Associations Between Tumor Necrosis Factor-α (TNF-α) –308 and –238 G/A Polymorphisms and Shared Epitope Status and Responsiveness to TNF-α Blockers in Rheumatoid Arthritis: A Metaanalysis Update

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ABSTRACT. ***Objective.*** To investigate whether tumor necrosis factor-α (TNF-α) promoter –308 A/G and –238 A/G polymorphisms and shared epitope (SE) status are associated with responsiveness to anti-TNF therapy in patients with rheumatoid arthritis (RA).

Methods. A comparative metaanalysis was conducted on A allele carriers (genotypes A/A + A/G) of the TNF-α promoter –308 and –238 A/G polymorphisms and SE status in responders and nonresponders to anti-TNF therapy.

Results. A total of 13 studies were included in the metaanalysis. Metaanalysis showed that the TNF-α –308 A/G polymorphism is not associated with responsiveness to TNF blockers in RA patients. Studies with a small number of subjects (< 100) showed that the odds ratio for the A allele carrier state was significantly lower among responders (OR 0.344, 95% CI 0.152–0.779, p = 0.01). Studies with a higher number of subjects (≥ 100) found no association between the TNF-α –308 A/G polymorphism and responsiveness to TNF blockers. The overall metaanalysis showed that the TNF-α –238 A/G polymorphism was not associated with the responsiveness of RA patients to TNF blockers, and stratification by TNF blocker revealed that the TNF-α –238 A/G polymorphism was associated with response of infliximab (OR 0.441, 95% CI 0.203–0.609, p = 0.039). SE status was found not to be associated with response to TNF blockers.

Conclusion. Metaanalysis of available data revealed an association between treatment response to infliximab and the TNF-α –238 A/G polymorphism, but no associations between treatment response and the TNF-α –308 A/G polymorphism or SE status. (First Release March 1 2010; J Rheumatol 2010;37:740–6; doi:10.3899/jrheum.090707)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR-α INHIBITORS
TUMOR NECROSIS FACTOR-α POLYMORPHISM
RESPONSIVENESS SHARED EPITOPE

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly affects synovial joints in up to 1% of the world's population[1]. Tumor necrosis factor-α (TNF-α) is a potent proinflammatory cytokine that plays an important role in inflammatory and immune responses, including those of RA[2]. Evidence regarding the central role played by TNF in the pathogenesis of RA has led to the introduction of anti-TNF therapy. HLA-DRB1 alleles containing the shared epitope (SE) at positions 70–74 of the ß chain influence susceptibility to RA and its severity, and possibly influence clinical responses to disease-modifying antirheumatic drugs[3].

TNF antagonists are among the most effective therapies for RA, but not all patients respond. The reasons for this lack of response are unclear but have generated considerable research interest; prediction of response to TNF inhibitors would be highly valuable, as it would prevent unnecessary anti-TNF therapy and reduce treatment costs, and represent a significant advance in patient care.

Several single-nucleotide polymorphisms have been identified in TNF-α promoter[4], and 2 common polymor-

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phisms, namely G to A substitutions at –308 (rs1800629) and –238 (rs361525), have been studied intensively as severity markers for RA[5-14].

Given the crucial roles played by the SE and TNF-α polymorphisms in the pathogenesis of RA, many studies have examined the potential contributions of the SE and the TNF-α promoter –308 and –238 A/G polymorphisms and SE status to responsiveness to TNF antagonists[15], with contradictory results. Possible explanations for these include (1) the biologic targets of TNF blockers differ; (2) type II error due to inadequate sample size; (3) type I error due to chance and/or multiple comparisons; (4) population stratification; and (5) linkage disequilibrium between TNF polymorphisms. However, shortcomings of inadequate cohort sizes and low statistical power can be resolved by conducting large multicenter studies or metaanalyses.

Accordingly, using a metaanalysis approach, we investigated whether TNF-α promoter 308 and 238 A/G polymorphisms and SE status are associated with responsiveness to anti-TNF therapy in patients with RA.

