EXTENDED REPORT

Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis

Jose Ramon Maneiro,[1] Alejandro Souto,[1] Eva Salgado,[1] Antonio Mera,[1,2] Juan J Gomez-Reino[1,2]

[1]Rheumatology Unit, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago, Spain
[2]Department of Medicine, Medical School, Universidad de Santiago, Santiago, Spain

Correspondence to
Dr Jose Ramon Maneiro; joseramon.maneiro.fernandez@sergas.es

ABSTRACT

Objective: To identify predictors of response to tumor necrosis factor (TNF) antagonists in ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: Systematic review and meta-analysis of clinical trials and observational studies based on a systematic search. Meta-analyses of similar observations were performed using random effects computing summary OR. Heterogeneity was tested using I^2, and risks of bias using funnel plots and the Egger test. Meta-regression was used to explore causes of heterogeneity.

Results: The electronic search captured 1340 references and 217 abstracts. 17 additional articles were identified after searching by hand. A total of 59 articles meet the purpose of the study and were reviewed. 37 articles (33 studies) included 6736 patients with AS and 23 articles (22 studies) included 4034 patients with PsA. 1 article included data on AS and PsA. Age (OR (95% CI) 0.91 (0.84 to 0.99), I^2=84.1%), gender (1.57 (1.10 to 2.25), I^2=0.0%), baseline BASDAI (1.31 (1.09 to 1.57), I^2=0.0%), baseline BASFI (0.86 (0.79 to 0.93), I^2=24.9%), baseline dichotomous C reactive protein (CRP) (2.14 (1.71 to 2.68), I^2=22.3%) and human leucocyte antigen B27 (HLA-B27) (1.81 (1.35 to 2.42), I^2=0.0%) predict BASDAI50 response in AS. No factor was identified as a source of heterogeneity. Only meta-analysis of baseline BASFI showed risk of publication bias (Egger test, p=0.004). Similar results were found for ASAS criteria response. No predictors of response were identified in PsA.

Conclusions: Young age, male sex, high baseline BASDAI, low baseline BASFI, high baseline CRP and HLA-B27 predict better response to TNF antagonists in AS but not in PsA.

Key messages

► At the group level, demographic, serological, clinical and genetic factors predict response to biological therapies in AS and PsA.
► However, the individual predictive value of these variables is limited.

respond to these therapies and, furthermore, they are not exempt from serious adverse events. TNF antagonists are associated with increased risk of infections, including reactivation of tuberculosis and other opportunistic infections.[8–10] In the past few years new therapies have been approved for the treatment of spondyloarthritis, increasing the therapeutic options for these patients.[11 12] How best to use these drugs remains unclear. An ability to identify which patients would have a better response to each biological therapy may help minimise the risks and costs associated with these treatments. The development of predictors of response might identify responders and thus help with making therapeutic decisions in clinical practice.

Several clinical and serological markers of response to biologics have been identified in rheumatoid arthritis (RA).[13–18] However, data about predictors of response in patients with ankylosing spondylitis (AS) or psoriatic arthritis (PsA) are limited. The main objective of this study is to summarise information regarding predictors of response to TNF antagonists in patients with AS and PsA.

INTRODUCTION

Tumor necrosis factor (TNF) antagonists are a major advance in the treatment of patients with inflammatory arthritis. The efficacy and safety of these drugs has been supported by clinical trials.[1–7] However, not all patients

MATERIALS AND METHODS

We performed a systematic literature review to identify all publications analysing predictors of response to TNF antagonists in patients with AS or PsA. The protocol of the review is

available by email on request. PRISMA consensus was followed for the review and meta-analysis.[19]

Systematic literature research

Medline, Embase, Web of Knowledge and the Cochrane Library were searched for articles published between 1998 and April 2013. The search strategy focused on synonyms for disease, TNF antagonist, predictor and response, and was limited to articles published in English, Spanish, French, Italian or Portuguese (see online supplementary text). We also included abstracts online from 2001 to 2013 of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) congresses.

Selection of articles

The selection criteria for articles and abstracts were: (1) studies in patients with a diagnosis of AS or PsA; (2) studies in patients treated with at least one TNF antagonist; (3) studies collecting data on predictor of response with some method of measurement; and (4) retrospective or prospective observational studies, or intervention studies. Two reviewers (JRM and AS) screened articles and abstracts for selection criteria independently, using a third reviewer (ES) for consensus. Once unrelated articles were excluded, the full report of all the selected studies was reviewed. Subsequently, articles not fulfilling all selection criteria were excluded. A table summarising the reasons for exclusion is included in the online supplementary material. A reverse search of included articles and a hand search of published clinical trials of TNF antagonist in AS or PsA, and of documents of the Food and Drug Administration (FDA) were also performed.

Data extraction

Data collected included publication details, study design, characteristics of patients, treatment, predictor and definition of response.

Risk of bias

We created an ad hoc checklist to analyse the risk of bias of included studies, containing 30 items with punctuation from 0 to 100 (from higher to lower risk). This checklist was based on the guidelines for assessing quality in prognostic studies on the basis of framework of potential biases proposed by Hayden et al[20] (available on request).

Statistical analysis

Results were presented as summary effect measures grouped by predictor and by response definition. When a measure of association was not available, this was calculated from the available data. Meta-analyses were performed using a random-effects approach, with the DerSimonian and Laird method computing the summary OR.[21] Meta-analysis was only planned if at least three studies or subanalyses with similar design were available. For each analysis the effect was plotted by the inverse of its

SE to identify risk of publication bias, assessing visually the symmetry of funnel plots, and its statistical significance using the Egger test.[22] Heterogeneity was tested as proposed by Higgins and Thompson using I^2.[23][24] An I^2 value >40% was arbitrarily chosen to represent high levels of heterogeneity. If high statistical heterogeneity was present, possible explanations were investigated using sensitivity analysis and meta-regression. Meta-regression aimed to determine the contribution of time to assess response, number of patients, quality of data, time of disease duration, biological used, design of the study, and levels of evidence to the summary effect. A p<0.10 was considered significant in the meta-regression and p<0.05 in other analyses. Stata V.11.1 (Stata/IC 11.1 for Windows, StataCorp LP, Texas, USA) was used in all statistical analyses.

RESULTS

The search identified a total of 1340 articles and 217 abstracts. After title/abstract screening, 125 articles were retrieved for full text review. After hand search and reverse search, 17 additional articles were included. A total of 83 articles were excluded after detailed review. Finally, 59 articles and abstracts were included in the present analysis (see online supplementary figure S1).

In 55 studies from these 59 documents, 10 770 patients were included (6736 with AS and 4034 with PsA). Thirty-seven articles (33 studies) included patients with AS[1][25–60] and 23 (22 studies) patients with PsA.[4][43][61–81] One of these articles included data about AS and PsA, and these data were analysed separately.[43] Quality of data was ≥70% in 33 (60.0%) of the studies; 20 (60.6%) in studies of AS and 13 (59.0%) in studies of PsA (tables 1 and 2). Individual results are presented according to predictors and disease in online supplementary material (see online supplementary tables S1–S8).

