Presence of anti-cyclic citrullinated peptide antibodies is associated with better treatment response to abatacept but not to TNF inhibitors in patients with rheumatoid arthritis: a meta-analysis

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Abstract

Objective

The objective of this study was to investigate whether anti-cyclic citrullinated peptide antibody (ACPA) status is associated with clinical responses to abatacept or TNF-α-inhibitors (TNF-α-i) in RA patients.

Methods

A systematic literature review (SLR) was performed in January 2018 to identify published studies and conference abstracts evaluating biologic DMARD response according to ACPA status. Mantel-Haenszel meta-analysis methods were used to pool risk ratios (RRs). In the base-case, treatment response was assessed using EULAR measure, while a scenario analysis assessed response by combining ACR20, DAS28 and EULAR measures. Subgroup analyses were performed for duration of study follow-up.

Results

Eighteen of the 30 SLR studies were included in the meta-analysis. The base-case showed a statistically significant positive association between ACPA positivity and EULAR response for patients treated with abatacept (RR: 1.13 [95% CI: 1.00, 1.26]), while ACPA positivity was associated with lower EULAR responses to TNF-α-i (RR: 0.91 [95% CI: 0.84, 0.98]). For the scenario analysis, results were consistent with the base-case for abatacept (RR 1.18 [95% CI 1.03, 1.35]), while for TNFα-i, no significant difference by ACPA status was observed (RR 0.97 [95% CI 0.86, 1.10]). Subgroups analyses showed results similar to the base-case for both abatacept and TNF-α-i.

Conclusion

This meta-analysis confirms that ACPA-positive RA patients are marginally more likely to achieve EULAR and ACR20 response to abatacept compared to ACPA-negative patients. Additionally, the analysis demonstrates that there is no association between ACPA status and response to TNF-α-i, consistent with findings of previously published studies.

Key words

anti-cyclic citrullinated peptide antibodies, biomarker, abatacept, TNF inhibitors, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that affects up to 1% of the world's population (1). The onset is most frequent between the ages of 35 and 50 and RA occurs more commonly in women than in men (ratio 3:1) (2). Patients with RA suffer from joint pain, which can lead to substantial loss of functioning and mobility resulting in disability and therefore affect quality of life. The burden of RA on patients, their caregivers, and society is substantial (3).

Autoantibodies, such as, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can be detected in serum of RA patients before the onset of symptoms (about 50% of RA patients are ACPA positive) (4, 5). In recent years, research on the role of ACPA in RA pathology has led to the conclusion that ACPA could increase bone destruction and joint inflammation (6-10). However, the direct impact of ACPA on the pathogenesis need further investigation (11).

Globally accepted consensus (12-14) for the management of RA recommend that RA treatment should be initiated with conventional disease-modifying anti-rheumatic drugs (cDMARDs). The most commonly used cDMARDs are methotrexate (MTX), sulfasalazine, hydroxylchloroquine and leflunomide. When monotherapy with cDMARDs leads to an insufficient response, other cDMARDs or biologic (b)DMARDs may be added (12). bDMARDs include abatacept (t-cell modulator), tumour necrosis factor (TNF)-α inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol and golimumab), and bDMARDs with other mechanisms of action such as anakinra (IL-1), rituximab (anti-CD20), and tocilizumab (anti-IL-6).

The results of the AMPLE trial demonstrated comparable efficacy of abatacept and adalimumab combined with MTX through two years of treatment (15). A recent post-hoc subgroup analysis of the AMPLE trial demonstrated improved efficacy of abatacept in patients with higher ACPA titres, a known diagnostic and prognostic biomarker for RA (16). The improved efficacy was observed in both clinical measures (DAS28 remission and ACR20/50/70/90 criteria) and patient-reported outcomes (HAQ-DI and patient global assessment). A US registry (Corrona registry) also showed association between positive ACPA status and treatment response to abatacept but not TNF-α inhibitors. The Corrona registry assessed treatment response with Clinical Disease Activity Index (CDAI), DAS 28 remission rates and ACR20 response rates (17-19). Moreover, data from several registries conducted in Europe demonstrated this association between ACPA positivity and EULAR good/moderate treatment response to abatacept *versus* TNF-α inhibitors (20, 21).

The objective of the present study was to conduct a systematic literature review (SLR) and meta-analysis (MA) to investigate the treatment effectiveness of abatacept and TNF-α inhibitors in RA subgroups based on ACPA status (positive/negative).

Methods

The SLR was performed according to the Preferred Reporting Items in Systematic Reviews and the Meta Analysis (PRISMA) statement. Using predefined search strategies, MEDLINE (through OVID), EMBASE (through OVID), LILACS (through LILACS) were systematically searched from January 1, 1988 to January 2, 2018. The predefined selection criteria were based on the PICOS (Patient population, Intervention, Comparators, Outcomes and Study design) criteria, available in the online supplementary file. Publications on adult human patients (≥18 years) were screened. No restrictions on the language or the publication type were applied (conference abstracts were included). A two-step screening process was applied. First, the relevance of each identified abstract was determined by screening the title and abstract according to predefined selection criteria. Second, full-text publications of selected abstracts were screened again according to pre-set selection criteria. The selection process involved two researchers for screening articles (double-screening). In case of disagreement for the selection of arti-

cles, a third researcher was involved to resolve discrepancies.

The search included RA patients for whom information on ACPA status was provided under patient baseline characteristics. For the intervention, publications on abatacept and TNF-α-inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol) were included regardless of any concomitant MTX use or previous treatments (biologics or other). Outcomes of interest were the American College of Rheumatology (ACR20/50/70) response criteria, the Disease Activity Score-28 (DAS28) remission or response criteria; European League Against Rheumatism (EULAR) response criteria (good or moderate or moderate/good or no response) and the Health Assessment Questionnaire-Disability Index (HAQ-DI) (change from baseline). For the study design, both randomised controlled trials (RCTs) and observational studies were of interest. A critical appraisal of each study was performed using the Quality in Prognosis Studies tool (QUIPS) to have an overview of possible sources of bias (22). Reference lists of the selected articles were cross-checked for relevant citations that the SLR could have missed.

In order to explore any source of outcome heterogeneity, a feasibility assessment was performed with the review of potential confounding factors through available study design and study characteristics parameters (duration of follow-up, ACPA test, age, gender, disease duration, use of MTX, CRP values, CDAI, and Lundex proportion).