MATERIALS AND METHODS

Identification of studies and data extraction. We considered all studies that examined the association between TNF-α promoter –308 A/G polymorphism, –238 A/G polymorphisms or SE status and responsiveness to anti-TNF therapy in patients with RA. A literature search was conducted using Medline citation. References in studies were reviewed to identify additional studies not indexed by Medline. The following key words and terms were searched: "tumor necrosis factor," "TNF-α," "polymorphism," "TNF blocker," "shared epitope," "SE," "etanercept," "infliximab," "adalimumab," and "rheumatoid arthritis." Language of origin was not restricted. A study was included in the analysis if (1) it was published before July 2009; (2) it presented original data (ensuring independence among studies); and (3) it provided sufficient data to calculate odds ratios (OR). The following information was sought from each article: author identification, year of publication, country of the study, TNF inhibitor names, length of followup period, response criteria used, and genotypes of the TNF-α –308 and –238 A/G polymorphisms and SE copy numbers in responders and nonresponders.

Evaluation of statistical associations. Because of the low frequency of the A/A genotypes of the 2 TNF-α promoter polymorphisms, the overall estimate of risk of TNF-α G/A + A/A for responsiveness to TNF inhibitors was calculated. We performed SE metaanalyses on the SE-positive versus SE-negative cases, and investigated the SE dose effect. Point estimates of risk, odds ratios, and 95% confidence intervals were calculated for each study. We also assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics (a heterogeneity test that assesses the null hypothesis that all studies evaluated the same effect)[16]. In addition, we quantified the effect of heterogeneity using I^2 values[17]. These values range between 0% and 100% and represent the proportion of between-study variability attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% are referred to as low, moderate, and high heterogeneity effects, respectively. Fixed effects assume that genetic factors show similar effects on RA susceptibility across all studies investigated, and that observed variations between studies are caused by chance alone[18]. The random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances[19]. If study groups show no heterogeneity, the fixed and random effects models produce similar results, and if not, the random effects model usually produces wider confidence intervals than the fixed effects model. The random effects model is used in the presence of significant between-study heterogeneity. Statistical manipulations were performed using a comprehensive metaanalysis computer program (Biosta, Englewood, NJ, USA).

RESULTS

Studies included in the metaanalysis. Nineteen relevant studies concerning the TNF-α promoter –308 A/G and –238 A/G polymorphisms and SE status in RA were identified by Medline and manual searching[5-15,20,21-27]. Six studies, 5 with data on other polymorphisms[22-26] and one review[27], were excluded. A total of 13 studies met the inclusion criteria[5-15,20,21], and selected characteristics of these 13 studies are summarized in Tables 1 and 2. Subject numbers ranged from 20 to 369 per study, and a total of 1817 patients with RA were included in our metaanalysis. One eligible study contained data on 2 different TNF blockers, namely etanercept and infliximab, and findings were treated separately[5]. Therefore, a total of 14 different datasets were considered. The TNF inhibitors used were etanercept in 6 studies, infliximab in 5, and adalimumab in 2, and all of them in one study. Twelve studies examined the TNF-α –308 A/G polymorphism, 5 the TNF-α –238 A/G polymorphism, and 4 SE status (Tables 1, 3). Followup periods ranged from 12 weeks to 1 year.

Heterogeneity and publication bias. Between-study heterogeneity was found during the metaanalyses of the TNF-α –308 A/G polymorphism and SE status, but no heterogeneity was found for TNF-α –238 A/G (Table 4). We were unable to use the funnel plot method usually employed to detect publication bias, because the number of studies for analysis was too small. However, Egger's regression analysis showed no evidence of publication bias for the TNF polymorphisms or SE status in all subjects (Egger's regression test p values > 0.1).

Association between TNF-α promoter Egger's regression analysis –308 A/G polymorphism and responsiveness to TNF-α blockers. The A/A genotype of TNF-α –308 A/G polymorphism was rare, and thus we compared the A/G + A/A genotypes (A allele carrier) versus the G/G genotype (A allele noncarrier). The overall metaanalysis showed that the TNF-α –308 A/G polymorphism was not associated with responsiveness to TNF blockers, but between-study heterogeneity was observed (I^2 = 62.1%, p = 0.002; Table 4). Stratification by cohort size revealed differences between the results obtained by studies with small numbers of subjects (< 100) and those with large numbers (≥ 100). Smaller-scale studies found that the OR of the A allele carrier state was significantly lower in responders (OR 0.291, 95% CI 0.153–0.555, p < 0.001), whereas larger studies showed no such association (Figure 1).