Demographic and environmental factors

Thirteen studies included data about a demographic or environmental factor as predictor of response in AS.[25][26][32][35][39][40][46][49][50–52][56][57][65] Age was analysed in 12 studies.[25][26][32][35][40][46][49–52][56][65] Individual results showed better ASAS20,[25][26] ASAS40[26][35][50] and BASDAI50 responses in younger patient.[26][35][40][46][50–52] Meta-analyses of age and BASDAI50 at 12 weeks were performed using data from two studies[26][51] and from subgroups of one study,[52] as well as with 24 weeks' data from three studies.[26][34][40] Analyses demonstrated a resulting OR (CI 95%) of 0.91 (0.84 to 0.99) with I^2 of 84.1% (figure 1A) and no risk of publication bias (Egger test p=0.178), and 0.98 (0.97 to 0.99) with I^2 12.3% (figure 1B) and no risk of publication bias (p=0.698) at 12 and 24 weeks, respectively. No factors were identified as a source of heterogeneity.

Gender was analysed in 10 studies.[25][26][32][35][39][40][46][49][52][56] Results of individual studies showed better ASAS20,[25][26] ASAS40[26] and ASDAS responses in men.[32][49] Meta-analysis

Table 1 Table of evidence of studies of AS

Study	Biological	Design	Duration	N	Q	LE	Age*	DD*	Women (%)	HLAB27+ (%)	Prior biologics (%)
Arends et al[26]	IFX, ETN, ADA	OP	24	220	0.91	2	42.9	15.0	31.0	81.0	0.0
Arends et al[27]	ETN	OP	48	92	0.75	2	41.2	9.0†	26.0	83.0	0.0
Braun et al[28]	IFX	RCT	12	34	0.65	3	40.6	16.4	32.0	91.0	0.0
Braun et al[29]	ADA	OP	12	1250	0.75	2	44.0	11.0	30.0	82.0	26.0
Davis et al[30]	ETN	RCT	24	138	0.83	3	42.1	10.1	24.0	84.0	0.0
de Vries et al[31]	IFX, ETN	OP	12	155	0.80	2	42.0	8.0†	35.0	79.0	0.0
Fagerli et al[32]	NA	OR	12	249	0.60	4	41.9	10.1	32.1	90.7	0.0
Fagerli et al[33]	NA	OR	12	289	0.61	4	42.4	9.9	32.6	90.5	0.0
FDA-103795/5123[25]	ETN	RCT	24	138	0.65	3	42.1	10.0	24.0	84.0	NA
Glintborg et al[34]	IFX, ADA, ETN	OR	24	842	0.76	4	41.0†	5.0†	28.0	NA	0.0
Haibel et al[35]	ADA	RCT	52	46	0.65	3	37.4	7.5	54.3	67.3	2.1
Huang et al[36]	IFX	OP	10	63	0.76	2	32.8	10.9	20.0	90.5	0.0
Inman et al[37]	GOL	RCT	14	278	0.75	3	38.0	5.2†	28.1	83.0	0.0
Kim et al[38]	IFX	OP	22	23	0.60	2	41.4	8.7†	17.3	100.0	0.0
Kristensen et al[39]	IFX, ETN, ADA	OP	96	243	0.83	2	43.0	16.0	25.5	NA	0.0
Lord et al[40]	IFX, ETN, ADA	OP	24	261	0.91	2	43.0†	13.0†	18.0	NA	0.0
Luc et al[41]	IFX, ETN, ADA	OR	144	175	0.81	4	27.1	12.1	22.0	88.0	0.0
Maria Lizzio et al[42]	IFX	OP	54	47	0.51	2	46.8	14.7	NA	NA	NA
Morales-Lara et al[43]	IFX	OP	48	33	0.50	2	NA	NA	NA	NA	NA
Mulleman et al[44]	IFX	RCT	14	26	0.66	3	44.1†	4.2†	23.0	NA	15.3
Navarro-Compan et al[45]	NA	OP	12	20	0.55	2	42.4	6.8	14.0	83.3	NA
Ottaviani et al[46]	IFX	OR	24	155	0.83	4	43.1†	8.0†	36.7	64.9	NA
Pedersen et al[47]	IFX, ETN, ADA	OP	22	60	0.90	2	40.0†	12.0†	20.0	82.0	0.0
Perez-Guijo et al[48]	IFX	OP	30	19	0.60	3	37.4	14.2	NA	100.0	0.0
Ramiro et al[49]	NA	OR	12	197	0.75	4	NA	NA	NA	NA	NA
Rudwaleit et al[52]	IFX. ETN	RCT	12	99	0.78	3	38.4	14.8	32.0	89.0	0.0
Rudwaleit et al[51]	ADA	OP	12	1159	0.75	2	NA	NA	NA	NA	NA
Rudwaleit et al[53]	IFX, ETN	RCT	12	46	0.78	3	38.1	14.6	34.8	89.1	0.0
Rudwaleit et al[50]	ADA	OP	12	1250	0.75	2	44.0	11.0	30.0	82.0	26.0
Seitz et al[54]	IFX, ETN, ADA	OP	24	22	0.68	2	38.9	12.2	13.0	NA	NA
Sieper et al[55]	ADA	RCT	240	315	0.83	3	42.3	11.0	25.1	78.8	0.0
Stone et al[56]	IFX	OP	52	22	0.83	3	37.9†	8.7†	18.1	100.0	0.0
Tong et al[57]	IFX, ETN	OP	12	99	0.75	2	41.6	9.4	22.2	91.2	0,0
van der Heijde et al[58]	IFX	RCT	24	201	0.61	3	40.0	7.7	21.9	86.5	NA
van der Heijde et al[1]	ADA	RCT	24	208	0.61	3	41.7	11.3	24.5	78.4	0.0
Visvanathan et al[59]	IFX	RCT	24	201	0.80	3	40.0	10.1	21.9	86.5	0.0
Wagner et al[60]	GOL	RCT	14	76	0.83	3	39.8	NA	30.2	77.6	0.0

*Data are expressed in means (years).
†Data are expressed in medians.
ADA, adalimumab; DD, disease duration; ETN: etanercept; GOL, golimumab; IFX, infliximab; LE, level of evidence; N, number of patients; NA, not available; OP, observational prospective; OR, observational retrospective; Q, quality; RCT, randomised clinical trial.

of gender and ASAS20 in three studies showed an OR of 2.58 (1.56 to 4.28) with an I^2 of 0.0% (figure 1C), and no risk of publication bias (p=0.854).[25 26 56] Individual studies that analysed BASDAI presented contradictory results.[26 35 40 52 56] Meta-analysis of gender and BASDAI50 including five studies showed an OR of 1.57 (1.10 to 2.25) with an I^2 of 0.0% (figure 1D), and no risk of publication bias (p=0.085).[26 35 40 46 52] In one study, high body mass index (BMI) was related with poor BASDAI.[46] Smoking was analysed in one study with not significant results.[40]

In PsA, eight studies analysed demographic factors as potential predictors of response.[63 64 67–70 78 81] Five studies included data about age.[64 67–70] Only one study showed significant reverse association between age and minimal disease activity (MDA) response.[70] Eight studies included data about gender.[63 64 67–70 78 81] Men showed better response than women in five studies.[63 67 69 78 81] One study showed a negative association of BMI with

MDA response.[63] Whereas another study showed no association between BMI and DAS28 remission.[69]

Clinical factors

Twenty-one articles included data about clinical factors as predictors of response in AS.[25 26 29 30 32 34 35 39 40–42 44 46 48–53 55 56] Five studies included data on BASDAI baseline.[26 40 52 55 56] Individual results showed that higher baseline BASDAI predicts better BASDAI50[40 52] and ASDAS,[55] but not ASAS20 response.[56] Meta-analysis of baseline BASDAI and BASDAI50 in one study[40] and subgroups of another study[52] showed an OR of 1.31 (1.09 to 1.57) with I^2 of 0.0%, and no risk of publication bias (p=0.673) (figure 2A). Eight studies analysed baseline BASFI.[26 30 34 40 51 52 55 56] Individual results showed that higher baseline BASFI predicts poor BASDAI50 response,[34 40 51 52] but not ASAS20 response.[26 30 56] A meta-analysis including four studies showed an OR of

