection events in patients with AS not exposed and exposed to TNF inhibitors. Continuous updates can aggregate data from new

✉ Li-qiong Hou
chuandahouliqiong@163.com

[1] Department of Rheumatology, The First Hospital of Lanzhou University, No 1, Donggang Road, Chengguan District, Lanzhou, Gansu 730000, China

[2] Department of Cardiology, The First Hospital of Lanzhou University, No 1, Donggang Road, Chengguan District, Lanzhou, Gansu 730000, China

[3] Department of Evidence-Based Medicine Center, The First Hospital of Lanzhou University, No 1, Donggang Road, Chengguan District, Lanzhou, Gansu 730000, China

studies, as well as provide more robust information for physicians to determine the most appropriate therapies. So we aim to comparatively update the key relevant safety profiles (i.e., overall serious adverse events, malignancy, serious infection, and discontinuation due to adverse events) of TNF inhibitors (i.e., adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) in AS patients.

Methods

Data Sources and Searches

Study selection, assessment of eligibility criteria, data extraction, and statistical analysis were performed based on a predefined, peer-reviewed protocol according to the Cochrane Collaboration guidelines (http://www.cochrane.org/resources/handbook/index.html). We undertook a systematic literature search including RCTs that selected adult patients with AS. We searched studies using MEDLINE via OVID and PubMed, the Cochrane databases, Google Scholar, Clinical trials.gov, and manual searches of reference lists from systematic reviews and original publications and identified studies published in English from 1990 to May 31, 2016. PubMed Auto Alerts was set up to provide weekly updates of new literature until May 31, 2016. The search terms included ankylosing spondylitis; etanercept; infliximab; adalimumab; certolizumab pegol; golimumab; randomized controlled trial; adverse effects; infection; malignancy; all adult.

Study Selection

We pre-specified the target population, interventions, comparators, outcome measures of interest, timing, and settings (PICOTS) following the PICOTS framework [8]. To be eligible, RCTs had to (1) compare the safety of any of the TNF inhibitor is against placebo and/or traditional disease-modifying anti-rheumatic drugs (DMARDs); (2) include only patients with AS; (3) report a minimum of 12 weeks of the study duration. We excluded studies that were open-labeled. We defined the target population as 18 years of age or older, with adult patients diagnosed with active AS, as defined by the modified NewYork criteria [9], were included in this analysis. Eligible interventions included all five currently available TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab). Eligible comparators included placebo or traditional DMARDs. Eligible outcomes included (1) serious adverse events, which was any adverse event that resulted in death, was life threatening, resulted in hospitalization or prolongation of hospitalization, or caused persistent or substantial disability [10];(2) serious infection, defined as an infection that requires antimicrobial therapy or hospitalization [11]; (3) malignancies, defined as each RCT specified [12]; (4) treatment discontinuation due to adverse events. Two investigators (Li-qiong Hou and Ga-xue Jiang) independently determined the eligibility of the studies and discrepancy was resolved by consensus.

Data Extraction and Study Quality Assessment

Two investigators (Lei Meng and Miao Xue) independently extracted baseline patient characteristics, drug doses and treatment duration, the number of subjects experiencing an event by outcomes in randomized groups, and the number of randomized patients for intention-to-treat analysis. Discrepancy was resolved by consensus. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence [13–15]. The ranks of the quality of evidence were based on the type of study design, the risk of bias in the body of evidence, the consistency of the results, and the precision of the overall estimate. For each outcome, the strength of the evidence was rated as high, moderate, low, or very low. We examined risk of bias in individual studies using the criteria from the Cochrane risk-of-bias tool [16]. To appraise the risk of bias, we used pre-defined criteria, which included random sequence generation, allocation concealment, masking of the treatment status, masking of outcome assessment, selective outcome reporting, and intention-to-treat principles. Consistency was obtained based on the pooled statistical heterogeneity at the significant level $\alpha = 0.1$.

Data Synthesis and Statistical Analysis

We compared each TNF inhibitors with placebo alone or in combination with traditional DMARDs. In addition, both odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. It is recommended that studies with zero events in both arms be excluded from meta-analyses of ORs [17]. To address the potential dose impact, we also compared the event rates according to TNF inhibitors dose (i.e., high dose vs normal dose), similar to a recent systematic review by Aaltonen et al. [18]. For this analysis, high dose referred to a higher than normal TNF inhibitors dose as per package insert of each TNF inhibitors as follows: infliximab 3 mg/kg/every 8 weeks, etanercept 50 mg/week (or 25 mg/twice per week), adalimumab 40 mg/every other week (or 20 mg/week), certolizumab pegol 400 mg/every 4 weeks, and golimumab 50 mg/every 4 weeks. Finally, to explore the impact of the study duration, a meta-analysis was performed on two subgroups of studies (risk difference by Mantel-Haenszel's method), according to the study duration (< vs ≥24 weeks). We explored heterogeneity between the trials using the chi-square test for heterogeneity and a 10% level of significance. In addition, the I^2 statistic was calculated from