Subgroup analysis was also performed for different TNF blockers, namely etanercept, infliximab, and adalimumab, but no associations were found between the TNF-α –308 A/G polymorphism responses to these TNF blockers (Table

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Table 1. Characteristics of studies in the metaanalysis.

Study	Country	TNF Inhibitor	No. Subjects	Followup	Response Criteria	Polymorphism
Maxwell 2008[5]	UK	Etanercept, infliximab	197 206	6 mo	DAS28	–308 A/G, –238 A/G
Miceli-Richard 2008[6]	France	Adalimumab	369	12 wks	ACR50	–308 A/G, –238 A/G, SE
Marotte 2008[8]	France	Infliximab	198	30 wks	ACR20	–308 A/G, –238 A/G, SE
Seitz 2007[20]	Switzerland	Infliximab, etanercept, adalimumab	33 12 9	24 wks	DAS28	–308 A/G
Guis 2007[21]	France	Etanercept	86	6 mo	DAS28	–308 A/G
Cuchacovich 2006[7]	Chile	Adalimumab	81	24 wks	DAS28	–308 A/G
Kang 2005[9]	Korea	Etanercept	70	12 wks	ACR20	–308 A/G, –238 A/G, SE
Fonseca 2005[10]	Portugal	Etanercept	36	25 mo	DAS28	–308 A/G
Criswell 2004[15]	USA	Etanercept	301	12 mo	ACR50	SE
Cuchacovich 2004[11]	Chile	Infliximab	20	22 wks	ACR20	–308 A/G
Balog 2004[12]	Hungary	Infliximab	23	1 yr	DAS28	–308 A/G
Padyukov 2003[13]	Sweden	Etanercept	123	12 wks	ACR20, DAS28	–308 A/G
Mugnier 2003[14]	France	Infliximab	53	22 wks	DAS28	–308 A/G

ACR20: American College of Rheumatology 20; DAS28: Disease Activity Score 28; SE: shared epitope.

Table 2. Characteristics of studies in the metaanalysis.

Study	Disease Duration, yrs, mean ± SD	Age, yrs, mean ± SD	Female, %	RF, %	SE, %	Current Smoking, %	Concomitant Therapy, mean ± SD
Maxwell 2008[5]	13.7 ± 14.2	56 ± 56	78 ± 77	90 ± 87	NA	NA	NA
Miceli-Richard 2008[6]	139.5 wks	54.1 ± 11.1	78	71	NA	NA	MTX 47%, DMARD 25%
Marotte 2008[8]	7.5 ± 7.0	52.7 ± 14.6	74.6	60.3	NA	NA	DMARD no. 2.1 ± 1.6
Seitz 2007[20]	14.4 ± 9.9	57.2 ± 12.5	68.5	100	NA	18	Pred 5.4 ± 2.6 mg, MTX 16.95 ± 4.73 mg/wk
Guis 2007[21]	11.5 ± 10.3	56.5 ± 14.2	80	67.4	80.2	NA	Pred 5.4 ± 6.1 mg MTX 9.7 ± 8.3 mg/wk
Cuchacovich 2006[7]	137.1 mo ± 143.7	50.1 ± 10.7	NA	83.9	NA	NA	NA
Kang 2005[9]	11.8 ± 6.8	45 ± 10	93	70	73	NA	Steroid 4.0 ± 2.2 mg DMARD no. 4.5 ± 1.5
Fonseca 2005[10]	10.3 ± 7.1	45.8 ± 11.1	NA	NA	NA	NA	NA
Criswell 2004[15]	13 mo	50	74	NA	72	NA	DMARD 41%
Cuchacovich 2004[11]	11.1 ± 9.1	53 ± 12.6	90	100	NA	NA	Pred 9.0 ± 2.69 mg MTX 8.4 ± 4.4 mg
Balog 2004[12]	NA	NA	NA	NA	NA	NA	NA
Padyukov 2003[13]	14	52	81.3	76	NA	NA	Steroid 60%, MTX 43% MTX + DMARD 5.7%
Mugnier 2003[14]	13.2 ± 9	56.0 ± 12.6	78	69.5	74.6	NA	Steroid 12.5 ± 11 mg DMARD no. 3.73 ± 1.5

RF: rheumatoid factor; SE: shared epitope; NA: not available; MTX: methotrexate; DMARD: disease modifying antirheumatic drug; Pred: prednisolone; No: number.

