Association of TNF-α polymorphism with prediction of response to TNF blockers in spondyloarthrosis and inflammatory bowel disease: a meta-analysis

Aim: To explore whether TNF-α promoter -308 A/G and -857 C/T polymorphisms have an association with responsiveness to TNF blockers in spondyloarthrosis and inflammatory bowel disease. Methods: A meta-analysis was performed. Pooled odds ratios (ORs) and 95% CIs were calculated. Results: Six relevant studies with a total of 211 spondyloarthrosis patients and 392 inflammatory bowel disease patients were included. The results showed that the common allele (G and C, respectively) showed a better responsiveness than the minor allele (A and T, respectively). The -308 G/G genotype (OR: 2.31; 95% CI: 1.36–3.91; p = 0.002) and -857 C/C genotype (OR: 3.66; 95% CI: 1.35–9.92; p = 0.01) responded better to therapy, which was different from the results of some studies included. Conclusion: Individuals with the TNF-α -308 G allele and -857 C allele showed better anti-TNF-α treatment responses than those with the TNF-α -308 A allele and -857 T allele. The -308 G/G genotype and -857 C/C genotype are predictors of good response.

Original submitted 30 May 2013; Revised submitted 25 July 2013

KEYWORDS: inflammatory bowel disease meta-analysis prediction spondyloarthrosis TNF blocker TNF-α -308 polymorphism TNF-α -857 polymorphism

Spondyloarthrosis (SpA) refers to a set of inflammatory disorders, including ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), enteropathic arthritis (inflammatory bowel disease [IBD]-related arthritis), juvenile SpA and undifferentiated SpA, which mainly afflict the spine, joints, ligaments and sometimes intestines, urinary tract, heart and skin.

IBD is a group of inflammatory conditions of the colon and small intestine. IBD is considered an autoimmune disease, in which the body’s own immune system attacks elements of the digestive system causing abdominal pain, vomiting, diarrhea, rectal bleeding, severe internal/cramps/muscle spasms in the region of the pelvis and weight loss. The major types of IBD are Crohn’s disease and ulcerative colitis. As for SpA, IBD is also considered an autoimmune disease. On the other hand, IBD is one of the features of SpA according to the new criteria for classification of axial SpA developed by the Assessment of Spondyloarthrosis International Society (ASAS) in 2009. SpA occurs in 10% of patients, and 70% of the latter also have gastrointestinal tract inflammation. Up to 12% of these patients will develop overt IBD. Furthermore, patients with SpA and IBD share similar immunologic alterations. E-cadherin is highly expressed in the gut of patients with SpA and IBD. Th1, Th17 and Treg cells are active in the intestinal mucosa of patients with IBD and synovial fluid of those with AS and SpA. The immunologic alterations shared by patients with IBD and SpA also include: TNF-α is a dominant cytokine in IBD and SpA; antigen-presenting cells with microorganisms; and the Toll-like receptors TLR-2 and TLR-4 also play an important role in both IBD and SpA. In addition, HLA-B27 transgenic rats develop IBD, psoriasis, enthesitis (inflammation at the sites where tendons or ligaments attach to bone), synovitis and epididymitis [101]. Accumulating evidence has emphasized that TNF-α is one of the potent proinflammatory cytokines that plays an important role in inflammatory and immune responses, including SpA and IBD [1–3]. The introduction of anti-TNF-α has revolutionized the management of SpA and IBD. TNF blockers had been proven to be highly effective in reducing SpA and IBD manifestations. However, both IBD and SpA patients showed variant responses to therapy with this group of drugs [4–8]. The reasons for this phenomenon remain unclear and worth exploring. One point requires weighing the risks and benefits of this expensive therapy. This background of uncertainty renders questions as to patient selection for such treatment and emphasizes the need for a reliable tool to predict the outcome.