the results of the meta-analysis as $I^2 = 100\% \times (Q - \mathrm{df})/Q$, where Q is Cochran's heterogeneity statistic (chi-square) and df is the degrees of freedom, to quantify inconsistencies across studies, and results were complied with the recommendations put forward in the Cochrane Handbook [19]. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity [20]. The study was considered heterogeneous when a p value of chi-square statistics was less than 0.1 or the value of I^2 was over 50% [21]. All statistical tests and creation of forest plots were conducted with STATA 12 and Meta-Analyst software [22].

Results

Search Results

The database search results are summarized in Fig. 1. Among the 28 full-text articles that were assessed for eligibility, 14 RCTs [5–7, 23–33] that fulfilled all the inclusion criteria and none of the exclusion criteria. The main reasons for the exclusion were no drug of interest, patients without AS, lack of randomization or a control group, and the study duration of <12 weeks. We excluded the study of Braundt J [34] because the study with zero events in both arms, the study Braundt J [35] did not compare the safety of the TNF inhibitor is against control group, the studies Dijkmans B [36] and Inman RD [37] are open-labeled studies (Fig. 1).

Study Characteristics

Of the 14 studies, 10 reported total serious adverse events, 3 reported malignancies, 8 reported serious infections, and 10 reported discontinuation due to adverse events. The mean age ranged from 29 to 48 years, 63 to 95% of patients were male, and the disease duration ranged from 3.2 to 16.4 years for patients with AS included in the analysis. From the 14 RCTs included in the systematic review, 2 used adalimumab, 7 etanercept, 2 golimumab, and 3 infliximab for intervention. The included trials have 3062 patients, of which 2032 and 1030 were in the treatment and control groups (Table 1).

Overall Serious Adverse Events

Nine trials and 11 comparisons provided data about the overall serious adverse events. There were 1992 patients in the TNF inhibitor group. There were 1118 patients in the control group. The risk of overall serious adverse events in patients treated with TNF inhibitors as a group was not significantly different from those treated with placebo and/or traditional DMARDs in the control arm (OR, 1.34; 95% CI, 0.87–2.05) (Fig. 2).

