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EXTENDED REPORT

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

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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.

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 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.

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*[62]	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 I^2 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 I^2 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 I^2 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 I^2 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 I^2 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 I^2 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 I^2 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 I^2 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

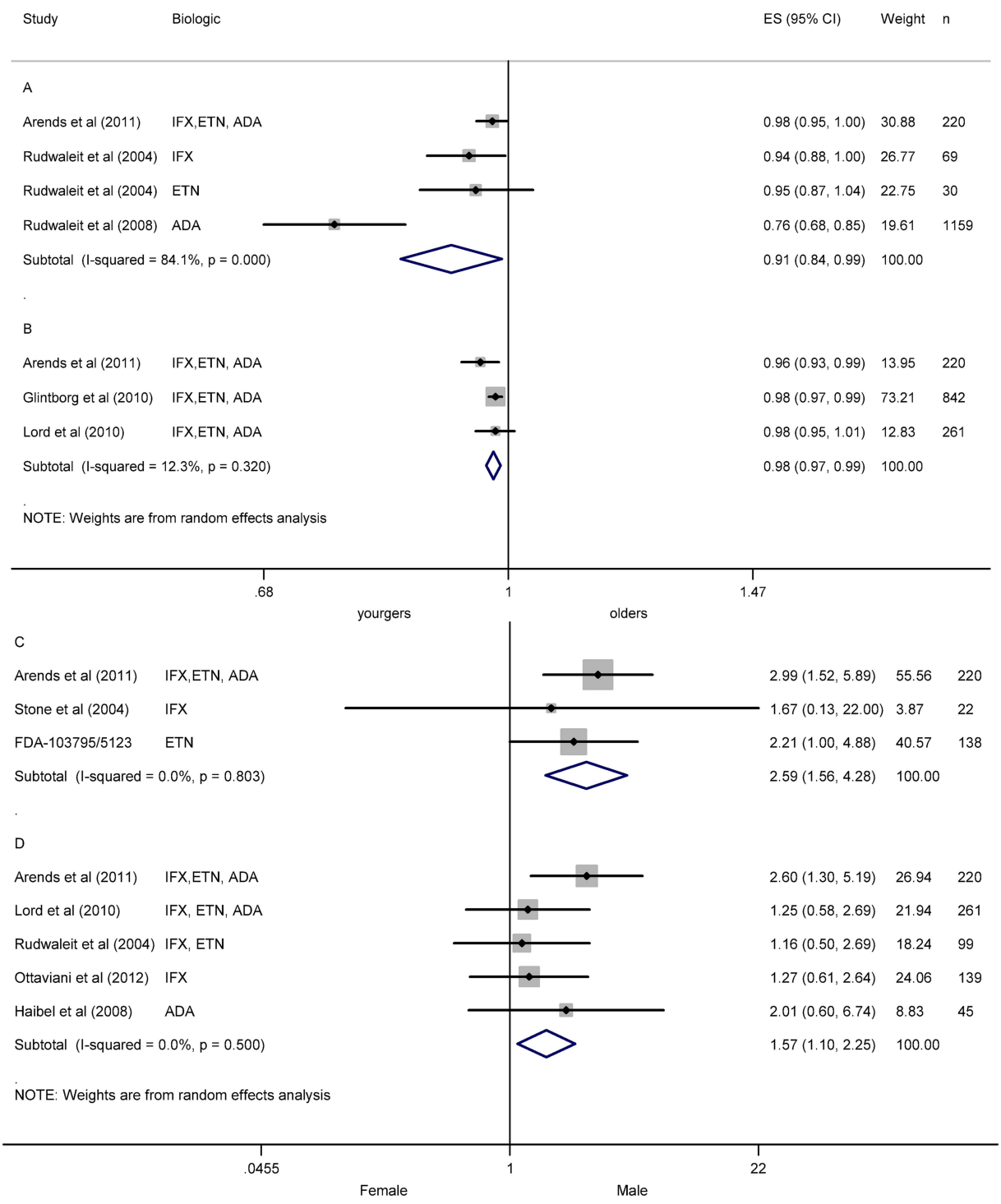

Figure 1 Meta-analysis of demographic factors as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of age and BASDAI50 at week 12 in AS. (B) Meta-analysis of age and BASDAI50 at week 24 in AS. (C) Meta-analysis of gender and ASAS20 in AS. (D) Meta-analysis of gender and BASDAI50 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]