4). The response criteria used, such as decrease in Disease Activity Score 28-joint count (DAS28) and American College of Rheumatology 20% (ACR20) or ACR50 response, and the followup periods differed among studies. However, no association was found between any of these criteria and response to treatment (data not shown).

Associations between TNF-α promoter –238 A/G polymorphism and treatment responsiveness. The A/A genotype of the TNF-α –238 A/G polymorphism was also rare, and thus we compared the A/G + A/A genotypes (A allele carrier) to the G/G genotype (A allele noncarrier). The overall meta-analysis showed that the TNF-α –238 A/G polymorphism

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Table 3. TNF genotypes and shared epitope (SE) in studies in the metaanalysis.

Study	TNF Inhibitor	TNF –308 A/G	Responders, n (%)	Nonresponders, n (%)	TNF –238 A/G	Responders, n (%)	Nonresponders, n (%)	SE	Responders, n (%)
Maxwell 2008[5]	Etanercept	GG/GG	73 (60.8)	51 (66.2)	GG/GG	113 (93.4)	69 (89.6)	+	NA
		G/A+A/A	47 (39.2)	26 (33.8)	G/A+A/A	8 (6.6)	8 (10.4)	–	
Maxwell 2008[5]	Infliximab	GG/GG	61 (60.4)	76 (72.4)	GG/GG	97 (93.3)	91 (86.7)	+	NA
		G/A+A/A	40 (39.6)	29 (27.6)	G/A+A/A	7 (6.7)	14 (13.3)	–	
Miceli-Richard 2008[6]	Adalimumab	GG/GG	100 (67.1)	163 (74.1)	GG/GG	135 (91.8)	204 (96.8)	+	68 (70.8)
		G/A+A/A	49 (32.9)	57 (25.9)	G/A+A/A	12 (8.2)	9 (4.2)	–	28 (29.1)
Marotte 2008[8]	Infliximab	GG/GG	99 (75.6)	48 (71.6)	GG/GG	127 (96.9)	62 (92.5)	+	61 (62.2)
		G/A+A/A	32 (24.4)	19 (28.4)	G/A+A/A	4 (3.1)	5 (7.5)	–	37 (37.8)
Seitz 2007	Mixed	GG/GG	37 (72.5)	0 (0)	GG/GG	NA	NA	+	NA
		G/A+A/A	14 (27.5)	3 (100)	G/A+A/A			–	
Guis 2007	Etanercept	GG/GG	56 (84.8)	12 (60)	GG/GG	NA	NA	+	NA
		G/A+A/A	10 (15.2)	8 (40)	G/A+A/A			–	
Cuchacovich 2006[7]	Adalimumab	GG/GG	51 (72.9)	10 (90.9)	GG/GG	NA	NA	+	NA
		G/A+A/A	19 (27.1)	1 (9.1)	G/A+A/A			–	
Kang 2005[9]	Etanercept	GG/GG	59 (98.3)	10 (100)	GG/GG	56 (93.3)	9 (90)	+	35 (68.6)
		G/A+A/A	1 (1.7)	0 (0)	G/A+A/A	4 (6.7)	1 (10)	–	16 (31.4)
Fonseca 2005[10]	Etanercept	GG/GG	11 (78.6)	15 (68.2)	GG/GG	NA	NA	+	NA
		G/A+A/A	3 (21.4)	7 (31.8)	G/A+A/A			–	
Criswell 2004[15]	Etanercept	GG/GG	NA	NA	GG/GG	NA	NA	+	52 (60.5)
		G/A+A/A			G/A+A/A			–	34 (39.5)
Cuchacovich 2004[11]	Infliximab	GG/GG	6 (46.2)	4 (57.1)	GG/GG	NA	NA	+	NA
		G/A+A/A	7 (53.8)	3 (42.9)	G/A+A/A			–	
Balog 2004[12]	Infliximab	GG/GG	10 (90.9)	4 (33.3)	GG/GG	NA	NA	+	NA
		G/A+A/A	1 (9.1)	8 (66.7)	G/A+A/A			–	
Padyukov 2003[13]	Etanercept	GG/GG	65 (65.6)	12 (50)	GG/GG	NA	NA	+	NA
		G/A+A/A	34 (34.3)	12 (50)	G/A+A/A			–	
Mugnier 2003[14]	Infliximab	GG/GG	33 (86.8)	8 (53.3)	GG/GG	NA	NA	+	NA
		G/A+A/A	5 (13.2)	7 (46.7)	G/A+A/A			–	