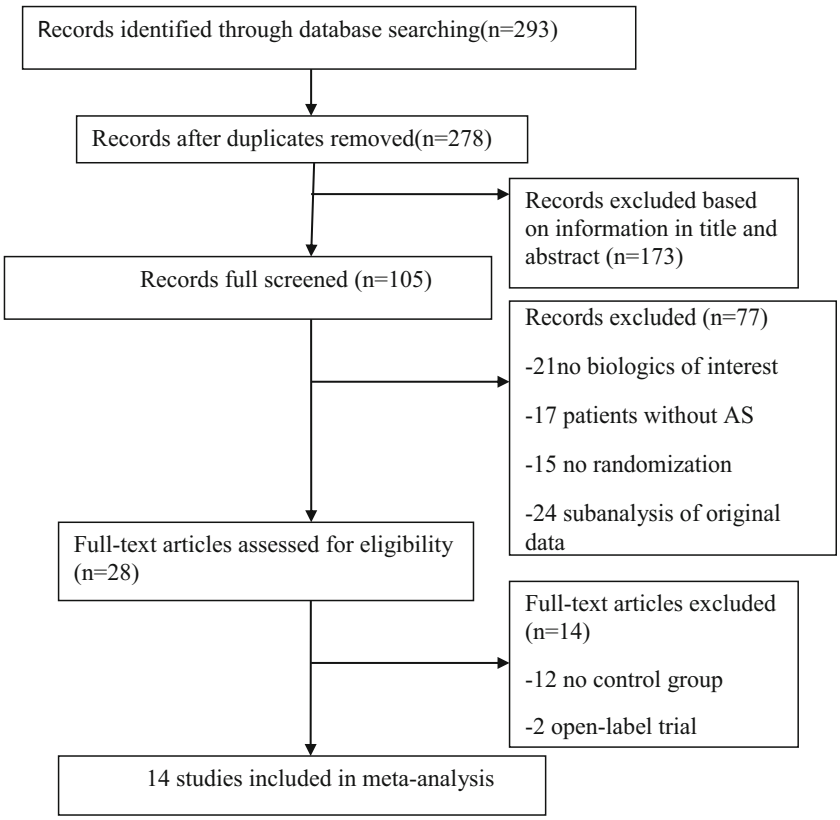

Fig. 1 Flow chart of search results

Table 1 Characteristic of randomized controlled trials included in the analysis

First author	Year	Lengths of trials (week)	Eligibility	Treatment group				Control group		
				N	Drug/dosage	Age (mean)	Man (%)	Mean duration of diseases (years)	*N*	Control
Braun J	2002	12	Patients with active AS	34	infliximab 5 mg/kg at 0, 2, 6 week	T 40.6 (8.0) C 39.0 (9.1)	T 23 (68%) C 22 (63%)	T 16.4 (8.3) C:14.9 (9.3)	35	Placebo
Gorman JD	2002	16	Patients with active AS	20	etanercept 25 mg twice-weekly	T 38.0 (10.0) C 39.0 (10.0)	T 13 (65%) C: 13 (65%)	T 15.0 (10.0) C 12.0 (9.0)	20	Placebo
Davis JC	2003	24	Patients with active AS	138	etanercept 25 mg twice-weekly	T 42.1 (24.0,70.0) C: 41.9 (18.0,65.0)	T 105 (76%) C 105 (76%)	T 10.1 (0,30.7) C 10.5 (0,35.3)	139	Placebo
Van der Heijde D	2004	24	Patients with active AS	201	infliximab 5 mg/kg at 0, 2, 6, 12, and 18 week	T 40.0 (32.0,47.0) C 41.0 (34.0,47.0)	T 157 (78%) C 68 (87%)	T 7.7 (3.3, 14.9) C 13.2(3.7,17.9)	78	Placebo
Calin A	2004	12	Patients with active AS	45	etanercept 25 mg twice-weekly	T 45.3 (9.5) C 40.7 (11.4)	T 36 (80%) C 30 (77%)	T 15.0 (8.8) C 9.7 (8.2)	39	Placebo
Marzo-Ortega H	2005	30	Patients with active AS	28	infliximab 5 mg/kg at weeks 0, 2, 6, 14, and 22. + methotrexate 7.5 mg at week 0, eventually increased to 10 mg a week	T 41.0 (28.0,74.0) C 39.0 (30.0,56.0)	T 23 (82%) C 11(78%)	T 8.0 (0,41.0) C 10.0 (0,35.0)	14	Placebo + methotrexate 7.5 mg at week 0, eventually increased to 10 mg a week
Van der Heijde D	2005	24	Patients with active AS	208	adalimumab, 40 mg every other week	T 41.7 (11.7) C 43.4 (11.3)	T 157 (76%) C 79 (74%)	T: 11.3(10.0) C: 10.0(8.3)	107	Placebo
Van der Heijde D	2006	12	Patients with active AS	50 mg (155) 25 mg (150)	1. etanercept 50 mg once weekly, 2. etanercept 25 mg twice weekly	T (50 mg): 41.5 (11.0) T (25 mg): 39.8 (10.7) C 40.1 (10.9)	T (50 mg): 108 (69%) T (25 mg): 114 (76%) C 40 (78%)	T (50 mg): 9.0 (8.7) T (25 mg): 10.0 (9.1) C 8.5 (6.8)	51	Placebo
Inman RD	2008	24	Patients with active AS	50 mg (138) 100 mg (140)	1. golimumab 50 mg every 4 weeks, 2. golimumab 100 mg every 4 weeks	T (50 mg): 38.0 (30.0,47.0) T (100 mg): 38.0 (29.0,46.0) C 41.0 (31.0,50.0)	T (50 mg): 102 (74%) T (100 mg): 98 (70%) C 55 (71%)	T (50 mg): 5.2(1.6,11.6) T (100 mg): 5.2 (1.5,13.3) C 7.3 (2.8,18.6)	77	Placebo
Barkham N	2010	12	Patients with active AS	20	etanercept 25 mg t wice weekly	T 40.8 (9.7) C 39.4 (10.1)	T 15 (75%) C 17 (85%)	T 11.0 (2.0,45.0) C 20 (0.3,30.0)	20	Placebo
Dougados M	2011	12	Patients with active AS	39	etanercept 50 mg once weekly	T 46.0 (11.0) C 48.0 (10.0)	T 37 (95%) C 39 (91%)	T 19.0 (10.0) C 23.0 (11.0)	43	Placebo
Braun J	2011	16	Patients with active AS	379	etanercept 50 mg once weekly	T 40.7 (11.7) C 40.9 (12.2)	T 279 (73.6%) C 140 (74.9%)	T 7.5 (9.5) C 8.0 (8.9)	187	

Table 1 (continued)