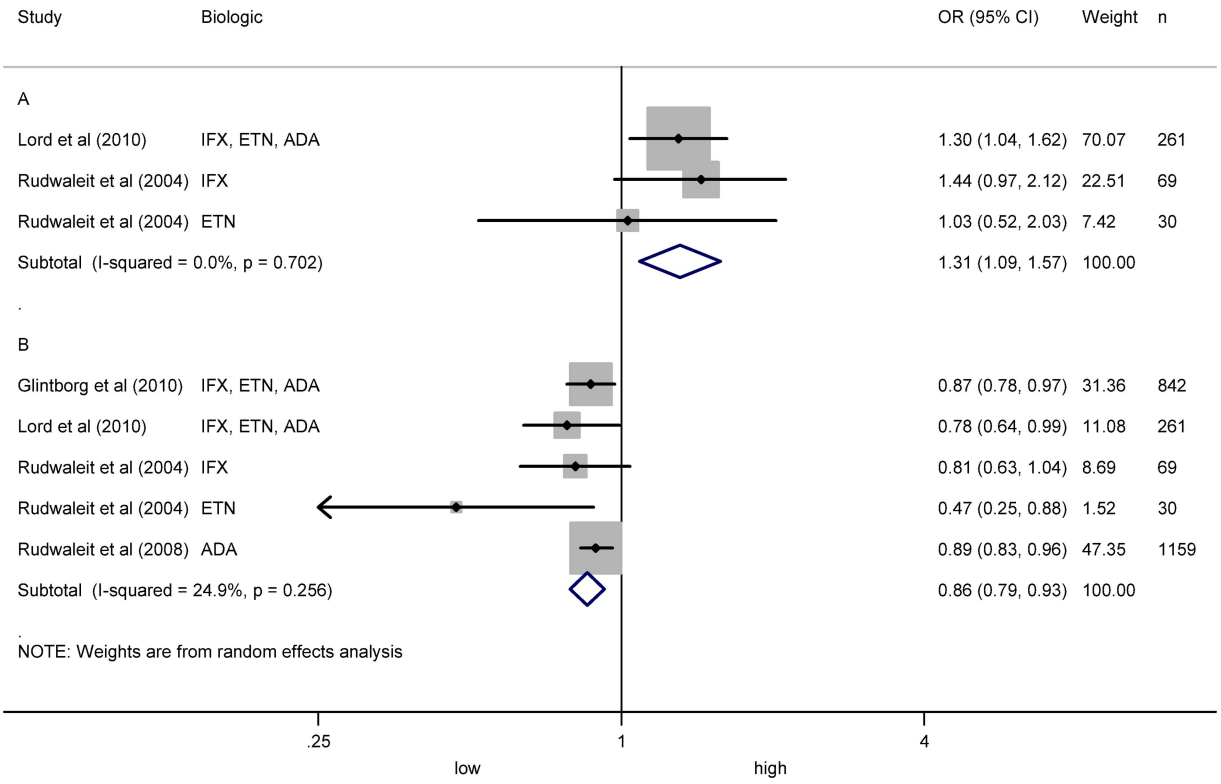

Figure 2 Meta-analysis of BASDAI baseline and BASFI baseline as predictors of response in ankylosing spondylitis (AS). (A) Meta-analysis of BASDAI baseline and BASDAI50 in AS. (B) Meta-analysis of BASFI baseline and BASDAI50 in AS.