SE: shared epitope; NA: not available.

Table 4. Metaanalysis of TNF-α –308, –238 G/A polymorphisms and shared epitope with responsiveness to TNF inhibitors in patients with RA.

Polymorphism	Population	No. of Studies	Test of Association			Test of Heterogeneity			
			OR	95% CI	p	Model	Q	p	I^2
TNF –308	Overall	13	0.996	0.779–1.272	0.973	R	31.7	0.002	62.1
AA + AG vs GG	No. < 100	7	0.291	0.153–0.555	0.000	F	7.86	0.248	23.7
	No. ≥ 100	6	1.225	0.940–1.597	0.133	F	7.54	0.183	33.7
	Etanercept	5	0.758	0.492–1.169	0.210	F	6.92	0.140	42.2
	Infliximab	5	0.662	0.295–1.487	0.318	R	16.1	0.003	75.1
	Adalimumab	2	1.463	0.937–2.284	0.094	F	0.78	0.377	0
TNF –238	Overall	5	0.777	0.473–1.276	0.319	F	6.70	0.152	40.3
AA + AG vs GG	Etanercept	2	0.616	0.241–1.570	0.310	F	0.00	0.968	0
	Infliximab	2	0.441	0.203–0.960	0.039	F	0.04	0.828	0
	Adalimumab	1	2.015	0.826–4.912	0.123	NA	NA	NA	NA
Shared epitope	SE+ vs SE–	4	1.264	0.909–1.706	0.171	F	2.28	0.516	0
	SE+/+ vs SE–/–	4	1.204	0.863–1.682	0.275	F	1.10	0.776	0
	SE +/+ vs SE+/–	4	0.986	0.540–1.799	0.962	R	7.74	0.052	61.2
	SE+/– vs SE–/–	4	1.336	0.911–1.960	0.138	F	4.39	0.222	31.6

F: fixed effect model; R: random effect model; NA: not applicable.

was not associated with treatment responsiveness. However, stratification by TNF blocker types revealed TNF-α –238 A/G polymorphism was associated with response to infliximab (OR 0.441, 95% CI 0.203–0.609, p = 0.039) but not etanercept (OR 0.616, 95% CI 0.241–1.570, p = 0.310; Table 3, Figure 2).

Association between SE status and response to treatment. We investigated the possible effects of SE status and dose on