First author	Year	Lengths of trials (week)	Eligibility	Treatment group		Age (mean)	Man (%)	Control group		
				N	Drug/dosage			Mean duration of diseases (years)	*N*	Control
										Sulfasalazine titrated to a maximum of 3 mg/day
Huang F	2014	12	Patients with active AS	229	adalimumab 40 mg every other week	T 30.1 (8.7) C 29.6 (7.5)	T 185 (81%) C 95 (83%)	T 3.0 (3.8) C 3.0 (3.2)	115	Placebo
Bao C	2013	16	Patients with active AS	108	golimumab 50 mg every 4 weeks	T 30.5 (10.3) C 3 0.6 (8.6)	T 90 (83%) C 87 (83%)	T 4.2 (5.2) C 3.7 (3.9)	105	Placebo

T, TNF inhibitors group; *C*, control group

Serious Infection Events

Eight trials provided data about the serious infection events. There were 1501 patients in the TNF inhibitor group. There were 707 patients in the control group. The risk of serious infection events in patients treated with TNF inhibitors as a group was not significantly different from those treated with placebo or traditional DMARDs in the control group (OR, 1.59; 95% CI, 0.63–4.01) (Fig. 3).

Discontinuation Due to Adverse Events

Ten trials and 12 comparisons provided data about the discontinuation due to adverse events. There were 1919 patients in the TNF inhibitor group. There were 1065 patients in the control group. The risk of discontinuation due to adverse events in the TNF inhibitor group was not significantly different from the control group (OR, 1.55; 95% CI, 0.95–2.54) (Fig. 4).

Malignancy Events

Three trials and four comparisons provided data about the malignancy events. There were 425 patients in the TNF inhibitor group. There were 302 patients in the control group. The risk of malignancy in the TNF inhibitor group was not significantly different from the control group (OR, 0.98; 95% CI, 0.25–3.85) (Fig. 5).

Additional Analyses

To address the potential dose impact, we compared the safety event rates according to TNF inhibitors dose (i.e., high dose vs normal dose). High-dose TNF inhibitors was not significantly associated with an increased risk of overall serious adverse events (OR, 1.43; 95% CI, 0.61–3.38), serious infection (OR, 1.26; 95% CI, 0.28–5.63), or discontinuation due to adverse events (OR, 2.70; 95% CI, 0.70–10.47) as compared with patients treated with a normal dose. Similarly, our subgroup analysis for these safety events according to duration of the trial did not appear to differ substantially (summary ORs, 1.72 vs 1.10 for overall serious adverse events and 4.27 vs 0.33 for serious infection events, respectively, and 1.32 vs 0.96 for discontinuation due to adverse events) (Table 2).

Quality of Evidence for Our Analyses

The study qualities of the selected trials were diverse: nine trials were classified as high quality (Jadad score ≥ 4) and five trials were classified as moderate quality (Jadad score = 3) (Table 3).

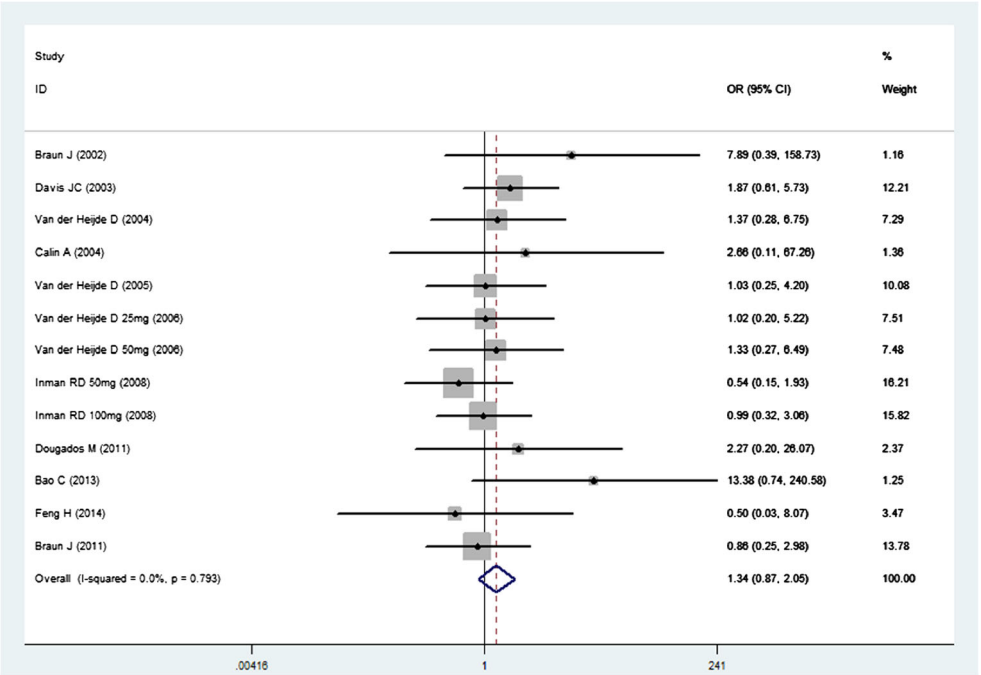

Fig. 2 Effect of TNF inhibitors vs control therapy on the occurrence of overall serious adverse events in patients with ankylosing spondylitis

Discussion

Our objective was to systematically update major safety profiles reported in the RCTs of all approved TNF inhibitors to date to inform the field.