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

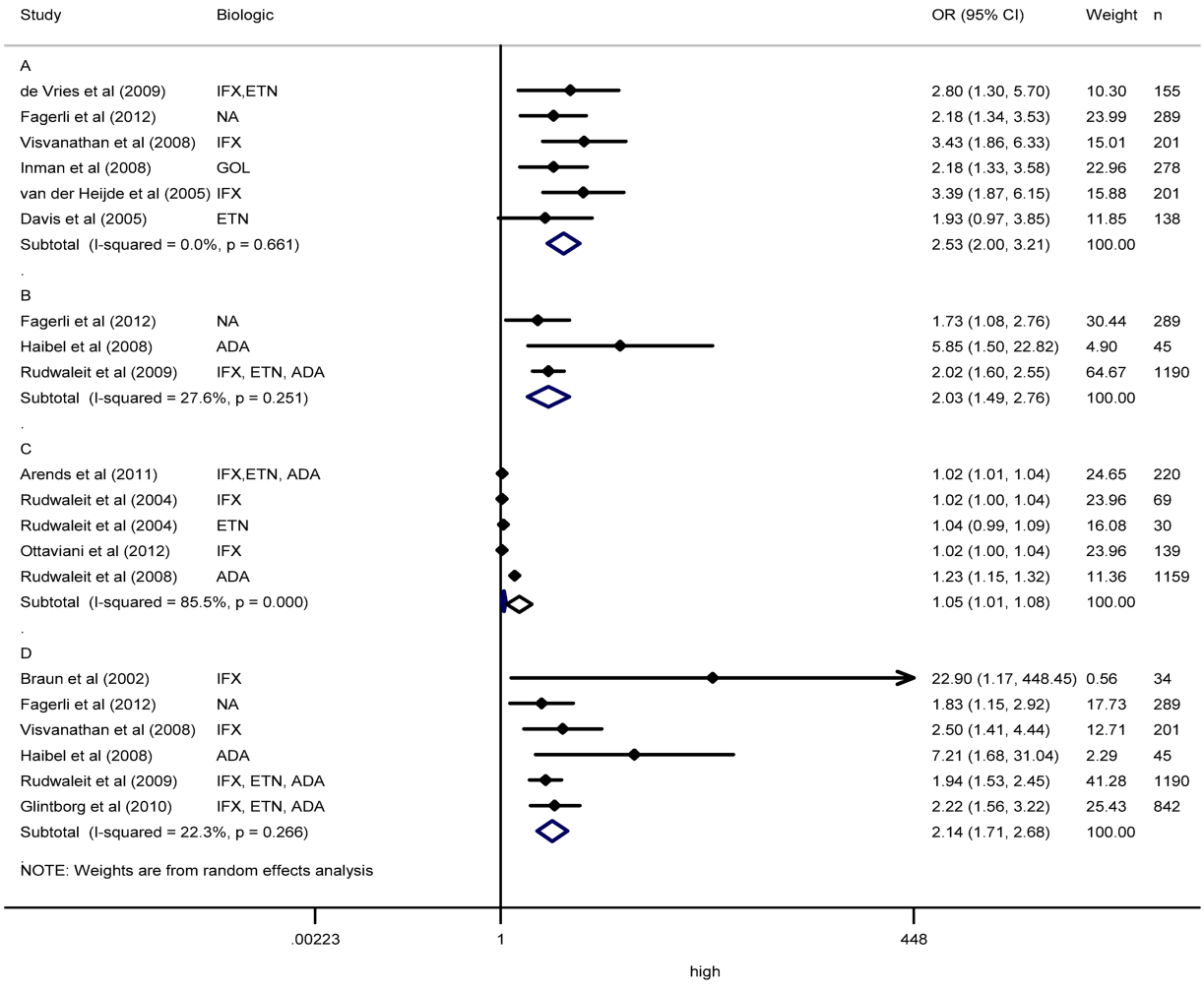

Figure 3 Meta-analysis of C reactive protein (CRP) as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of dichotomous CRP and ASAS20 in AS. (B) Meta-analysis of dichotomous CRP and ASAS40 in AS. (C) Meta-analysis of continuous CRP and BASDAI in AS. (D) Meta-analysis of dichotomous 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