Table 2 Table of evidence of studies of PsA

Study	Biologic	Design	Duration	N	Q	LE	Age*	DD*	Women (%)	HLAB27+(%)	Prior biologics (%)
Antoni et al[4]	IFX	RCT	24	100	0.67	3	47.1	8.4	29.0	NA	0.0
Chandran et al[61]	NA	OP	11	40	0.66	2	44.0	12.0	30.0	NA	NA
Chimenti et al[62]	ADA, ETN	RCT	22	55	0.89	3	48.7	6.5	51.0	NA	0.0
di Minno et al[63]	IFX, ETN, ADA	OP	96	270	0.88	2	51.7	9.2	45.9	NA	0.0
Eder et al[64]	IFX, ETN, ADA, GOL	OP	48	95	0.75	2	45.7	11.8	67.9	NA	9.6
Gladman et al[66]	ADA	RCT	48	285	0.61	3	NA	NA	NA	NA	NA
Gladman et al[65]	ADA	RCT	24	144	0.90	3	47.8	9.9	43.7	NA	0.0
Glintborg et al[67]	IFX, ADA, ETN	OR	24	746	0.76	4	47.0†	5.0†	52.0	NA	0.0
Gratacos et al[68]	IFX	OP	38	69	0.85	2	42.5	8.0	60.8	NA	0.0
Iannone et al[69]	IFX, ETN, ADA	OR	NA	135	0.86	4	53.2‡	10.0‡	49.6	NA	0.0
Iervolino et al[70]	IFX, ETN, ADA	OP	12	136	0.90	2	45.6	5.2	58.4	NA	0.0
Karanikolas et al[71]	ADA	RCT	48	113	0.88	3	46.3	7.9	55.7	23.0	0.0
Kavanaugh et al[72]	IFX	RCT	54	100	0.67	3	47.1	8.4	29.0	NA	0.0
Kavanaugh et al[73]	GOL	RCT	24	292	0.65	3	46.9	7.4	40.0	NA	0.0
Kristensen et al[74]	IFX, ETN, ADA	OP	48	261	0.70	2	47.3	8.4	50.5	NA	0.0
Marotta et al[75]	ADA	OP	12	24	0.53	3	NA	NA	NA	NA	NA
Mease et al[76]	ADA	RCT	12	151	0.68	3	48.6	9.8	43.7	NA	0.0
Morales-Lara et al[43]	IFX	OP	48	16	0.50	2	NA	NA	NA	NA	NA
Ramirez et al[77]	IFX, ETN, ADA	OP	24	103	0.78	2	49.0†	12.0†	47.6	23.3	0.0
Saber et al[78]	IFX, ETN, ADA	OP	12	152	0.73	2	45.0†	8.0†	52.3	NA	0.0
Spadaro et al[79]	ETN	OP	NA	82	0.56	3	51.8	9.1	42.6	NA	NA
Van den Bosch et al[80]	ADA	OP	12	442	0.76	2	47.8	10.6	50.0	23.3	14.9
Wagner et al[81]	GOL	RCT	14	74	0.80	3	48.5	NA	36.0	NA	0.0

*Data are expressed in mean (years).
†Data are expressed in medians.
‡Data were calculated in the review.
ADA, adalimumab; DD, disease duration; ETN, etanercept; GOL, golimumab; IFX, infliximab; LE, level of evidence; N, number of patients; NA, not available; OP, observational prospective; OR, observational retrospective; Q, quality; RCT, randomised clinical trial.

0.86 (0.79 to 0.93) with I² of 24.9% (figure 2B) and risk of publication bias (p=0.004).[34 40 51 52]

Use of concomitant DMARDs was analysed in seven studies,[25 39 40 41 44 48 56] with only one reporting significant results.[40] Meta-analysis of concomitant DMARD and ASAS20 including four studies showed an OR of 1.47 (0.81 to 266) with I² of 55.5%, and no risk of publication bias (p=0.471).[25 44 48 56] Sensitivity analysis was performed identifying one study as a possible source of heterogeneity.[48] This study was removed from the meta-analysis showing an OR of 1.11 (0.52 to 2.11) with I² of 0.0%. Concomitant methotrexate (MTX) was analysed in five studies.[25 39 40 44 48] One study showed significant association with BASDAI50,[40] and another with BASDAI50, ASAS20 and ASAS50 responses.[48] Meta-analysis of concomitant MTX and ASAS20 including three studies showed an OR of 1.62 (0.74 to 3.54) with I² of 72.2%, and no risk of bias (p=0.115).[25 44 48] No factor was identified as a source of heterogeneity. Other concomitant drugs such as sulfasalazine,[25] non-steroidal anti-inflammatory drugs[40 56] or corticosteroids[25 40] were not associated with response.

Disease duration was analysed in six studies with contradictory results.[25 26 35 40 46 52] Meta-analysis of disease duration and BASDAI50 including one study[40] and subgroups of another study[52] showed an OR of 0.96 (0.91 to 1.02) with I² of 63.6%, and no risk of publication bias (p=0.118). No factor was identified as a source of heterogeneity.

Seven studies included data about peripheral arthritis and obtained contradictory results.[26 29 32 35 39 42 52] Meta-analysis of peripheral arthritis and ASAS40 in three studies showed an OR of 0.94 (0.74 to 1.19) with an I² of 79.2%, and no risk of publication bias (p=0.327).[29 32 35] Meta-analysis of peripheral arthritis and BASDAI50 in five studies[26 29 32 35 42] and subgroups of another study[52] showed an OR of 1.13 (0.64 to 1.97) with an I² of 70.8%, and no risk of publication bias (p=0.780). No factor was identified as a source of heterogeneity. Three studies analysed enthesitis and BASDAI50 and showed an OR of 0.92 (0.84 to 101) with an I² of 0.0%, and no risk of publication bias (p=0.378).[29 52] Extra-articular manifestations such as uveitis, psoriasis or inflammatory bowel disease (IBD) did not present an association with response.[25 29] One study that analysed baseline MRI scores showed association with BASDAI50.[53] Syndesmophytes also showed association with poor response.[55]