Our study shows that the risk of overall serious adverse events in patients treated with TNF inhibitors was not significantly different from those treated with placebo and/or traditional DMARDs in the control arm. This null conclusion has been consistently reported in previous meta-analysis [3], but our meta-analysis included the recently published RCTs [7, 32]. The most recent meta-analysis [3] also shows the same results; the difference is that we excluded the open-labeled study. Open-labeled studies usually lack a control group, consequently establishing causality between a treatment and an event is impossible. Our study shows that there was no significant difference in the risk of serious infection events between TNF inhibitors and placebo. The lack of significant increase in

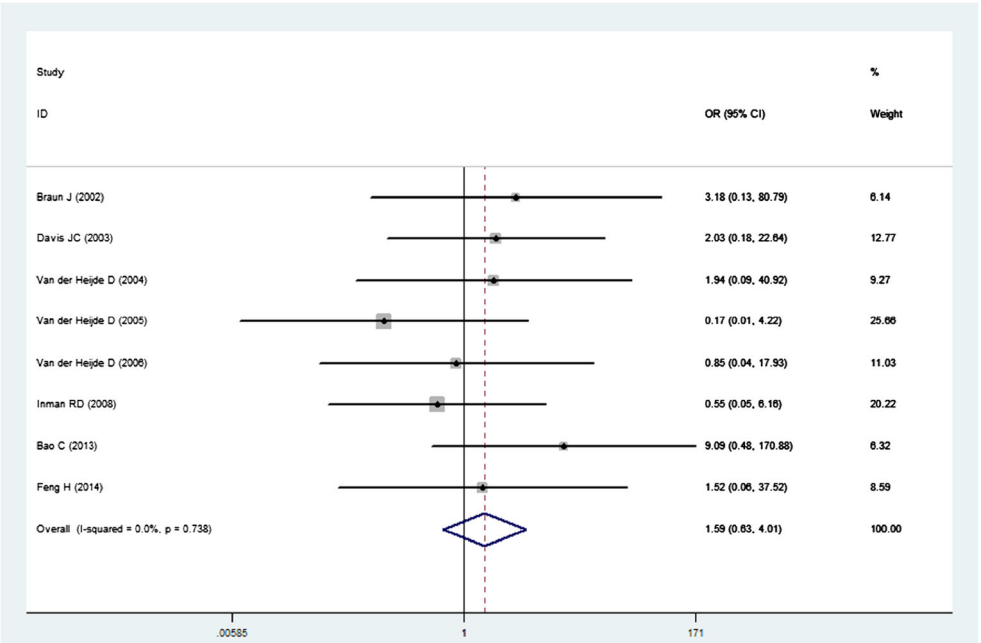

Fig. 3 Effect of TNF inhibitors vs control therapy on the occurrence of overall serious infection events in patients with ankylosing spondylitis

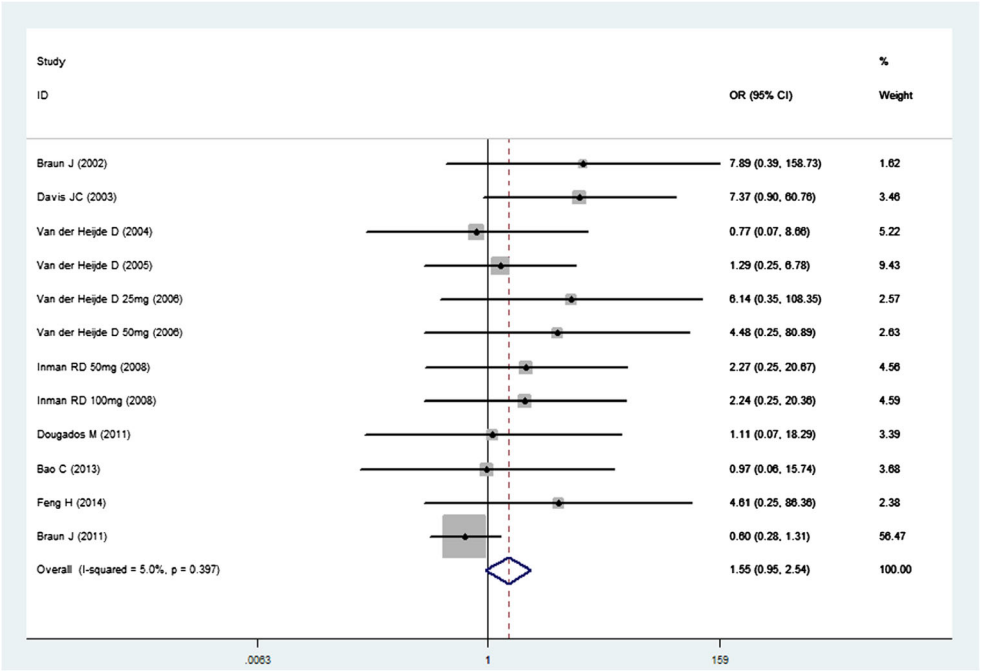

Fig. 4 Effect of TNF inhibitors vs control therapy on the occurrence of discontinuation due to adverse events in patients with ankylosing spondylitis