The meta-analysis was performed by estimating the pooled risk ratio for a response to anti-TNF-α treatment and/or abatacept by ACPA status. The point estimate of the RR and 95% confidence intervals (CIs) were calculated for each of the included studies using the Mantel Haenszel method for estimating the pooled RR and 95% CI (23). The Mantel Haenszel method has been shown to have better statistical properties when there are few events and is generally preferable to alternative methods, *i.e.* inverse variance and Peto (24).

Base case analyses were performed to investigate the association between ACPA status and response to anti-TNF-α agents or abatacept considering response rates based on the EULAR criteria (25) (good or moderate response; with good response for significant decrease in DAS28 score (>1.2) and a low level of disease activity (≤3.2) and moderate response for decrease in DAS28 score ≤1.2 (but >0.6) or level of disease activity >3.2).

Since most studies reported outcomes based on other composite measures such as ACR, DAS28 response, a scenario analysis assessed the ACPA status/response association based on various definitions of treatment response including ACR20 and EULAR for abatacept and ACR20, DAS28 responses and EULAR for anti-TNF-α therapy. DAS 28 response was defined as DAS 28 improvement criteria. This scenario analyses was initially performed to include all studies eligible for this meta-analysis.

Subgroup analyses were performed according to the follow-up duration of the studies. The heterogeneity of the effect sizes across studies was assessed using the Chi square test and I^2 values.

For the purpose of this analysis, both fixed and random effects models were initially employed and the model selection was data-driven, based on the number of studies included in each analysis. The random effects model was the most appropriate regarding the observational nature of studies included. Therefore, only the random-effects results were interpreted.

Risk of bias assessment

The results of the risk of bias assessment using the QUIPS tool are available in the online supplementary file. For study participation bias, nine of the 30 studies obtained a low risk of bias rating, describing the source of the population, method of recruitment and baseline characteristics to an appropriate level. Studies only available in abstract form were rated as high risk of bias (7 studies), because they did not provide enough information on the participant selection and identification process for judgment. The remaining 14 studies obtained a partial risk of bias judgment, mostly because of a lack of reporting on the source of the population and the method of recruitment.

Study attrition bias investigates the likelihood that the relationship between ACPA status and treatment response is different for completing and non-completing participants. The study attrition domain is likely to be associated with bias among the included studies. Little information is provided on participants that dropped out of the studies and their key characteristics and treatment responses. However, this bias domain is deemed of little influence for the included studies, as they mostly include participants who were part of retrospective databases or registries.

To avoid prognostic factor measurement-bias homogeneity should exist between the measurements of ACPA status among studies. Twelve studies adequately reported the methodology (laboratory kit) and cut-off value of ACPA status. However, the other eighteen studies provided no or partial information on this prognostic factor measurement.

To judge the risk of bias related to outcome measurement the definition of treatment response and validity of the definition is assessed. Except for the some of the studies available in abstract form only, all studies properly defined treatment response and used widely accepted response criteria. Even though, response was measured the same for all participants within studies, between study heterogeneity existed. Different treatment response measures were used across studies, such as DAS28 response, EULAR response and ACR20 response criteria.

Besides ACPA status, other factors can influence treatment response, such as age, disease severity and duration and previous medical treatment, bias can occur when not all confounding factors are measured and accounted for. Most studies gathered data on confounding factors; however, they were poorly defined and imputation methods for missing data were often not described.

Lastly, statistical analysis and presentation bias was assessed. The majority of studies adequately described the statistical analyses that were performed and did not seem selective in reporting

results. A major drawback of including studies only available as conference abstracts is limited reporting on methodology; consequently, these studies obtained a partial risk of bias judgment. Overall, most studies were of reasonable quality and some bias is expected mainly due to poor reporting of participation selection, study attrition and prognostic factor measurement. The results of the meta-analysis presented should therefore be interpreted with caution.

Results

Systematic literature review

The study selection process is depicted in Figure 1. EMBASE, Medline and LILACS databases provided 1,172 abstracts for studies on RA subgroups according to ACPA status/levels. Of these, 312 were identified as duplicates between databases based on identical titles, authors and journal details (name, volume, issue, and page numbers), leaving 872 unique abstracts for review. As shown in Figure 1, most records at the first screening phase were excluded because of inappropriate study design (349 records), followed by irrelevant patient population (229 records) and research on an intervention not of interest (43 records). After the first screening phase, 239 records were included and full text publications were obtained for the second screening step. Among the included studies, 80 records were conference abstracts for which complete posters were searched. The poster search returned no results; therefore, the decision on inclusion or exclusion of conference proceedings was based solely on the abstract.

During the second screening step, 206 records were excluded; most did not report outcomes of interest (109 studies), used an inappropriate study design (58 studies), or unfit patient population (12 studies), or studied an intervention not of interest (15 studies). After the second step review, 34 publications covering 30 studies were identified and provided the evidence base for data-extraction.

The SLR study characteristics are reported in Table I. Ten out of the 30 studies investigated the effectiveness of abatacept in ACPA subgroups: seven were single arm studies (20, 26-31) and three studies compared abatacept to TNF-α inhibitors (16, 19, 32). Eight studies investigated infliximab, adalimumab, and etanercept, either by combining the three treatments into one TNF-α inhibitor group (33-38) or by separating them (39, 40). One study (41) provided effectiveness results for both the combined TNF-α inhibitor group and the individual treatments. The remaining 11 studies focused on one of the treatments of interest, *i.e.* one study (42) on etanercept, six studies (43-48) on infliximab and four studies (49-52) on adalimumab. Out of all studies, 26 were observational cohort studies, while three were observational case-control studies and one was an RCT (16). Twenty-two studies included a comparison between ACPA-positive and ACPA-negative RA subgroups; five studies (16, 33, 36, 44, 48) included comparisons between different ACPA levels, one study (40) included a comparison between ACPA-positive good/moderate EULAR responders and no EULAR responders and two studies (41, 52) included data only on ACPA-positive patients.

The sample size varied among the identified studies, with the largest cohort size being 2,281 patients (19). The reported outcomes were similar across studies, with the most prevalent outcome being DAS28 response/remission (15 studies), followed by EULAR response (13 studies). The duration of follow-up varied from 12 weeks (35-37, 41) to 260 weeks (31) (5 years). Lastly, the ACPA cut-off value for positivity varied across studies. Although the most widely used test was the ELISA kit, the cut-off values ranged from 4.5 U/ml (28, 30, 35) to 25 U/ml (16, 44, 45, 49, 51).