Sixteen articles analysed several clinical factors in PsA.[4 63 64 66–74 76 78–80] Six studies looked at HAQ baseline and obtained contradictory results.[64 68–70 78 80] Other measures such as joint count, VAS pain, VAS global or DAS28 baseline also returned with variable results.[63 64 70] Thirteen articles analysed concomitant DMARDs as predictor of response.[4 64 66 67 69–74 76 79 80] No significant results were reported regardless of the type of concomitant DMARD, including MTX. One study showed better response with concomitant MTX than monotherapy.[67] In four studies, meta-analysis of
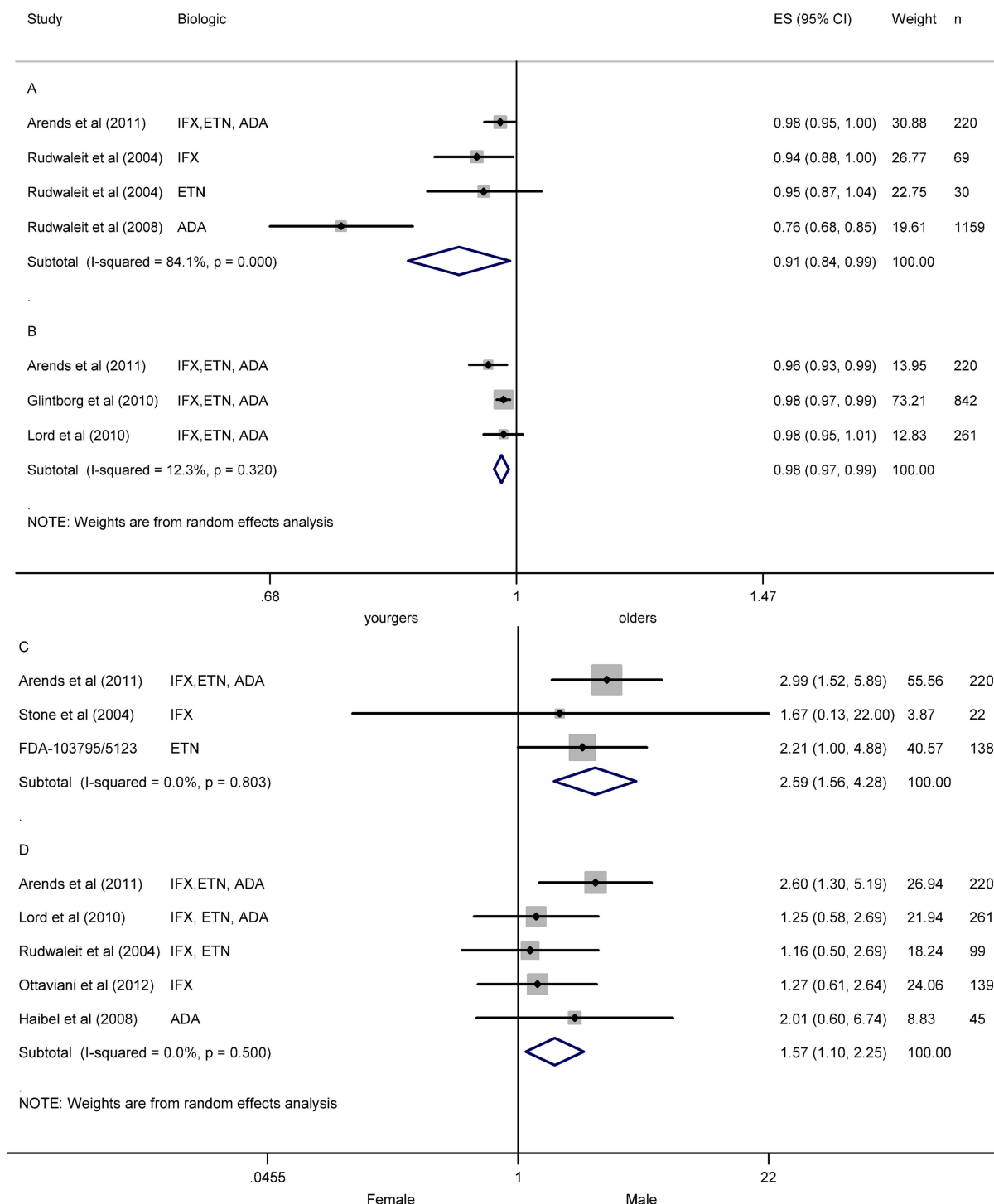
Figure 1 Meta-analysis of demographic factors as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of age and BASDAI50 at week 12 in AS. (B) Meta-analysis of age and BASDAI50 at week 24 in AS. (C) Meta-analysis of gender and ASAS20 in AS. (D) Meta-analysis of gender and BASDAI50 in AS. ES: effect size (OR).

concomitant MTX and ACR20 showed an OR of 1.18 (0.92 to 1.50) with an I^2 of 55.1%, and no publication bias (p=0.092).[4 66 67 76] No factor was identified as a source of heterogeneity. In three studies, meta-analysis of concomitant MTX and ACR50 produced an OR of 1.23 (0.82 to 1.83) with an I^2 of 0.0%, and no risk of publication bias (p=0.782).[4 66 76] In three studies, meta-analysis of concomitant MTX and ACR70

presented an OR of 0.70 (0.50 to 1.25) with an I^2 of 0.0%, and no risk of publication bias (p=0.144).[4 66 76] Other DMARDs such as cyclosporine[71] or sulfasalazine[80] showed a better response in a combined group than in TNF antagonists monotherapy. Other variables such as large joint involvement,[68 80] axial involvement,[68] dactylitis,[64 70] erosive arthritis[68] or disease duration showed contradictory or not significant results.[64 68 69]
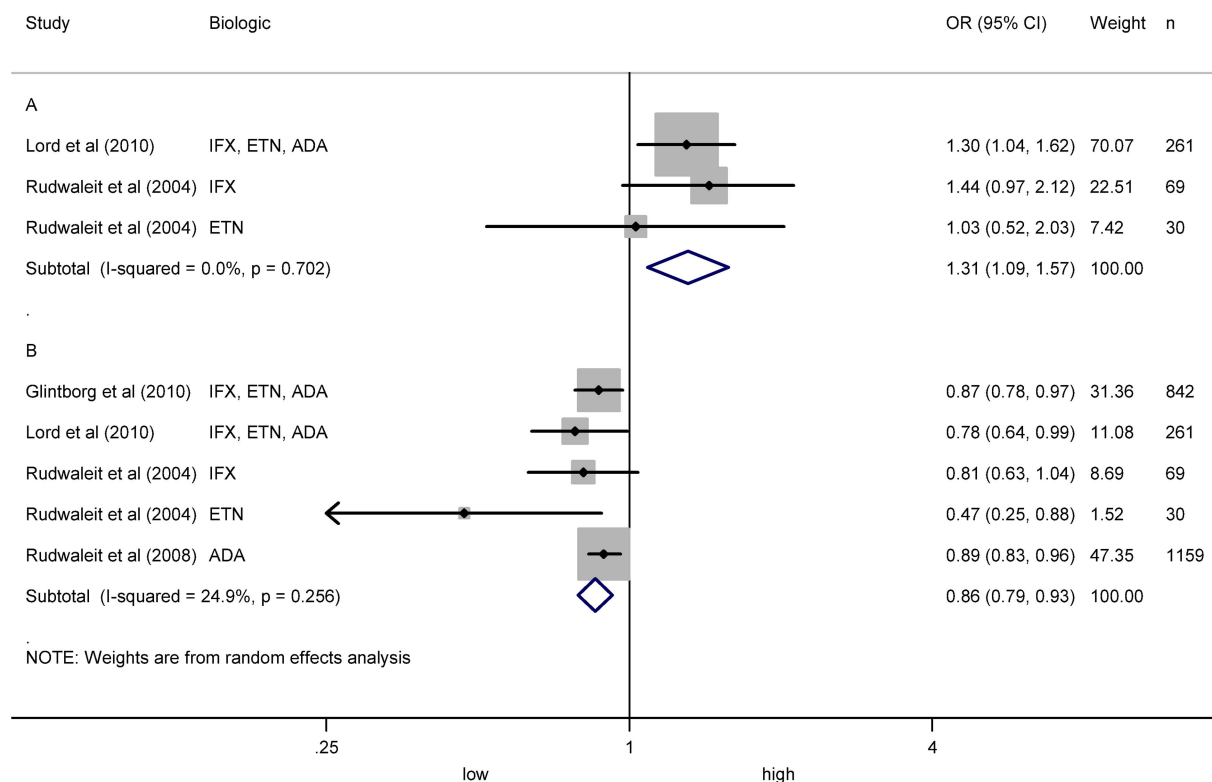
Figure 2 Meta-analysis of BASDAI baseline and BASFI baseline as predictors of response in ankylosing spondylitis (AS). (A) Meta-analysis of BASDAI baseline and BASDAI50 in AS. (B) Meta-analysis of BASFI baseline and BASDAI50 in AS.