risk of serious infections with TNF inhibitors may be explained by a lack of power. Indeed, more infections were detected in the TNF inhibitors group; it would, however, necessitate a RCT of more than 5000 patients to reach statistical significance with the difference in risks observed. The few serious infections reported in the articles reviewed here were very heterogeneous, both viral and bacterial infections. In 2010, a meta-analysis of nine trials suggested that the serious infections with TNF inhibitors compared with placebo were not significant [38]. Different from the previous study, the studies with zero events in both arms be excluded from our meta-analyses of OR, and we included the latest RCTs. Furthermore, no significant risk difference was found among increased doses of TNF inhibitors-treated patients and patients treated with normal doses in the included trials. A prospective cohort study indicated a high incidence of serious infections with infliximab treatment in AS [39]. However, they had a small population and no comparison with placebo. As for tumor incidence, AS has not been linked with malignancy, unlike rheumatoid arthritis (RA), which is associated with an increased incidence of lymphoma. Two studies assessing

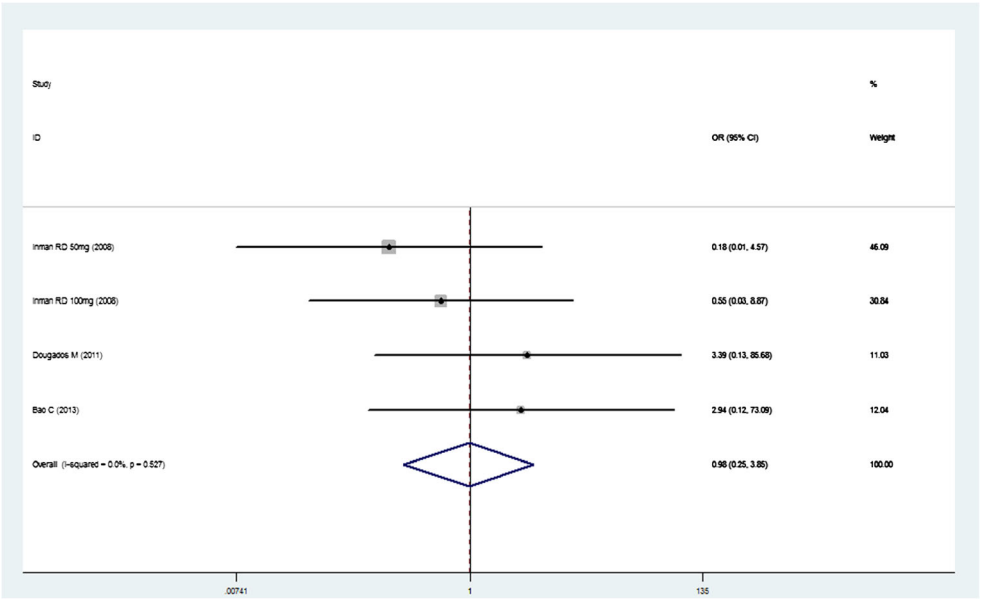

Fig. 5 Effect of TNF inhibitors vs control therapy on the occurrence of malignancy events in patients with ankylosing spondylitis

Table 2 The results of the subgroup analyses

Variables	Sample size treatment/control	Number of comparison	Net change (95% CI)
Overall serious adverse events			
Type of TNF inhibitors			
infliximab	263/127	2	2.27(0.58,8.94)
etanercept	906/510	6	1.37(0.73,2.59)
adalimumab	437/222	2	0.89(0.26,3.10)
golimumab	386/259	3	1.24(0.59,2.61)
Duration			
< 24 weeks	1167/640	8	1.72(0.89,3.35)
≥ 24 weeks	825/478	5	1.10(0.63,1.92)
Dose			
high dose	403/204	3	1.43(0.61,3.38)
normal dose	1589/914	10	1.31(0.80,2.14)
Serious infection events			
Type of TNF inhibitors			
infliximab	235/113	2	2.45(0.26,22.84)
etanercept	443/190	2	1.48(0.22,10.11)
adalimumab	437/222	2	0.51(0.07,3.63)
golimumab	386/182	2	2.58(0.47,14.16)
Duration			
< 24 weeks	371/255	3	4.27(0.74,24.53)
≥ 24 weeks	1130/452	5	0.33(0.10,1.15)
Dose			
high dose	375/190	3	1.26(0.28,5.63)
normal dose	1126/517	5	1.25(0.45,3.48)
Discontinuation due to adverse events			
Type of TNF inhibitors			
infliximab	235/113	2	2.46(0.42,14.29)
etanercept	861/471	5	1.32(0.72,2.44)
adalimumab	437/222	2	1.96(0.48,7.99)
golimumab	386/259	3	1.88(0.50,7.17)
Duration			
< 24 weeks	1094/587	7	1.32(0.73,2.40)
≥ 24 weeks	825/478	5	0.96(0.49,1.87)
Dose			
high dose	375/190	3	2.70(0.70,10.47)
normal dose	1544/875	9	21.44(0.85,2.45)