Patient characteristics of included studies are shown in Table II. Most studies reported baseline data on age, gender, ACPA status, DAS28 score, concomitant MTX use, disease duration and prior biologics. The age of patients varied at a range between 19 and 83 years, with the highest mean age being 63.2 years (28). In all studies, the proportion of female patients and ACPA-positive patients was higher than proportion of males, and ACPA-negative patients, respectively. Mean DAS 28 score at baseline was between 4.4 (27) and 5.4 (35) for DAS28-CRP and between 5.0 (20) and 12.2 (40) for DAS28-ESR. The percentage of patients using concomitant MTX ranged between 15% of patients receiving adalimumab (36) to 100% of patients receiving infliximab in four studies (32, 39, 43, 46) and adalimumab

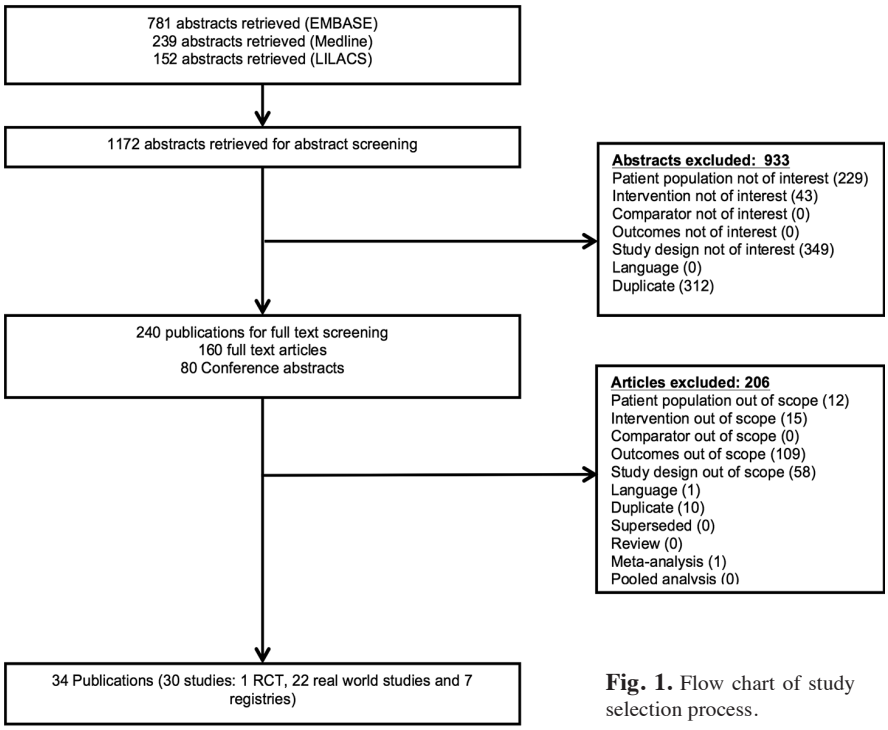

Fig. 1. Flow chart of study selection process.

Table I. SLR study characteristics.

Author / year	Treatment	Comparison	Sample size	Study design	Efficacy outcomes	Duration of follow-up	ACPA test	ACPA cut-off value
Canhao 2012[40]	adalimumab; etanercept; infliximab	ACPA-positive *vs*. negative	617	Cohort study	Primary: EULAR response; Secondary: Time to EULAR good response	1 year	NR	NR
Sato 2014[29] (abstract)	abatacept	ACPA-positive *vs*. negative	45	Cohort study	EULAR response	24 weeks	ELISA kit	NR
Sato 2014[32] (abstract)	infliximab; tocilizumab; abatacept	ACPA-positive *vs*. negative	295	Cohort study	DAS28ESR remission; achievement of Boolean based remission criteria and its components	52 weeks	NR	NR
Matsutani 2013[30] (abstract)	abatacept	ACPA-positive *vs*. negative	45	Case-control study	DAS28-CRP remission rate; DAS28-CRP CFB	24 weeks	Elia CCP; ELISA kit	>4.5U/mL
Smolen 2011[42] (abstract)	etanercept + MTX	ACPA-positive *vs*. negative ACPA >3 x ULN *vs*. ≤3 x ULN	758	Cohort study	DAS28 remission ; SDAI remission; CDAI remission	36 weeks	NR	NR
Takahashi 2011[33] (abstract)	infliximab; etanercept; tocilizumab; adalimumab	ACPA low titres (<100 U/mL) ACPA moderate titres (100-499 U/mL) ACPA high titres (500 U/ml)	64	Cohort study	EULAR response; DAS28-ESR	14 weeks	ELISA kit	ACPA low titres (<100 U/mL); ACPA moderate titres (100-499 U/mL); ACPA high titres (500 pg/ml)
Klaasen 2009[45] (abstract)	infliximab	ACPA-positive *vs*. negative	104	Cohort study	DAS28 response	16 weeks	ELISA kit	>25 U/ml
Potter 2009[34]	etanercept; infliximab; adalimumab	ACPA-positive *vs*. negative	642	Cohort study	Primary: DAS28 CFB; Secondary: EULAR response	5 years	Diastat Anti-CCP kit	≥5 U/μL
Bobbio-Pallavicini 2007[39]	infliximab + MTX; etanercept ± MTX; adalimumab ± MTX/leflunomide	ACPA-positive *vs*. negative	132	Cohort study	EULAR response; ACR20 response	1 year	ELISA kit	≥5 U/mL
Avila-Pedretti 2015[41]	infliximab; etanercept; adalimumab	ACPA-positive only	348	Cohort study	EULAR response; DAS28 activity score	12 weeks	NR	NR
Takahashi 2014[35] (abstract)	infliximab; etanercept; adalimumab; tocilizumab	ACPA-positive *vs*. negative ACPA low titre (<100 U/mL) *vs*. ACPA moderate titre (100-499 U/mL) *vs*. ACPA high titre (≥500 U/mL)	57	Cohort study	EULAR response; DAS28 remission	12 or 14 weeks	STACIA® MEBLux™ CCP test	>4.5 U/mL
Pomirleanu 2013[36]	adalimumab; etanercept; infliximab	Anti-CCP level at baseline <40 IU/mL *vs*. ≥40 IU/mL	90	Cohort study	EULAR-DAS28 remission; DAS28 remission; DAS28 low disease activity	12 months	PHA-DIA250; Phadia	10 IU/ml
Gottenberg 2012[31]	abatacept	ACPA-positive *vs*. negative	558	Cohort study	EULAR response	5 years	NR	NR
Gremese 2013[37]	adalimumab; etanercept; infliximab	ACPA-positive *vs*. negative	641	Cohort study	DAS28 remission Primary: relationship between obesity and clinical response. Secondary relationship between obesity and treatment outcome for the 3 biologic drugs.	12 months	NR	>5 IU/ml
Klaasen 2011[43]	infliximab + MTX	ACPA-positive *vs*. negative	89	Cohort study	DAS28 response; EULAR response	16 weeks	Kit RA-96RT, Immunoscan RA Mark 2; Euro-Diagnostica	NR
Soto 2011[49]	adalimumab	ACPA-positive *vs*. negative	52	Cohort study	Primary: DAS28 response; Secondary: ACR20/50/70 response	24 weeks	Euro-Diagnostica kit (Sweden)	≥25 IU/ml
Cuchacovich 2008[51]	adalimumab	ACPA-positive *vs*.	59	Cohort study	ACR20 response; DAS28 response	24 weeks	Euro-Diagnostica kit (Sweden)	≥25 IU/ml
Atzeni 2006[52]	adalimumab + MTX	ACPA-positive *vs*. negative	57	Case-control study	ACR20/50/70	1 year	ELISA kit	>15 IU/ml
Braun-Moscovici 2006[48]	infliximab	Anti-CCP >100 u/ml *vs*. anti-CCP <100 u/ml	30	Case-control study	EULAR response	18 months	ELISA kit	>5 U/mL