Serological factors

Twenty four articles reported serological factors as predictors of response to TNF antagonists in AS.[26–28 30 31 33–35 37–39 41 45–47 49–52 55 56 58–60] Individual results showed better response in patients with high levels of C reactive protein (CRP) in 22 articles.[26 28 30 31 33 34 35 37 39 41 45–47 49–52 55 56 58–60] Meta-analysis of CRP and ASAS20 in six articles showed an OR of 2.53 (2.00 to 3.21) with an I^2 of 0.0% (figure 3A), and risk of publication bias (p=0.015).[30 31 33 37 58 59] Meta-analysis of CRP and ASAS40 in three articles showed an OR of 2.03 (1.49 to 2.76) with an I^2 of 27.6% (figure 3B), and no risk of publication bias (p=0.563).[33 35 50] Meta-analysis of CRP and BASDAI50 in three articles,[26 46 51] and subgroups of another study[52] showed an OR of 1.05 (1.01 to 1.08) with an I^2 of 85.5% (figure 3C), and risk of publication bias (p=0.008). No factor was identified as a source of heterogeneity. Sensitivity analysis showed one study as a source of heterogeneity, and when this study was removed from the meta-analysis, the OR was of 1.02 (1.01 to 1.03) with an I^2 of 0.0%.[51] Meta-analysis of dichotomous CRP and BASDAI50 in six articles showed an OR of 2.14 (1.71 to 2.68) with an I^2 of 22.4% (figure 3D), and no risk of publication bias (p=0.267).[28 33–35 50 59] High levels of serum amyloid A presented an association with better response in one study.[31] Erythrocyte sedimentation rate (ESR) showed contradictory results in two studies.[26 31] High levels of interleukin (IL)-6 at baseline were related with ASAS but not with BASDAI50 response.[47 59 60] Other biomarkers such as matrix metalloproteinase-3 (MMP-3),

osteocalcin, insulin, leptin, tissue inhibitor of metalloproteinases 1, apolipoprotein CIII, IgM, N-terminal propeptide of type 1collagen (P1NP), deoxypyridinoline and vascular endothelial growth factor were not consistently associated with response.[27 47 59 60]

Twelve studies analysed serological factors as predictor of response in PsA.[61 62 64 67–70 75 77 80 81] Nine articles included CRP as a predictor of response, and presented significant association with ACR and MDA response, but this was contradictory with EULAR response.[62 63 67–70 75 77 80] No significant results were observed in four studies that analysed ESR.[64 68 69 70] In two studies, MMP-3 levels have contradictory results.[61 81] Elevated baseline C3 complement levels showed poor association with response in one study.[62] Other biomarkers such as adiponectin, ENRAGE (S100A12), IgA, IL-16, insulin and serum glutamic oxaloacetic transaminase were associated with EULAR response but not with ACR20. In contrast, pyridinoline showed association with ACR20 response but not with EULAR response.[81]

Genetic factors

Twelve articles analysed genetic factors as predictors of response to TNF antagonists in AS.[1 25 26 32 35 43 46 50–52 54 57] Human leucocyte antigen B27 (HLA-B27) was investigated in nine articles with contradictory results.[1 25 26 32 35 46 50–52] Meta-analysis of HLA-B27 and ASAS20 in three studies showed an OR of 2.81 (0.95 to 7.16) with an I^2 of 81.5% (figure 4A), and no risk of publication bias (p=0.075).[1 25 26] No factor was

identified as a source of heterogeneity. Meta-analysis of HLA-B27 and ASAS40 in three studies showed an OR of 1.83 (1.39 to 2.42) with an I^2 of 0.0% (figure 1B), and no risk of publication bias (p=0.628).[25 35 50] Meta-analysis of HLA-B27 and BASDAI50 in three studies,[35 46 51] and subgroups of other study,[52] showed an OR of 1.81 (1.35 to 2.42) with an I^2 of 0.0% (figure 1C), and no risk of publication bias (p=0.074). No association was shown between −308 TNF gene polymorphism and BASDAI response.[54 57] Association was reported of the rs396991 Fc γ-receptor (FCGR) 3A polymorphism with BASDAI50 response.[43]

Two studies analysed potential genetic predictors of response in PsA.[43 77] FCGR3A was reported not to be associated with response to all TNF antagonists in two studies.[43 77] However, significant results were observed in a subanalysis of etanercept, but not monoclonal antibodies.[77]

DISCUSSION

Our review showed that age, gender, baseline BASDAI, baseline BASFI, CRP and HLA-B27 predicts response to TNF antagonists in patients with AS. In contrast, robust predictors of response in PsA were not identified.

In RA, observational studies have suggested that smokers have a poorer response to TNF antagonists than ex-smokers or never smokers.[16 82] Higher HAQ baseline has also been related to poor response.[13 14 16 82] Other possible predictors of remission with TNF antagonists such as age or gender have been proposed.[13 15 82] Better response in younger patients and poor clinical response in women in our meta-analysis of AS was previously reported in patients with RA treated with TNF antagonists.[15 17] Studies in PsA also suggest poor response in women, but this could not be confirmed in our meta-analysis.

High BASDAI and high CRP levels predict better response in AS. This could indicate that a subgroup of patients with higher baseline activity may have more benefit from treatment with TNF antagonists. In contrast, BASFI baseline levels are inversely related to response, possibly due to the fact that high BASFI is related in part with established disease and radiological damage. In-line with this, syndesmophytes have also been related with poor response.[55] HAQ was also related
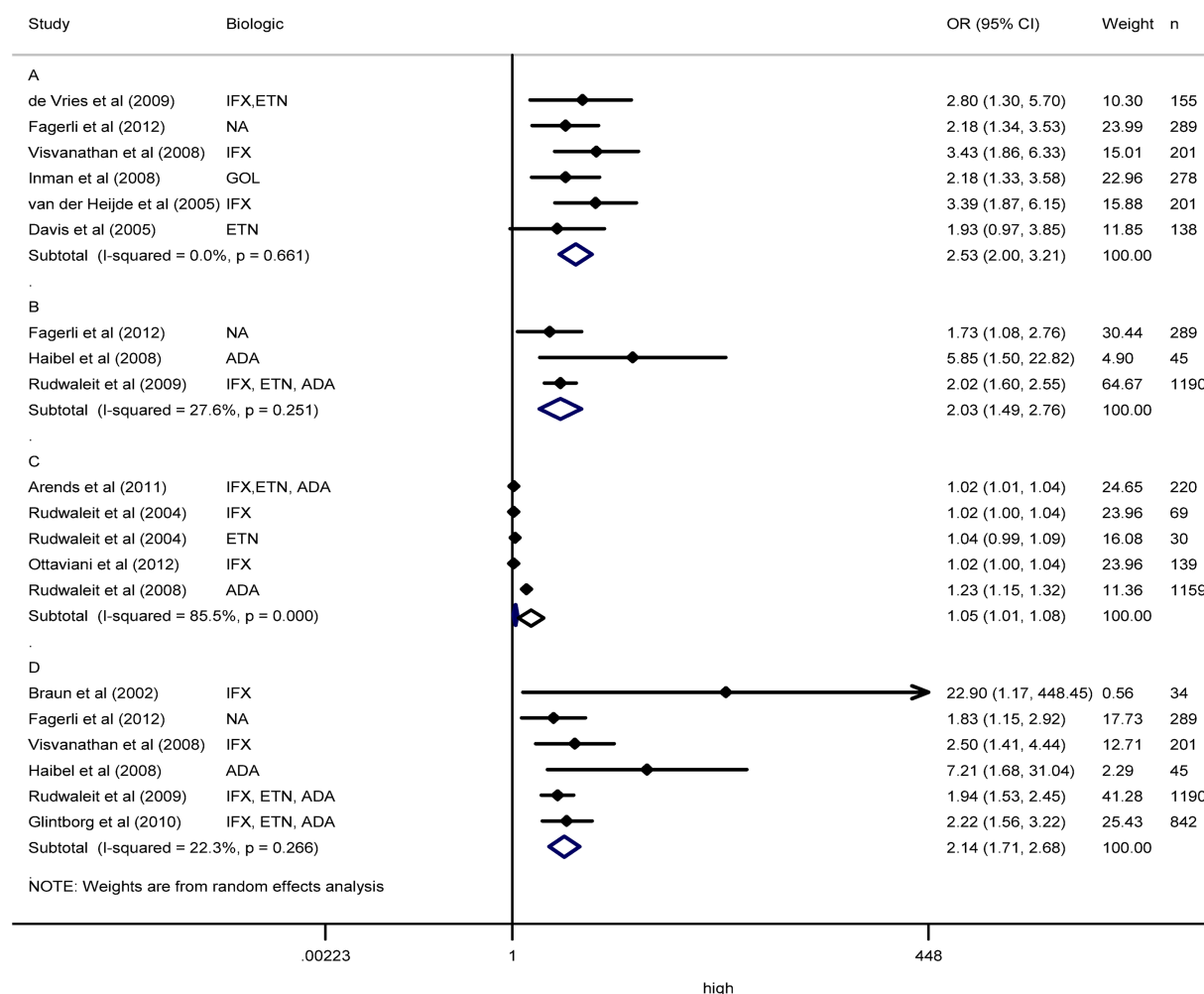