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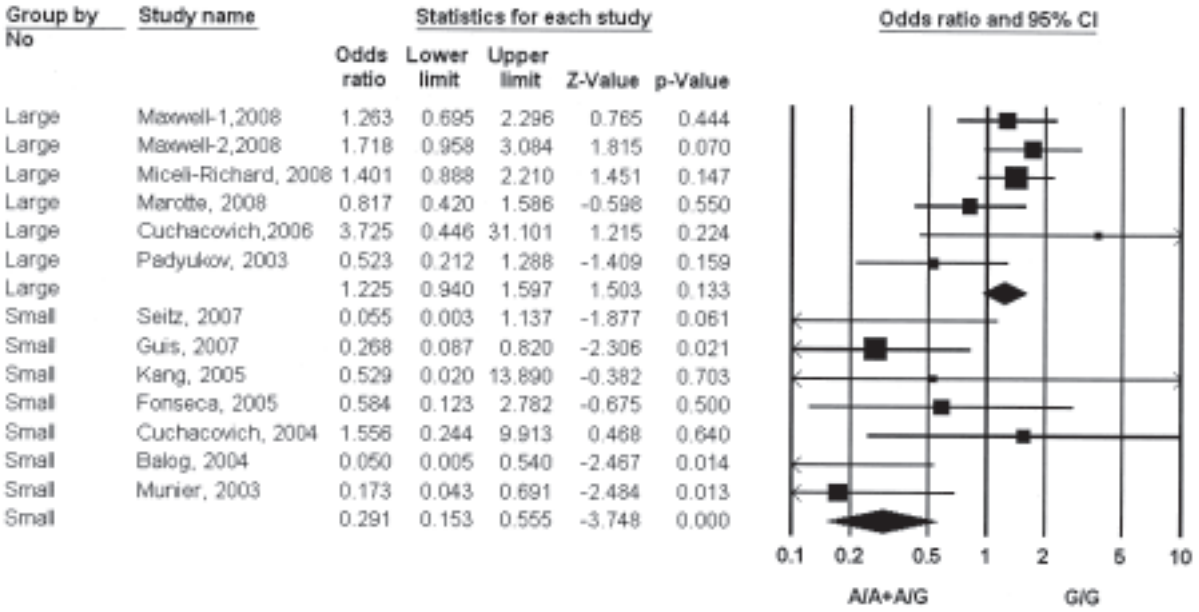

Figure 1. Association between TNF-α –308 A/G polymorphism and response to TNF inhibitor treatment in RA. OR of the A allele carrier state (A/A + A/G genotypes) was significantly lower for responders in studies with a small cohort (< 100 patients), but not in studies with a large cohort (≥ 100 patients).

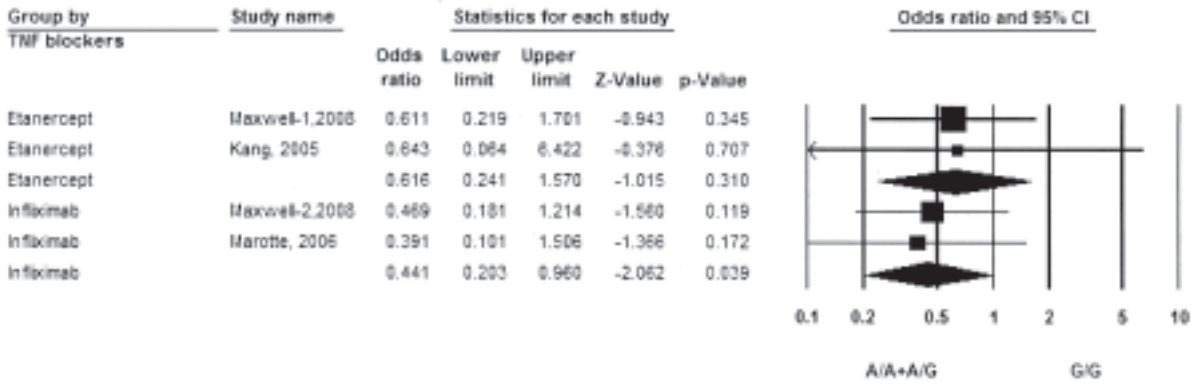

Figure 2. Association between TNF-α –238 A/G polymorphism and treatment response to TNF inhibitors in RA. OR of the A allele carrier state (A/A + A/G genotypes) was significantly lower for infliximab responders, but not for etanercept responders.

TNF blocker responses. We found that neither SE status (OR 1.264, 95% CI 0.909–1.706, p = 0.171) nor SE copy number was significantly associated with response to treatment (Table 4).

DISCUSSION

We have updated our previous metaanalysis[28] of the relation between the TNF-α –308 A/G polymorphism and response to TNF blocker treatment in RA. In the previous study, we found a significant association between the TNF-α –308 A/G polymorphism and responsiveness to therapy. Individuals carrying the A allele were found to respond less well to anti-TNF therapy than those with the G allele. However, in the present study, the metaanalysis of all included data shows that the TNF-α –308 A/G polymorphism was not associated with treatment response to TNF blockers in patients with RA. However, study stratification by cohort size showed that smaller studies (< 100 patients) found that the presence of the A allele predicts a poor treatment response, whereas larger studies found no such association. Further, the present study shows that for all studies no association exists between the TNF-α –308 A/G polymorphism and response to TNF blocker.