Author / year	Treatment	Comparison	Sample size	Study design	Efficacy outcomes	Duration of follow-up	ACPA test	ACPA cut-off value
Bruns 2009[44]	infliximab + DMARD	Anti-CCP > 1000 IU/ml *vs*. anti-CCP < 1000 IU/ml	36	Cohort study	EULAR response	48 weeks	ELISA kit	>25 U/mL
Bos 2008[50]	adalimumab (± DMARD)	ACPA-positive non-response *vs*. moderate *vs*. good response	188	Cohort study	EULAR response	28 weeks	ELISA kit	>5AU/ml
Vasilopoulos 2011[38]	infliximab + MTX; etanercept ± MTX; adalimumab ± MTX/leflunomide	ACPA-positive *vs*. negative	100	Cohort study	DAS28 response	6 months	ELISA kit	>5 U/mL
Wijbrandts 2008[46]	infliximab + MTX	ACPA-positive *vs*. negative	103	Cohort study	DAS28 response	16 weeks	NR	NR
Lequerre 2007[47]	infliximab + MTX/leflunomide	ACPA-positive *vs*. negative	76	Cohort study	EULAR response	14 weeks	ELISA kit	NR
Gottenberg 2016[20]	abatacept	ACPA-positive *vs*. negative	1903	Cohort study	EULAR response	1.6 years (median)	NR	NR
Sekiguchi 2016[28]	abatacept	Elderly (≥65 years) *vs*. younger (<65 years) patients	277	Cohort study	DAS28-CRP, HAQ-DI	48 weeks	ELISA	≥4.5 U/ml
Sokolove 2016[16]	abatacept adalimumab	abatacept *vs*. adalimumab	508	RCT	DAS28-CRP, HAQ-DI, DAS28-CRP<2.6, ACR/EULAR remission rates and ACR50/70 response rates	729 days	ELISA	≥25 AU/mL
Alten 2017[26]	abatacept	ACPA-positive *vs*. negative	552	Cohort study	EULAR, CDAI score, Boolean remission rates, HAQ-DI	6 months	NR	NR
Shim 2017[27] (abstract)	abatacept	Bio-naive *vs*. Bio-failure patients	342	Cohort study	DAS-28 CRP scores	24 weeks	NR	NR
Harrold 2017[19]	abatacept TNF-α inhibitors	ACPA-positive *vs*. negative	2281	Cohort study	CDAI, ACR20, ACR50, ACR70	6 months	NR	NR

NR: not reported; RCT: randomised controlled trials.

Table II. Patient characteristics of SLR studies.

Author / year	Treatment	n	Age, years Mean (SD)	Female %	ACPA+ %	ACPA- %	Disease duration, years, Mean (SD)	DAS 28 score, ESR or CRP, Mean (SD)		Concomitant MTX, %	Prior biologics, %
Canhao 2012[40]	adalimumab	161	50.9 (12.0)	88%	76%	NR	9.5 (7.6)	ESR	9.8 (7.1)	79%	0%
	etanercept	250	52.4 (12.1)	91%	73%		10.4 (8.6)		11.5 (7.3)	74%	
	infliximab	206	54.1 (11.9)	85%	76%		11.2 (9.4)		12.2 (8.1)	89%	
Sato 2014[29] (abstract)	abatacept	45	61.5 (NR)	NR	73%	27%	8.9 (NR)		NR	NR	NR
Sato 2014[32] (abstract)	infliximab	142	NR	NR	82%	18%	NR	ESR	6.5 (1.3)	100%	0%
	tocilizumab	93			87%	13%			6.6 (1.5)	55%	56%
	abatacept	60			93%	7%			5.9 (1.9)	57%	58%
Matsutani 2013[30] (abstract)	abatacept	45	NR	NR	84%	16%	NR		NR	NR	NR
Smolen 2011[42] (abstract)	etanercept + MTX	758	NR	NR	NR	NR	NR		NR	NR	NR
Takahashi 2011[33] (abstract)	infliximab etanercept tocilizumab adalimumab	64	36 (18)	NR	86%	14%	7.8 (4.1)	ESR	5.4 (1.5)	NR	NR
Klaasen 2009[45] (abstract)	infliximab	104	NR	NR	76%	24%	NR		NR	NR	NR
Potter 2009[34]	etanercept	278	57 (11)	80%	86%	15%	13 (9)	NR	6.7 (1.0)	55%	8.00%
	infliximab	296	58 (11)	77%	81%	19%	15 (10)		6.7 (1.0)	94%	3.00%
	adalimumab	68	59 (12)	75%	68%	32%	13 (10)		6.5 (1.0)	56%	4.00%
Bobbio-Pallavicini 2007[39]	inflixmab	63	59.1 (10.9)	73%	NR	NR	9.1 (8.1)	NR	5.9 (1.1)	100%	NR
	etanercept	35	58.4 (12.0)	80%			6.2 (4.7)		6.0 (1.1)	83%	
	adalimumab/leflunomide	34	52.6 (14.9)	79%			9.6 (6.7)		5.5 (0.7)	68%	
Avila-Pedretti 2015[41]	infliximab	126	43.1 (11.6)	85%	73%	31%	10.1 (6.7)	NR	5.6 (1.1)	NR	0%
	adalimumab	95	45.9 (12.6)	80%	86%	17%	9.7 (9.1)		5.3 (1.0)		
	etanercept	127	42.2 (13.3)	82%	77%	25%	10.8 (9.1)		5.7 (1.2)		