Figure 3 Meta-analysis of C reactive protein (CRP) as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of dichotomous CRP and ASAS20 in AS. (B) Meta-analysis of dichotomous CRP and ASAS40 in AS. (C) Meta-analysis of continuous CRP and BASDAI in AS. (D) Meta-analysis of dichotomous CRP and BASDAI50 in AS. NA: not available.

with poor response in RA and perhaps PsA, as suggested by the individual articles in our review.[13 14]

In AS and PsA, data from clinical trials have suggested that use of concomitant DMARD does not add benefit to the treatment with TNF antagonists in monotherapy.[4 72 73] This is supported by our meta-analysis. Nevertheless, it is reported that the use of concomitant DMARDs decreases the development of antidrug antibodies, and this may be reflected by a lower rate of discontinuation of the biological for any cause.[83]

Positive HLA-B27 predicts better response to TNF antagonists in patients with AS. TNF is associated with activation of the HLA-B27promoter, and TNF has a pivotal role in the inflammatory component of spondyloarthritis.[84] This is consistent with findings from animal model studies, in which a blockade of TNF is related with prevention of IBD and enthesitis in HLA-B27 transgenic rats.[85 86] Several other biomarkers of inflammation were found to be related to TNF antagonist response in AS and PsA, but only in a small number of observations. This should be confirmed in subsequent studies.

The principal limitation of the meta-analyses was the variance in the design of studies included in the analysis (clinical trials, and prospective and retrospective observational studies). Furthermore, none of the clinical trials were designed to test the studied association and, thus, they were somehow similar to an observational prospective study regarding risk of bias. In observational studies there is a potential for bias from unmeasured confounding. There is some disagreement on whether meta-analyses should be restricted to include only randomised clinical trials. However, observational studies often represent the best available evidence. Observational studies are thought to over-estimate treatment or exposure effects. Nevertheless, meta-analyses of observational studies continue to be valuable and are commonly used for assessing efficacy and effectiveness, and are increasingly being published in the scientific literature.[87] Our review is of predictor factors of response, but not of efficacy. Although the study design is important, there are many other factors influencing the reporting of predictors. The validated Hayden checklist assesses how each study meets the research question (not related to efficacy). All RCTs were of efficacy and predictive variables were not the primary variables. The use of random effects computing summary OR may have potentially accounted for this drawback. Also, to minimise this issue, our analysis of heterogeneity includes not only quality of data but design and level of evidence of the studies. Heterogeneity may help to point out factors that influence the results of the outcome that
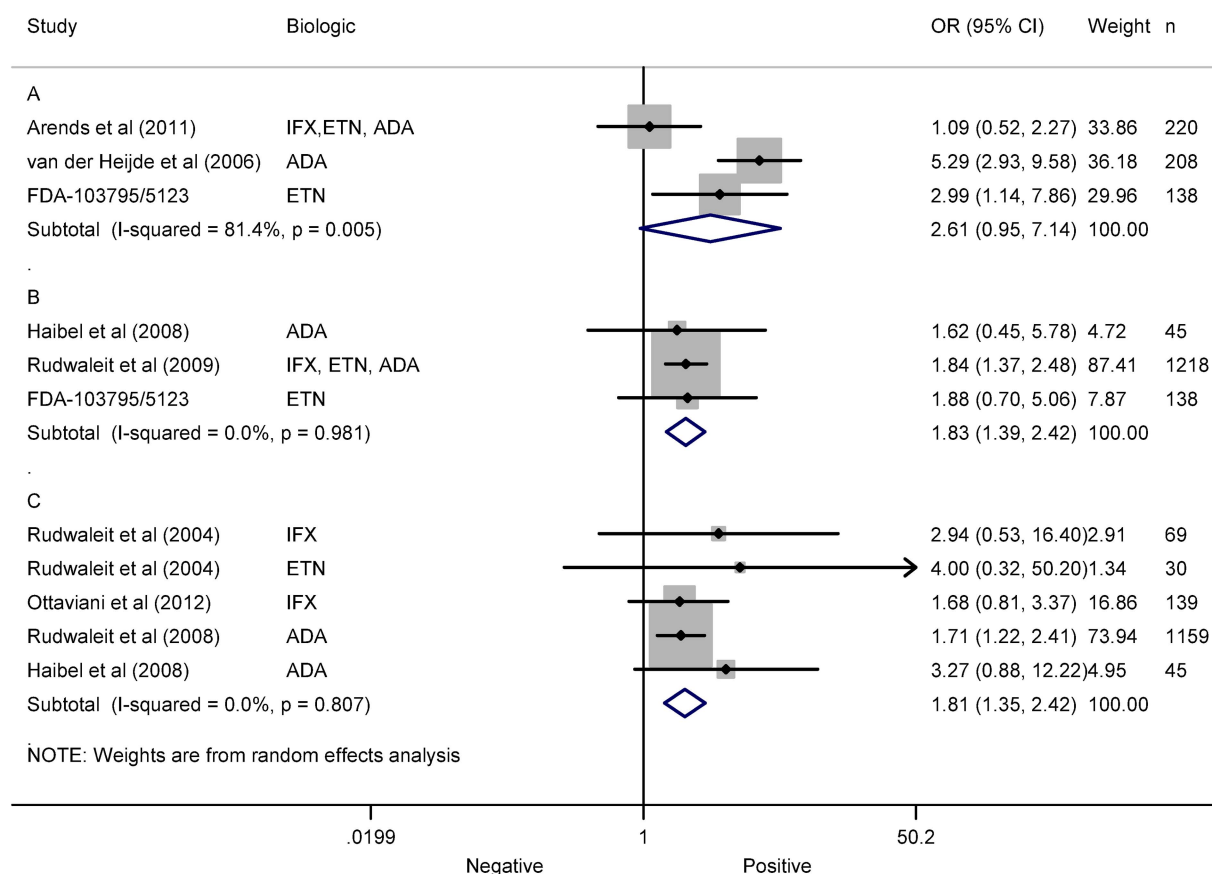