solid malignancy rates with TNF inhibitors have failed to show an increased risk compared with the general population [40]. Our findings confirm no increased risk of malignancy associated with TNF inhibitors either as a group or individual in AS. A meta-analysis public in 2009 analysis included 19, 041 patients exposed to adalimumab in 36 global clinical trials in RA, psoriatic arthritis (PsA), AS, Crohn's disease (CD), psoriasis, and juvenile idiopathic arthritis (JIA) has the same conclusion [41]. A single-center series and systematic review of RCTs of malignancies in patients with RA, PsA, and AS receiving TNF inhibitors have the same conclusion too. Furthermore, findings from observational studies as well as from a large long-term extension study of a RCT have reported no increased risk of malignancy across all TNF inhibitors [42]. However, there were few RCTs report the risk of malignancy event with TNF inhibitors treatment in AS, addressing this issue in future studies would be valuable. Our study shows that the risk of overall serious adverse events in patients treated with TNF inhibitors was not significantly different from those treated with placebo

Table 3 Quality of included trials

Study	Allocation concealment	Blinding	Randomization	Withdrawals	Generation of random number	Jadad score
Braun J, 2002	Yes	Yes Double blind	Yes	Yes	Low risk	5
Gorman JD, 2002	Yes	Yes Double blind	Yes	Yes	Low risk	5
Davis JC, 2003	Yes	Yes Double blind	Yes	Yes	Not clear	4
Van der Heijde D, 2004	Not clear	Yes Double blind	Yes	Yes	Low risk	4
Calin A, 2004	Not clear	Yes Double blind	Yes	Yes	Not clear	3
Marzo-Ortega H, 2005	Yes	Yes Double blind	Yes	Yes	Not clear	4
Van der Heijde D, 2005	Not clear	Yes Double blind	Yes	Yes	Not clear	3
Van der Heijde D, 2006	Not clear	Yes Double blind	Yes	Yes	Not clear	3
Inman RD, 2008	Not clear	Yes Double blind	Yes	Yes	Low risk	4
Barkham N, 2010	Not clear	Yes Double blind	Yes	Yes	Not clear	3
Dougados M, 2011	Not clear	Yes Double blind	Yes	Yes	Not clear	3
Braun J, 2011	Yes	Yes Double blind	Yes	Yes	Low risk	5
Huang F, 2014	Not clear	Yes Double blind	Yes	Yes	Low risk	4
Bao C, 2013	Not clear	Yes Double blind	Yes	Yes	Low risk	4

and/or traditional DMARDs in the control arm. This conclusion has been consistently reported in the previous meta-analysis [3]. A recently meta-analyses report the risk of all cause withdrawals in patients treated with TNF inhibitors was not significantly different from those treated with placebo in the control arm [4]. It should be noted that the discontinuation due to adverse events rate in our meta-analysis is different from all cause withdrawals rates, which include a lack of efficacy.

The present systematic review has several advantages. This systematic review was performed using all available literature sources and included all published data to date. Furthermore, the meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration. No evidence for significant publication bias was apparent on a funnel plot (data not shown) and no statistical heterogeneity was detected. Furthermore, several methods of meta-analysis were applied, assessing the risk difference vs the OR. Both methods confirmed the robustness of the results. Several sensitivity analyses were also performed and confirmed the results. Therefore, we consider these results to be valid.

Although we believe that the current meta-analysis provides useful information, some potential limitations should be addressed. First, some safety data are not available in all finally selected articles and thus could not be included in our analysis. Disease severity was not taken into account in our study, partly due to the difficulties associated with the different severity measures across the trials. Third, the study durations were short (from 12 to 30 week). So more trials are needed to investigate the safety of TNF inhibitors in patients treated for AS.