Author / year	Treatment	n	Age, years Mean (SD)	Female %	ACPA+ %	ACPA- %	Disease duration, years, Mean (SD)	DAS 28 score, ESR or CRP, Mean (SD)		Concomitant MTX, %	Prior biologics, %
Takahashi 2014[35] (abstract)	infliximab	27	55.6 (14.8)	89%	84%	16%	8.2 (3.2)	CRP	5.4 (1.5)	96%	0%
	etanercept	17	NR		NR	NR	NR		NR	NR	41.2%
	adalimumab	7							86%		
	tocilizumab	6							67%		
Pomirleanu 2013[36]	adalimumab	33	53.6 (11.9)	88%	67%	33%	NR	ESR	7.5 (0.4)	15%	0%
	etanercept	30	55.1 (10.0)	70%	53%	47%			7.4 (0.3)	33%	
	infliximab	27	58.4 (9.8)	85%	59%	41%			7.6 (0.4)	30%	
Gottenberg 2012[31]	abatacept	558	NR	80%	70%	30%	NR	ESR	NR	77%	88.9%
Gremese 2013[37]	adalimumab	260	52.5 (12.8)	80%	67%	33%	9.7 (9.3)	ESR	5.4 (1.3)	NR	0%
	etanercept	227	52.3 (14.6)	82%	63%	37%	8.4 (8.6)		5.7 (1.3)		
	infliximab	154	51 (13)	83%	85%	15%	6.5 (7.8)		5.8 (1.3)		
Klaasen 2011[43]	infliximab (DAS28 responders)	60	52 (14)	78%	82%	18%	NR	NR	6.1 (1.0)	100%	0%
	infliximab (DAS28 non-responders)	29	55 (12)	66%	72%	28%			5.5 (1.2)		
Soto 2011[49]	adalimumab (ACPA+)	39	52.1 (1.6)	87%	100%	0%	12 (13)	NR	6.1 (1.4)	NR	NR
	adalimumab (ACPA-)	13	43.7 (2.9)	92%	0%	100%	10 (9)		5.2 (1.2)		
Cuchacovich 2008[51]	adalimumab (ACPA+)	52	50.2 (9.5)	87%	100%	0%	12 (12)	NR	NR	NR	
	adalimumab (ACPA-)	18	45.3 (14.0)	89%	0%	100%	10 (8)				
Atzeni 2006[52]	adalimumab	57	56 (NR)	93%	81%	19%	8	NR	5.4 (1.3)	100%	NR
Braun-Moscovici 2006[48]	infliximab (anti-CCP >100 u/ml)	9	58 (13)	NR	NR	NR	14.0 (11.2)	ESR	7.1 (1.3)	NR	NR
	infliximab (anti-CCP <100 u/ml)	21	47 (14)				12.0 (8.6)		7.4 (0.8)		
Bruns 2009[44]	infliximab + DMARD	36	50.5 (10.2)	75%	89%	11%	10.2 (5.8)	NR	92%	NR	
Bos 2008[50]	adalimumab (EULAR non-responders)	43	53.9 (13.1)	86%	72%	28%	9.5 (NR)	NR	4.9 (1.3)	56%	NR
	adalimumab (EULAR moderate responders)	79	54.6 (12.0)	82%	72%	33%	8.5 (NR)		5.4 (1.2)	73%	
	adalimumab (EULAR good responders)	66	52.4 (10.8)	71%	80%	20%	8 (NR)		4.9 (1.0)	88%	
Vasilopoulos 2011[38]	infliximab + MTX etanercept ± MTX adalimumab ± MTX/leflunomide	100	57.4 (10.8)	92%	66%	34%	13.6 (6.5)	NR	5.6 (0.3)	NR	0%
Wijbrandts 2008[46]	infliximab	103	55 (13)	69%	76%	24%	10 (9)	NR	5.9 (1.1)	100%	0%
Lequerre 2007[47]	infliximab + MTX/leflunomide	76	53.8 (12.4)	82%	NR	NR	10.5 (8.6)	NR	5.8 (1.0)	75%	0%
Gottenberg 2016[20]	abatacept	1357	57.2 (13.0)	79%	100%	0%	11.4 (8.5)	ESR	5.0 (1.4)	NR	NR (2 previous lines)
		546	55.8 (13.6)	82%	0%	100%	10.7 (8.7)		5.0 (1.4)		
Sekiguchi 2016[28]	abatacept	277	63.2 (13.3)	84.8%	84.4%	43.3%	7.9 (8.8)	CRP	4.6 (1.1)	69.0%	0%
Sokolove 2016[16]	abatacept	66	NR	84.8%	0.0%	100.0%	NR	CRP	NR	NR	NR
	adalimumab	54		85.2%	0.0%	100.0%					
Alten 2017[26]	abatacept (ACPA+)	364	59.8 (12.4)	NR	100%	0%	7.7 (8.5)	CRP	4.7 (1.0)	69.4%	0%
	abatacept (ACPA-)	188	59.7 (13.3)	NR	0%	100%	5.4 (6.1)		4.9 (1.1)	62.1%	
Shim 2017[27]	abatacept (ACPA+/bio-naive)	160	NR	NR	100%	0%	NR	CRP	4.7 (1.1)	78.3%	0%
	abatacept (ACPA+/bio-failure)	87			100%	0%			4.7 (1.3)		100%
	abatacept (ACPA-/bio-naïve)	44			0%	100%			4.5 (1.1)		0%
	abatacept (ACPA-/bio-failure)	51			0%	100%			4.4 (1.1)		100%
Harrold 2017[19]	abatacept (ACPA+)	204	NR	82.3%	100%	0%	NR		NR	59.8%	88.7%
	abatacept (ACPA-)	362		80.1%	0%	100%				60.8%	85.6%
	TNFi (ACPA+)	602		78.9%	100%	0%				65.0%	36.2%
	TNFi (ACPA-)	1113		75.7%	0%	100%				67.0%	31.5%