Figure 4 Meta-analysis of human leucocyte antigen B27 (HLAB27) as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of HLAB27 and ASAS20 in AS. (B) Meta-analysis of HLAB27 and ASAS40 in AS. (C) Meta-analysis of HLAB27 and BASDAI50 in AS.

were not observable in individual trials.[88][89] Our statistics included analysis of heterogeneity, risk of bias and quality of data with stringent predefined criteria. The quantitative scales are main tools for assessing risk of bias. The Hayden scale in our study is appropriate because it allows for evaluation of the risk of bias as a relevant variable to identify causes of heterogeneity. Sensitivity analysis was carried out by stratification of meta-analyses by variable causing heterogeneity. Although OR is not the best estimate of association, we used OR because it is readily estimated from the different studies. The review identifies several possible predictors in PsA. However, no conclusive predictors were identified due to the limited number of studies and the heterogeneity of response measures. Also, it is not possible to know whether CRP quantification was carried out using similar or different techniques, and meta-analyses of dichotomous CRP included different cut-offs. Finally, although the findings of some meta-analyses should be interpreted with caution because of the risk of publication bias, our study has several strengths including good consistency of results and inclusion of approximately 60% of studies of high quality.

In conclusion, younger, male sex, high baseline BASDAI, low baseline BASFI, high CRP baseline and positive HLA-B27 predict individually better response in AS. In contrast, no conclusive predictors of PsA are identified.

REFERENCES

1. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.
2. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;356:385–90.
3. Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003;48:1667–75.
4. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005;64:1150–7.
5. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014;73:39–47.
6. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73:48–55.
7. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60:976–86.
8. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;48:2122–7.
9. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;69:380–6.
10. Perez-Sola MJ, Torre-Cisneros J, Perez-Zafrilla B, et al. Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry. *Med Clin (Barc)* 2011;137:533–40.
11. Gottlieb A, Menter A, Mendelsohn A, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009;373:633–40.
12. Schett G, Wollenhaupt J, Papp K, et al. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2012;64:3156–67.
13. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* 2006;45:1558–65.
14. Kristensen LE, Kapetanovic MC, Gulfe A, et al. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 2008;47:495–9.
15. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al; GISEA group. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. *J Rheumatol* 2007;34:1670–3.
16. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. *J Rheumatol* 2009;36:1180–7.
17. Radovits BJ, Kievit W, Fransen J, et al. Influence of age on the outcome of antitumour necrosis factor alpha therapy in rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1470–3.
18. Maneiro RJ, Salgado E, Carmona L, et al. Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum* 2013;43:9–17.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
20. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
22. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
24. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
25. Department of Health & Human Services. Food & Drug Administration. 103795/5123, Etanercept in Ankylosing Spondylitis. Medical Review. 2003. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/103795–5123_Enbrel_medr.pdf

26. Arends S, Brouwer E, van der Veer E, *et al*. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011;13:R94.

27. Arends S, van der Veer E, Groen H, *et al*. Serum MMP-3 level as a biomarker for monitoring and predicting response to etanercept treatment in ankylosing spondylitis. *J Rheumatol* 2011;38:1644–50.

28. Braun J, Brandt J, Listing J, *et al*. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187–93.

29. Braun J, Rudwaleit M, Kary S, *et al*. Clinical manifestations and responsiveness to adalimumab are similar in patients with ankylosing spondylitis with and without concomitant psoriasis. *Rheumatology (Oxford)* 2010;49:1578–89.

30. Davis JC, van der Heijde D, Dougados M, *et al*. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. *J Rheumatol* 2005;32:1751–4.

31. de Vries MK, van Eijk IC, van der Horst-Bruinsma IE, *et al*. Erythrocyte sedimentation rate, C-reactive protein level, and serum amyloid a protein for patient selection and monitoring of anti-tumor necrosis factor treatment in ankylosing spondylitis. *Arthritis Rheum* 2009;61:1484–90.

32. Fagerli KM, Lie E, Heiberg MS, *et al*. Predictors of ASDAS major improvement in patients with ankylosing spondylitis receiving their first TNF inhibitor. Results rrom a longitudinal observational study. *Arthritis Rheum* 2011;63:S204–5.

33. Fagerli KM, Lie E, van der Heijde D, *et al*. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. *Rheumatology* 2012;51:1479–83.

34. Glintborg B, Ostergaard M, Krogh NS, *et al*. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010;69:2002–8.

35. Haibel H, Rudwaleit M, Listing J, *et al*. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008;58:1981–91.

36. Huang F, Zhu J, Zhang L, *et al*. Response to one infusion predicts subsequent improvement as well as the rate of relapse of ankylosing spondylitis infused with three pulses of infliximab. *Clin Rheumatol* 2007;26:920–6.

37. Inman RD, Davis JC Jr, Heijde D, *et al*. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008;58:3402–12.

38. Kim TH, Stone M, Payne U, *et al*. Cartilage biomarkers in ankylosing spondylitis: relationship to clinical variables and treatment response. *Arthritis Rheum* 2005;52:885–91.

39. Kristensen LE, Karlsson JA, Englund M, *et al*. Presence of peripheral arthritis and male sex predicting continuation of anti-tumor necrosis factor therapy in ankylosing spondylitis: an observational prospective cohort study from the South Swedish Arthritis Treatment Group Register. *Arthritis Care Res (Hoboken)* 2010;62:1362–9.

40. Lord PA, Farragher TM, Lunt M, *et al*. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)* 2010;49:563–70.

41. Luc M, Gossec L, Ruyssen-Witrand A, *et al*. C-reactive protein predicts tumor necrosis factor-alpha blocker retention rate in axial ankylosing spondylitis. *J Rheumatol* 2007;34:2078–81.

42. Maria Lizzio M, Peluso G, Zoli A, *et al*. Analysis of response to infliximab in ankylosing spondylitis according to the axial and/or peripheral involvement: autoantibodies and drop outs are more frequent in the peripheral subset. *Ann Rheum Dis* 2007;66:427–8.

43. Morales-Lara MJ, Conesa-Zamora P, Garcia-Simon MS, *et al*. Association between the FCGR3A V158F polymorphism and the clinical response to infliximab in rheumatoid arthritis and spondyloarthritis patients. *Scand J Rheumatol* 2010;39:518–20.

44. Mulleman D, Lauferon F, Wendling D, *et al*. Infliximab in ankylosing spondylitis: alone or in combination with methotrexate? A pharmacokinetic comparative study. *Arthritis Res Ther* 2011;13:R82.

45. Navarro-Compan V, Ariza-Ariza R, Mondejar-Garcia R, *et al*. Metalloproteinase-3 (MMP-3) is a predictor for anti-TNF-alpha response in patients with ankylosing spondylitis (AS). *Clin Exp Rheumatol* 2012;30:638.

46. Ottaviani S, Allanore Y, Tubach F, *et al*. Body mass index influences the response to infliximab in ankylosing spondylitis. *Arthritis Res Ther* 2012;14:R115.