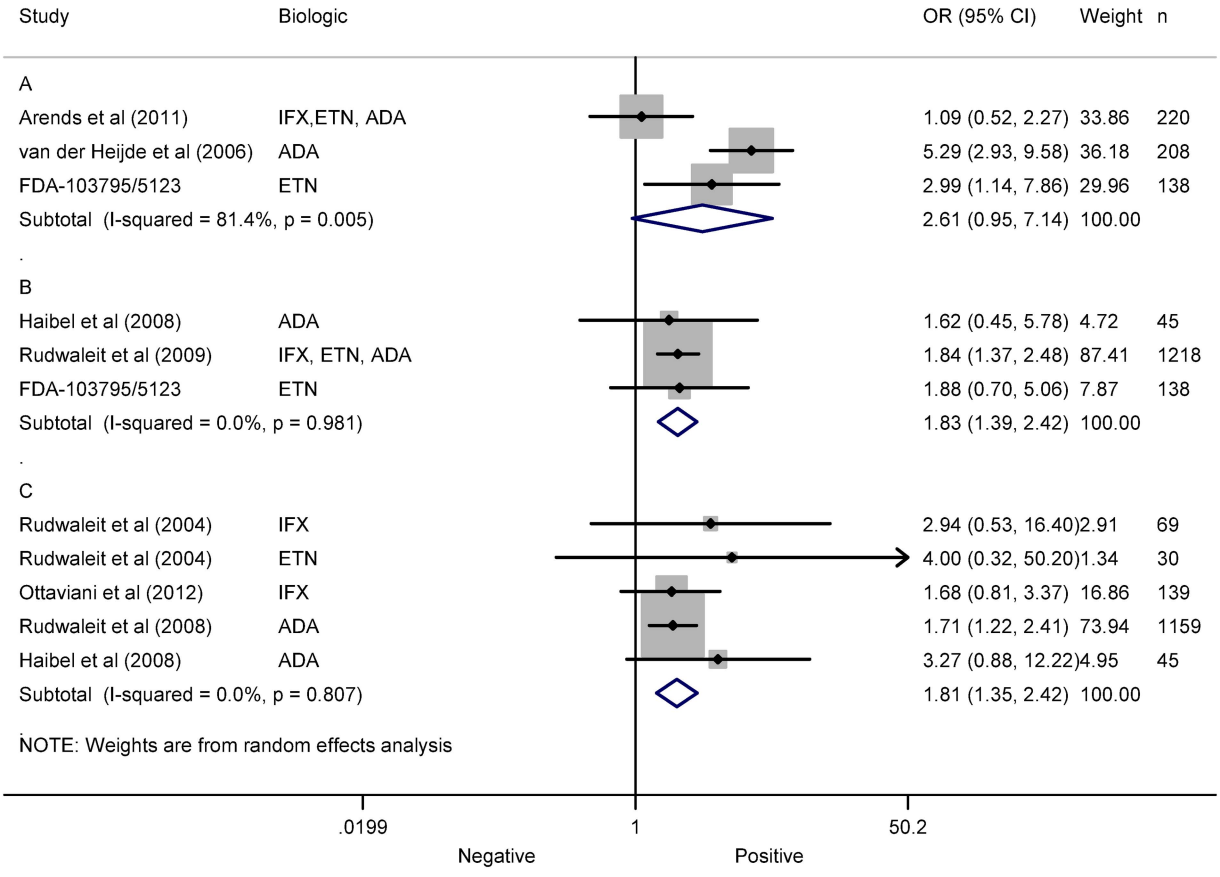

Figure 4 Meta-analysis of human leucocyte antigen B27 (HLAB27) as predictor of response in ankylosing spondylitis (AS). (A) Meta-analysis of HLAB27 and ASAS20 in AS. (B) Meta-analysis of HLAB27 and ASAS40 in AS. (C) Meta-analysis of HLAB27 and BASDAI50 in AS.

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.

Contributors JRM was involved in the data collection, interpretation of data, drafting the article, literature search and selection papers for inclusion. AS was involved in the selection papers for inclusion. ES was involved in the selection papers for inclusion. AM was involved in the study design, interpretation of data, drafting the article and revising it critically for important intellectual content. JJG-R was involved in the conception and study design, interpretation of data, drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be published.

Competing interests JJG-R is on the Advisory Boards of Abbvie, BMS, Pfizer, Roche, MSD and UCB SA; has received lecture fees from Abbvie, BMS, Jansen and Jansen, MSD, Pfizer, Roche and UCB; and has received research grants from Roche, Pfizer, MSD and UCB.

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