NR: not reported.

in one study (52). Information on MTX concomitant use was not given in 13 studies. Mean disease duration ranged from 5.4 years in the abatacept treatment arm of ACPA-negative patients (26) to 14.0 years in the infliximab treatment arm of patients with anti-CCP >100 u/ml (48). Lastly, information on prior use of biologic DMARDs (including anti-TNF) was reported in 16 studies. This was between 0% in 11 studies (bio-naïve patients) and 88.9% in one abatacept study (31). One study (32) reported 0% of prior use of biologics in the infliximab treatment arm while 56% and 58% of patients used biologics prior to the study in the tocilizumab and abatacept arms, respectively. One

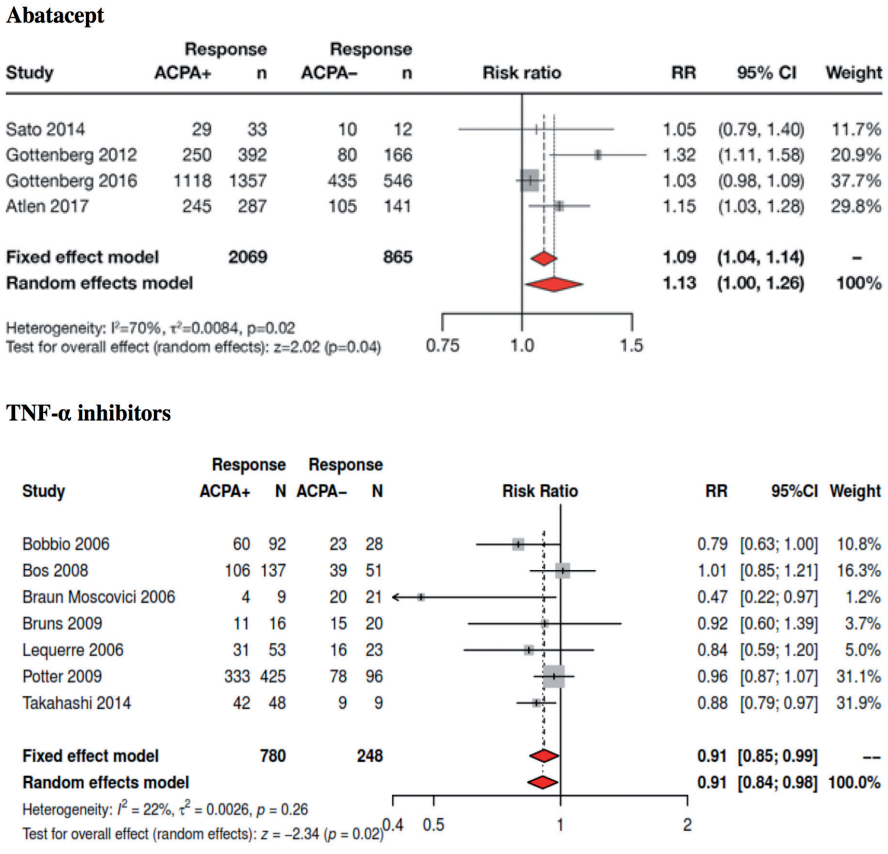

Fig. 2. Meta-analysis of pooled risk ratio (RR) of ACPA status for a response to anti-TNF-α treatment and abatacept according to EULAR criteria for treatment response: Base case analysis.

abatacept study (27) was stratified in subgroups of bio-naïve or bio-failure patients. One other abatacept study (20) reported a mean number of two previous lines of biologic therapy.

The three effectiveness outcomes reported across the studies were ACR20/50/70 criteria, DAS28 response and remission criteria, and EULAR response criteria. Only four studies (34, 37, 40, 49) stated primary and secondary outcomes. Primary outcomes were EULAR response (40), DAS 28 response (34, 49) and DAS 28 remission (37) (Table I).

Feasibility assessment

Following the feasibility assessment, time-point of study follow-up was found to be a potential confounder and subgroup analyses based on study follow-up at 12, 24 and 52 weeks with a 4 weeks margin were possible. Other potential confounders such as MTX use, prior biologics or baseline disease activity measure could have been investigated in additional subgroup analyses but these were not systematically reported across the studies. Indeed, concomitant MTX use was reported in only 17 studies out of 30. This was reported as percentages (between 15% and 100%), making difficult to establish subgroup analyses. Similarly, information on prior biologics was given in only 16 studies out of 30. Percentage of patient using biologics prior to the study was between 0% and 88.9%. Studies with TNF-α inhibitors were mostly on bio-naïve patients (11 studies out of 12); only one TNF-α inhibitors' study (34) included a small percentage of patients who experienced biologics (3% to 8%). The four remaining studies (20, 27, 31, 32) with abatacept, included patients who were previously treated with biologics. Therefore, performing analyses per treatment type (TNF-α inhibitors or abatacept) could solve potential heterogeneity in prior use of biologics. For disease activity at baseline, DAS 28 scores were reported in 21 studies out of 30. Only 11 studies specified if DAS 28 scores were measured as DAS28-CRP or DAS28-ESR. For these reasons, it was not possible to perform analyses according to disease activity at baseline.

Meta-analysis

As described previously, 30 studies were identified during the screening process and selected for data-extraction. Not all studies could be included in the meta-analyses; twelve studies were excluded from the analysis. Three TNF-α inhibitor studies (36, 37, 42) reported an odds ratio for response comparing ACPA-positive to ACPA-negative patients, however, did not provide information on the number of patients responding, therefore input data for the meta-analysis could not be generated. Another three studies (33, 41, 52) provided the number of ACPA-positive responding patients, but not the number of ACPA-negative responding patients, making a comparison between the two groups impossible. Another study (40) did not provide outcomes per ACPA status and was excluded for the meta-analysis. Three abatacept studies (27, 28, 30), one infliximab study (32) and one adalimumab RCT (16) (AMPLE trial) were excluded because remission rates according to DAS28 criteria were reported instead of response rates.

Ultimately, the evidence base identified through the SLR consisted of 18 observational studies providing data on treatment response of ACPA-positive and negative patients. Four studies reported data on the effectiveness of abatacept, thirteen studies provided data on TNF-α inhibitors and one study included both abatacept and TNF-α inhibitor treatments.