47. Pedersen SJ, Sorensen IJ, Garnero P, *et al*. ASDAS, BASDAI and different treatment responses and their relation to biomarkers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis treated with TNFalpha inhibitors. *Ann Rheum Dis* 2011;70:1375–81.

48. Perez-Guijo VC, Cravo AR, Castro Mdel C, *et al*. Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. *Joint Bone Spine* 2007;74:254–8.

49. Ramiro S, Machado P, Roque R, *et al*. Predictive factors of response at 12 weeks in patients with ankylosing spondylitis starting biological therapies—results from the portuguese register—Reuma.Pt. *Clin Exp Rheumatol* 2012;30:641–2.

50. Rudwaleit M, Claudepierre P, Wordsworth P, *et al*. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36:801–8.

51. Rudwaleit M, Claudepierre P, Wordsworth P, *et al*. Predictors of good clinical response (BASDAI 50 or ASAS partial remission) in 1,250 patients treated with adalimumab (humira (R)) for active ankylosing spondylitis (AS). *Clin Exp Rheumatol* 2008;26:744.

52. Rudwaleit M, Listing J, Brandt J, *et al*. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:665–70.

53. Rudwaleit M, Schwarzlose S, Hilgert ES, *et al*. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Ann Rheum Dis* 2008;67:1276–81.

54. Seitz M, Wirthmuller U, Moller B, *et al*. The -308 tumour necrosis factor-alpha gene polymorphism predicts therapeutic response to TNFalpha-blockers in rheumatoid arthritis and spondyloarthritis patients. *Rheumatology* 2007;46:93–6.

55. Sieper J, van der Heijde D, Dougados M, *et al*. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;71:700–6.

56. Stone MA, Payne U, Pacheco-Tena C, *et al*. Cytokine correlates of clinical response patterns to infliximab treatment of ankylosing spondylitis. *Ann Rheum Dis* 2004;63:84–7.

57. Tong Q, Zhao DB, Bajracharya P, *et al*. TNF-alpha -857 and -1031 polymorphisms predict good therapeutic response to TNF-alpha blockers in Chinese Han patients with ankylosing spondylitis. *Pharmacogenomics* 2012;13:1459–67.

58. van der Heijde D, Dijkmans B, Geusens P, *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52:582–91.

59. Visvanathan S, Wagner C, Marini JC, *et al*. Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. *Ann Rheum Dis* 2008;67:511–17.

60. Wagner C, Visvanathan S, Braun J, *et al*. Serum markers associated with clinical improvement in patients with ankylosing spondylitis treated with golimumab. *Ann Rheum Dis* 2012;71:674–80.

61. Chandran V, Shen H, Pollock R, *et al*. Soluble biomarkers predict response to anti-tumour necrosis factor (TNF) therapy in psoriatic arthritis (PsA). *Arthritis Rheum. 2009; Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 09 Atlanta, GA United States.* Conference Start: 20101106 Conference End: 20101111. Conference Publication: (var.pagings). 60:1778.

62. Chimenti MS, Perricone C, Graceffa D, *et al*. Complement system in psoriatic arthritis: a useful marker in response prediction and monitoring of anti-TNF treatment. *Clin Exp Rheumatol* 2012;30:23–30.

63. di Minno MN, Peluso R, Iervolino S, *et al*. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. *Arthritis Care Res (Hoboken)* 2013;65:141–7.

64. Eder L, Chandran V, Schentag CT, *et al*. Time and predictors of response to tumour necrosis factor-alpha blockers in psoriatic arthritis: an analysis of a longitudinal observational cohort. *Rheumatology (Oxford)* 2010;49:1361–6.

65. Gladman DD, Mease PJ, Choy EH, *et al*. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. *Arthritis Res Ther* 2010;12:R113.

66. Gladman DD, Mease PJ, Ritchlin CT, *et al*. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007;56:476–88.

67. Glintborg B, Ostergaard M, Dreyer L, *et al*. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011;63:382–90.

68. Gratacos J, Casado E, Real J, *et al*. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. *Ann Rheum Dis* 2007;66:493–7.

69. Iannone F, Fanizzi R, Scioscia C, *et al*. Body mass does not affect the remission of psoriatic arthritis patients on anti-TNF-alpha therapy. *Scand J Rheumatol* 2013;42:41–4.

70. Iervolino S, Di Minno MN, Peluso R, *et al*. Predictors of early minimal disease activity in patients with psoriatic arthritis treated with tumor necrosis factor-alpha blockers. *J Rheumatol* 2012;39:568–73.

71. Karanikolas GN, Koukli EM, Katsalira A, *et al*. Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: results from a prospective 12-month nonrandomized unblinded clinical trial. *J Rheumatol* 2011;38:2466–74.

72. Kavanaugh A, Krueger GG, Beutler A, *et al*. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis* 2007;66:498–505.

73. Kavanaugh A, van der Heijde D, McInnes IB, *et al*. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum* 2012;64:2504–17.

74. Kristensen LE, Gulfe A, Saxne T, *et al*. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008;67:364–9.

75. Marotta A, Van Kuijk AW, Maksymowych WP, *et al*. 14-3-3 Eta is a modifiable serum biomarker that marks adalimumab response in psoriatic arthritis. *Arthritis Rheum. 2012 October; Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals 2012 Washington, DC United States*. Conference Start: 20121109 Conference End: 20121114. Conference Publication: (var.pagings). 64:S247.

76. Mease PJ, Gladman DD, Ritchlin CT, *et al*. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279–89.

77. Ramirez J, Fernandez-Sueiro JL, Lopez-Mejias R, *et al*. FCGR2A/CD32A and FCGR3A/CD16A variants and EULAR response to tumor necrosis factor-alpha blockers in psoriatic arthritis: a longitudinal study with 6 months of followup. *J Rheumatol* 2012;39:1035–41.

78. Saber TP, Ng CT, Renard G, *et al*. Remission in psoriatic arthritis: is it possible and how can it be predicted? *Arthritis Res Ther* 2010;12:R94.

79. Spadaro A, Ceccarelli F, Scrivo R, *et al*. Life-table analysis of etanercept with or without methotrexate in patients with psoriatic arthritis. *Ann Rheum Dis* 2008;67:1650–1.

80. Van den Bosch F, Manger B, Goupille P, *et al*. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. *Ann Rheum Dis* 2010;69:394–9.

81. Wagner CL, Visvanathan S, Elashoff M, *et al*. Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. *Ann Rheum Dis* 2013;72:83–8.

82. Abhishek A, Butt S, Gadsby K, *et al*. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. *J Clin Rheumatol* 2010;16:15–18.

83. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. *JAMA Intern Med* 2013;173:1416–28.

84. Zhao L, Fong Y, Granfors K, *et al*. Identification of cytokines that might enhance the promoter activity of HLA-B27. *J Rheumatol* 2008;35:862–8.

85. Milia AF, Ibba-Manneschi L, Manetti M, *et al*. Evidence for the prevention of enthesitis in HLA-B27/hbeta(2)m transgenic rats treated with a monoclonal antibody against TNF-alpha. *J Cell Mol Med* 2011;15:270–9.

86. Milia AF, Manetti M, Generini S, *et al*. TNFalpha blockade prevents the development of inflammatory bowel disease in HLA-B27 transgenic rats. *J Cell Mol Med* 2009;13:164–76.

87. Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.

88. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* 1992;267:374–8.

89. Biggerstaff BJ, Tweedie RL. Incorporating variability in estimates of heterogeneity in the random effects model in meta-analysis. *Stat Med* 1997;16:753–68.