In conclusion, our meta-analysis of RCTs to date indicates TNF inhibitors generally safe for treatment of AS. Our findings should be relevant to clinical comparative effectiveness guidelines on treatment for AS patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Funding There is no funding source.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

References

1. Senabre JM, Santos C, Santos G et al (2013) Long-term safety and efficacy of etanercept in the treatment of ankylosing spondylitis. Patient Prefer Adherence 10:961–972
2. Wu D, Guo YY, Xu NN et al (2015) Efficacy of anti-tumor necrosis factor therapy for extra-articular manifestations in patients with ankylosing spondylitis: a meta-analysis. BMC Musculoskelet Disord 10:2016–2019
3. Machado MA, Barbosa MM, Almeida AM et al (2013) Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int 33:2199–2213. doi:10.1007/s00296-00013-02772-00296
4. Liu W, Wu YH, Zhang L et al (2016) Efficacy and safety of TNF-alpha inhibitors for active ankylosing spondylitis patients: multiple treatment comparisons in a network meta-analysis. Sci Rep 10: 32768
5. Inman RD, Davis JC, Heijde D 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 10:3402–3412

6. 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 70:799–804. doi:10.1136/ard.2010.1392617
7. Bao C, Huang F, Khan MA et al (2014) Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. Rheumatology (Oxford) 53:1654–1663. doi:10.1093/rheumatology/keu1132
8. Counsell C (1997) Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 127: 380–387
9. 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
10. Benucci M, Saviola G, Baiardi P et al (2011) Efficacy and safety of leflunomide or methotrexate plus subcutaneous tumour necrosis factor-alpha blocking agents in rheumatoid arthritis. Int J Immunopathol Pharmacol 24:269–274
11. Billiau AD, Loop M, Le P et al (2010) Etanercept improves linear growth and bone mass acquisition in MTX-resistant polyarticular-course juvenile idiopathic arthritis. Rheumatology (Oxford) 49: 1550–1558. doi:10.1093/rheumatology/keq1123
12. Bliddal H, Terslev L, Qvistgaard E et al (2006) A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol 35:341–345
13. Blumenauer B, Judd M, Wells G et al (2002) Infliximab for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 3
14. Boesen M, Boesen L, Jensen KE et al (2008) Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. J Rheumatol 35:584–591
15. Breedveld FC, Emery P, Keystone E et al (2004) Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 63:149–155
16. Breedveld FC, Han C, Bala M et al (2004) Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Ann Rheum Dis 64:52–55
17. Chang J, Girgis L (2007) Clinical use of anti-TNF-alpha biological agents—a guide for GPs. Aust Fam Physician 36:1035–1038
18. Anis A, Zhang W, Emery P et al (2009) The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford) 48:1283–1289. doi:10.1093/rheumatology/kep1239
19. Deeks JJ, Higgins J, Altman DG (2008) Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions, Cochrane Book Series, pp 243–296
20. Higgins JP, Thompson SG, Deeks JJ et al (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
21. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
22. Wallace BC, Schmid CH, Lau J et al (2009) Meta-analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 10:2080
23. Braun J, Brandt J, Listing J et al (2002) Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 359:1187–1193
24. Gorman JD, Sack KE, Davis JC et al (2002) Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 346:1349–1356
25. Davis JC, Van Der Heijde D, Braun J et al (2003) Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 48:3230–3236
26. 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 52:582–591
27. 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 2063:1594–2600
28. Marzo 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 64:1568–1575
29. 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 54:2136–2146
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 65:1572–1577
31. 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 69:1926–1928. doi:10.1136/ard.2009.121327
32. Huang F, Gu J, Zhu P et al (2014) Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 73:587–594. doi:10.1136/annrheumdis-2012-202533
33. Braun J, van der Horst 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 63:1543–1551
34. 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: 1667–1675
35. Brandt J, Listing J, Sieper J et al (2004) Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. Ann Rheum Dis 63:1438–1344
36. Dijkmans B, Emery P, Hakala M et al (2009) Etanercept in the longterm treatment of patients with ankylosing spondylitis. J Rheumatol 36:1256–1264. doi:10.3899/jrheum.081033
37. Inman RD, Maksymowych WP (2010) A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol (37):1203–1210. doi:10.3899/jrheum.091042
38. Fouque A, Jette L, Combescure C et al (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 69:1756–1761. doi:10.1136/ard.2008.098822
39. Baeten D, Kruithof E, Van den Bosch F et al (2003) Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Ann Rheum Dis 62:829–834
40. Askling J, Fored CM, Brandt L et al (2005) Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 64:1421–1426
41. Burmester GR, Mease P, Dijkmans BA et al (2009) Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis 68:1863–1869. doi:10.1136/ard.2008.102103
42. Nannini C, Cantini F, Niccoli L et al (2009) Single-center series and systematic review of randomized controlled trials of malignancies in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis receiving anti-tumor necrosis factor alpha therapy: is there a need for more comprehensive screening procedures? Arthritis Rheum 61:801–812