Treatment response to abatacept

For the base case analysis, the pooled RR was 1.13 (1.00, 1.26), showing a significant positive association between ACPA status and good/moderate EULAR response to abatacept. However, there is moderate to high heterogeneity across the four studies (20, 26, 29, 31) quantified by I2=70% (Fig. 2). In probability terms, this corresponds to a 13% increased likelihood of responding to abatacept in ACPA positive *versus* ACPA-negative patients.

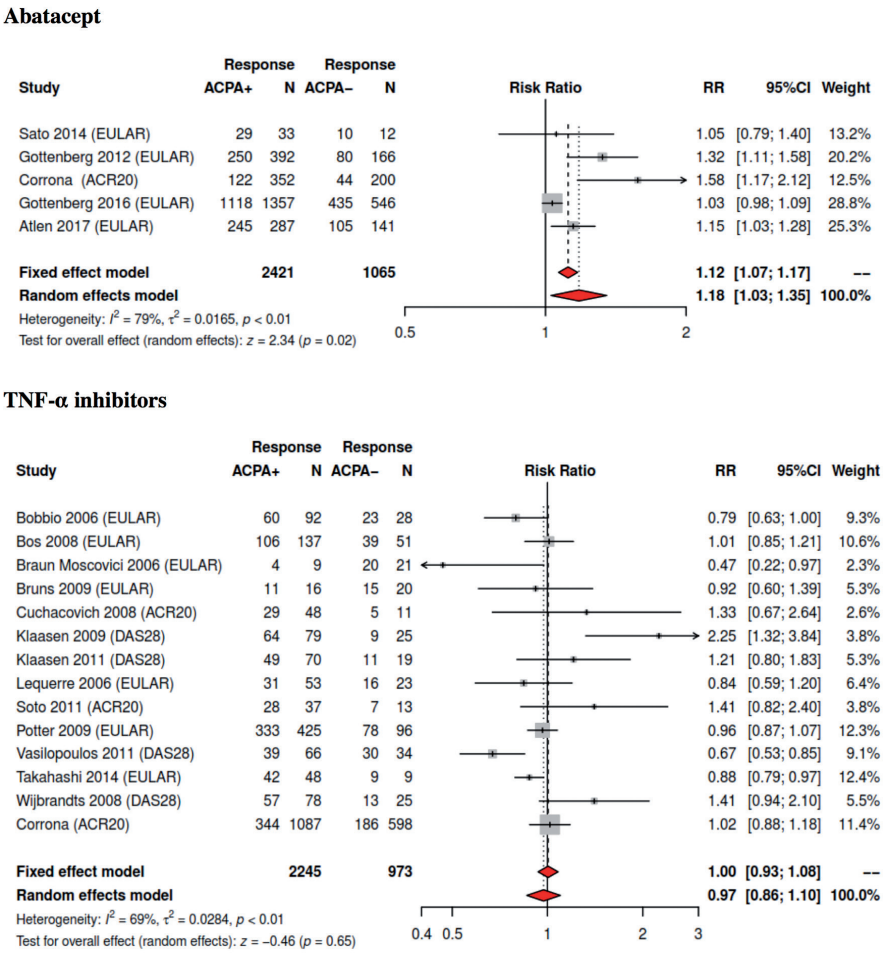

Fig. 3. Meta-analysis of pooled risk ratio (RR) of ACPA status for a response to anti-TNF-α treatment and abatacept according to EULAR/DAS28/ACR20 criteria for treatment response: scenario analysis.

For the scenario analysis with the additional Corrona study (19) evaluating treatment response based on ACR20 criteria (in addition to EULAR criteria in the base case), RE pooled risk ratio was to 1.18 (1.03–1.35) (Fig. 3). A positive association between ACPA status and response to abatacept (according to EULAR and ACR20 criteria) was also found in this analysis, indicating that there is an 18% increase in risk of responding to abatacept for ACPA-positive patients compared to ACPA-negative patients.

In the subgroup analysis for the good/moderate EULAR response, two studies (26, 29) with a study follow-up duration of 24 weeks were included. The pooled RR was 1.13 (1.03, 1.25) (similar to the base case) with no heterogeneity across the studies (I2=0%) (Fig. 4). These two studies were prospective observational studies, while the two other studies from the base case analysis were registries with longer study follow-up of 1.6 years (20) and 5 years (31). Therefore, the study follow-up duration could be a source of heterogeneity in the base case analysis.

Treatment response to TNF-α inhibitors

In the base case analysis, seven studies (34, 35, 39, 44, 47, 48, 50) were included and the pooled RR was 0.91 (0.84, 0.98) when using the random effects model (I2=22%), thus a negative association between ACPA positivity and EULAR response rates to TNF-inhibitors, with low heterogeneity across the studies (Fig. 1).

For the scenario analysis, with seven additional studies (19, 38, 43, 45, 46, 48, 49, 51) including ACR20 and DAS28 responses, the pooled RR was 0.97 (0.86, 1.10), confirming no association between ACPA status and treatment response (I^2=69%) (Fig. 2). When combining EULAR, ACR20 and DAS28 treatment response in this analysis, the in-between study heterogeneity appeared to be substantial compared to the low heterogeneity observed in the base case with EULAR treatment response only. Overall, subgroup analyses showed similar results with no association between ACPA status and treatment response; high heterogeneity was observed for patient follow-up at 12 weeks (I^2=73%) and no heterogeneity was observed for follow-up at 24 weeks or 52 weeks (Fig. 3).

Discussion

The SLR identified 18 studies investigating the effectiveness of abatacept and TNF-α inhibitors (4 studies for abatacept, 13 studies for TNF-α inhibitors and one study including both abatacept and TNF-α inhibitors) according to ACPA status or ACPA levels. The meta-analysis showed a significant difference in treatment response between ACPA-positive and ACPA-negative patients treated with abatacept. ACPA-positive patients were 13% more likely to respond to treatment compared to the ACPA-negative patients (95% CI: 1.00–1.26), with respect to good and moderate responses according to EULAR criteria. Scenario analyses for abatacept confirmed this result for EULAR and ACR20 response. Subgroup analyses with study follow-up at 24 weeks confirmed the pooled RR of the base case analysis. This suggests that the duration of study follow-up was a source of heterogeneity in the base case analysis. Positive ACPA status was associated with lower risk of EULAR good/moderate treatment response to TNF-α inhibitor treatment than negative ACPA status, with a risk ratio of 0.91 (95% CI: 0.84–0.98). Scenario and subgroups analyses for TNF-α inhibitors confirmed this result for EULAR, DAS28 and ACR20 response.