Regarding the TNF-α –238 A/G polymorphism, an association was found for response to infliximab, but not to etanercept. More specifically, the presence of the A allele was found to be associated with a poor treatment response to infliximab, but did not predict response to etanercept. These findings raise questions concerning the modes of action of these 2 drugs, and the manner in which genotype differen-

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tially influences treatment response. It was reported previously that patients may respond to one TNF blocking agent but not another. Several biological factors influence response to TNF-soluble receptors and neutralizing anti-TNF antibodies; for example, infliximab (but not etanercept) is approved for the treatment of Crohn's disease. Further, infliximab is known to bind to transmembrane TNF on activated immune cells, whereas etanercept binds only soluble TNF[29]. In addition, etanercept also binds a related molecule, lymphotoxin-α, whereas infliximab does not, and the 2 drugs may induce granulomatous infections at different rates[30].

Our analysis differed from a previous metaanalysis of the TNF-α –308 A/G polymorphism and responsiveness to TNF-α blockers in RA performed by O'Rielly, *et al*[27]. They analyzed 9 studies, and found that the odds of having the A allele were lower in responders compared to nonresponders, irrespective of the TNF-α inhibitors prescribed[7-11,13,14,20,21]. In contrast, we performed a metaanalysis of 12 studies of the TNF-α –308 A/G polymorphism[5-14,20,21], including 3 more studies[5,6,12], of which 2 had large numbers of patients (n = 369 and 206, respectively) and were published recently[6,12]. In addition, we analyzed TNF-α –238 A/G polymorphism and shared epitope. Analysis of the TNF-α –308 A/G polymorphism showed no significant association of TNF-α –308 A/G polymorphisms and responsiveness to TNF-α blockers, unlike the results of O'Rielly, *et al*. The differences in results for the TNF-α –308 A/G polymorphism between these 2 studies are due to the use of different sets of studies.

The shortcoming of our report is that only a relatively small number of studies have been conducted on the relation between TNF-α –238 A/G polymorphism and response to infliximab. Our subgroup analysis regarding the TNF-α –238 variant and infliximab should be assessed with caution due to the small number of patients in it. Accordingly, the associations demonstrated must be regarded as preliminary, and confirmatory studies are required.

The association between SE and RA susceptibility and severity is well established, but studies on the effect of SE on response to TNF inhibitors in RA have produced contradictory results. For example, one study showed increased response to etanercept in patients with 2 copies of the SE[15], but 3 later studies failed to replicate this finding[5,8,9]. We found no relation between SE status and response to TNF blockers.

Some limitations of our study warrant consideration. First, the frequencies of the TNF –308 and –238 alleles are low in Asians. Kang, *et al*[9] found only one case with the TNF –308 G/A genotype and 4 with either the TNF –238 G/A or A/G genotype among 70 Korean patients with RA. Second, publication bias could have distorted our metaanalysis, because of the small number of studies, especially in the subgroup analysis. Third, it is unclear whether the TNF-α –308 and –238 G/A polymorphisms alone or in combination with other polymorphisms or genes are responsible for response to anti-TNF therapy. Fourth, heterogeneity and confounding factors may have affected the metaanalysis. The following explanations may account for discrepancies among previous studies. The ACR criteria are a measure of change, whereas the DAS28 index is an absolute measure of disease activity, and a continuous variable. Further, variables such as response criteria used as a primary endpoint (DAS28 decrease, ACR20 or ACR50 response) and followup period (range from 12 weeks to 1 year) differed among studies. However, in the present study, no association was found between any of these variables and response to treatment.

We observed that the TNF-α –238 A/G polymorphism was associated with treatment response to infliximab in patients with RA, but that the TNF-α promoter –308 A/G polymorphism and SE status were not associated with treatment response.

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