Some limitations can be found in our study regarding the evidence synthesis part. First, a degree of publication bias is present since some observational studies failed to be published (29) while others were published in abstract form only and thus presented limited information. Second, publication of out-

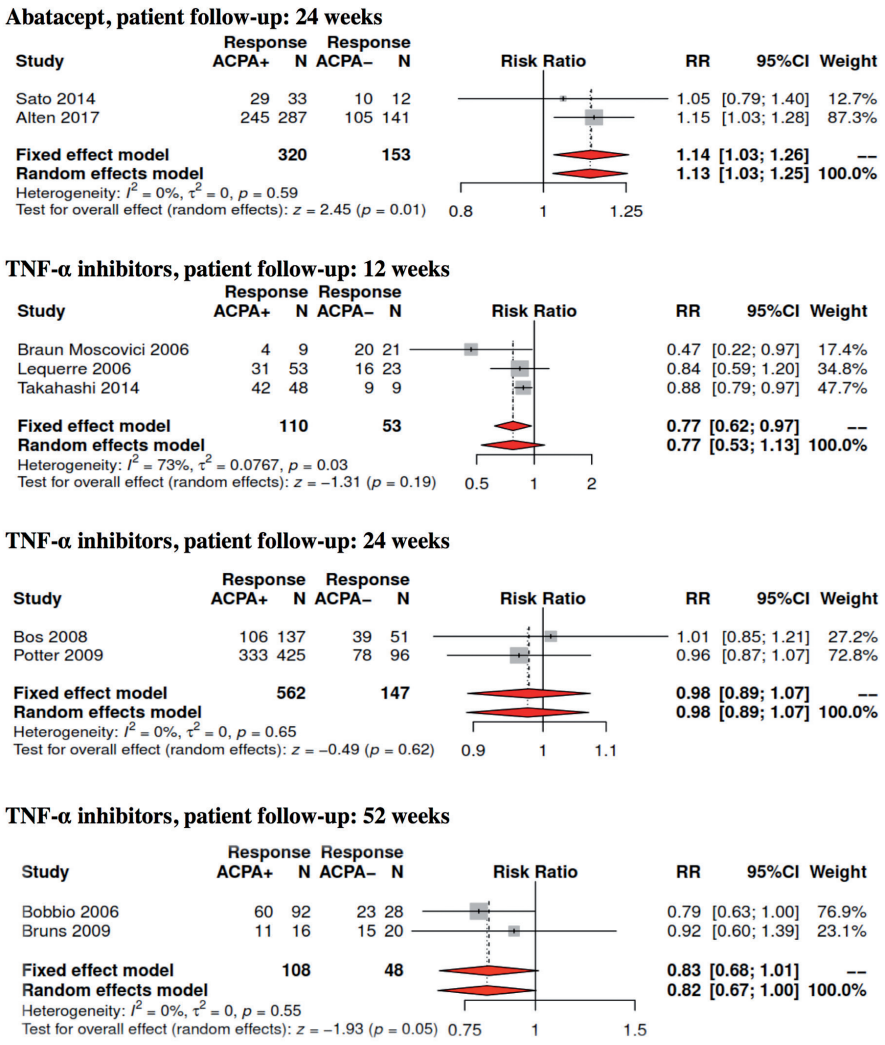

Fig. 4. Meta-analysis of pooled risk ratio (RR) of ACPA status for treatment response according to EULAR criteria: Subgroups analyses per duration of study follow-up.

come data relevant to this meta-analysis may be incomplete or absent in a report, in which case, the publication must be excluded from analyses as well. These processes may lead to reporting bias (53). In order to assess the degree of bias within the current study, a risk of bias assessment was performed, which showed most studies were of reasonable quality, however some bias is expected due to poor reporting of participation selection, study attrition and prognostic factor measurement.

A substantial in-between study heterogeneity (I^2=70%) was observed in the base case analysis looking at treatment response to abatacept according to EULAR criteria. This heterogeneity was probably due to different durations of follow-up as shown in subgroup analysis for the 24-week follow-up. The two studies included in this subgroup had a follow-up of 24 (29) and 26 weeks (26). The two other studies from the base case analyses were prospective registries with longer follow-up of 1.6 (20) and 5 years (31). A substantial heterogeneity (I^2=69%) was also found in the scenario analysis looking at treatment response to TNF-α inhibitor according to DAS28/ACR20/EULAR criteria. This heterogeneity was low (I^2=22%) in the base case analysis looking at treatment response according to EULAR criteria only. This suggests that combining different response criteria (DAS28, ACR20 and EULAR criteria in this case) can lead to potential heterogeneity. Lastly, some potential confounders such as concomitant MTX use, prior biologic treatments or disease severity score at baseline, could have an effect on the outcomes across the studies included in our meta-analysis. However, the performance of subgroup analyses was not feasible given the sparsity of evidence base in relation to these parameters.

There are several strengths for this study. As mentioned observational studies included in our-meta-analysis reflect daily clinical practice, both in terms of the medical interventions that patients receive and the heterogeneous patient populations that are included. Therefore, observational studies can provide clinically relevant information (which is not necessarily provided by RCTs). Second, by systematically reviewing the literature for studies in RA subgroups, all available relevant evidence for abatacept and TNF-α inhibitors in ACPA subgroups is identified and condensed into one overview.

In summary, limitations in terms of publication bias, reporting bias and confounding can be present in our study. Thus, results of the meta-analysis should be interpreted with caution taking into account these biases and limitations.

Our findings are supported by recent studies that could not be included in our SLR and meta-analysis, since these were not fitting our PICOS criteria due to the study design (letter to editors or cost-effectiveness analysis are criteria of exclusion). One Italian cohort (54) (letter to editors) showed the improved effectiveness of abatacept in terms of good/moderate EULAR response for ACPA-positive patients with RA and this was regardless of the body mass index at baseline. In a broader context, a recent cost-effectiveness analysis (55) suggested that ACPA-positive RA patients treated with abatacept led to lower costs per response (DAS28 remission) compared to those treated with adalimumab.

Conclusion

This meta-analysis confirms the result of a previously published study demonstrating that there is no association between ACPA status and response to TNF-α inhibitor treatment in RA (16, 19). The analysis was expanded to include abatacept, which has demonstrated improved efficacy for ACPA-

positive patients in a *post-hoc* analysis of the AMPLE trial (16). ACPA status is associated with treatment response to abatacept, both in randomised controlled trials and observational studies.

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