The TNF-α gene contains several SNPs, which have been found relevant to susceptibility...
and severity of SpA and IBD, as well as the response of anti-TNF treatment [9, 19–21]. Among the SNPs, there are two common polymorphisms that have been studied extensively. One is a G to A substitution at position -308 (rs1800629) while the other is a C to T substitution at position -857 (rs1799724). Several studies have examined the potential contribution of TNF-α promoter -308 A/G and -857 C/T polymorphisms to responsiveness to TNF blockers in SpA and IBD [22–27]. Our previous study showed that polymorphism at the -308 position of the TNF-α gene was unable to predict TNF-α-blocker response, while -857 C/C genotype had the ability to predict good response [26]. However, Seitz et al. showed that rheumatic disease patients (rheumatoid arthritis [RA], PsA or AS) with the TNF-α -308 G/G SNP showed greater response to therapy with the anti-TNF-α agents [24]. These inconsistent results of the studies are due to the small sample sizes and low statistical power.

Meta-analysis could increase the sample size by combining inconsistent results from several studies, thus reducing the probability of random errors that would produce false-positive or false-negative associations [28]. Several meta-analyses have been performed to detect the association of TNF-α polymorphism with responsiveness to TNF blockers in RA; however, there is no similar study performed for SpA or IBD. Therefore, the present study aims to explore whether TNF-α promoter -308 A/G and -857 C/T polymorphisms have association with responsiveness to TNF blockers in SpA and IBD.

**Methods**

**Identification of eligible studies & data extraction**

We performed a search for studies that examined the association of the TNF-α polymorphisms with responsiveness to TNF blockers with SpA and IBD patients within the electronic databases PubMed and Elsevier Science Direct up to February 2013. We also checked all references of retrieved articles to identify additional studies when key information relevant to the meta-analysis was missing and contacted the investigators for additional data. The following keywords and subject terms were searched: (‘tumor necrosis factor’ or ‘TNF-α’ or ‘TNF α’ or ‘polymorphism 308’ or ‘polymorphism 857’) and (‘TNF blocker’ or ‘TNF therapy’ or ‘etanercept’ or ‘infliximab’ or ‘adalimumab’) and (‘spondyloarthritis’ or ‘SpA’ or ‘ankylosing spondylitis’ or ‘AS’ or ‘psoriatic arthritis’ or ‘PsA’ or ‘IBD’ or ‘Crohn’s disease’ or ‘CD’ or ‘enteropathic arthritis’). No language, race, ethnicity or geographic area restrictions were applied.

The following study criteria were used: it was original data (independent among studies); involving TNF-α gene promoter -308 or -857 polymorphism genotype (AA, GA, GG/CC, CT, TT) frequencies and/or allele frequencies of both responders and nonresponders; it provided enough data to calculate the odds ratios (ORs). Extraction from each study was conducted independently by two authors and a consensus was achieved concerning the data.

**Statistical analysis**

Statistical manipulations were undertaken using the program RevMan 5.0 (Cochrane Collaboration [102]). For TNF-α gene promoter -308, we examined the contrast of the allelic effect of G (common allele) versus A (minor allele), the G/G versus the (A/A+A/G) genotypes and the (A/G+G/G) versus A/A genotypes. For TNF-α gene promoter -857, we examined the contrast of the allelic effect of C (common allele) versus T (minor allele), the C/C versus the (C/T+T/T) genotypes and the (C/T+C/T) versus T/T genotypes. Dichotomous data were presented as the OR with the 95% CI. A p-value < 0.05 was considered to be statistically significant. Z test was used to determine the significance of the pooled OR.

We assessed within- and between-study variations, or heterogeneity, by testing Cochran’s Q-statistic [29]. This heterogeneity test assesses the null hypothesis that all studies were evaluating the same effect. A significant Q-statistic (p < 0.10) indicates heterogeneity across studies. We also quantified the effect of heterogeneity by using I². I² ranges between 0 and 100% and this represents the proportion of the between-study variability that can be attributed to heterogeneity rather than chance. I²-values of 25, 50 and 75% were assigned as low, moderate and high estimates, respectively. A fixed effects model was used by the Mantel–Haenszel method when the results of the trials were not heterogeneous. Otherwise, a random effects model was used according to the DerSimianon and Laird method [29].

Publication bias was assessed using a funnel plot in which the standard error of log of each study was plotted against its OR. Usually, it needs at least five studies to draw a funnel plot. An asymmetric plot suggested possible publication bias [29].
Results

Characteristics of selected studies
A total of six relevant studies met the inclusion criteria for the meta-analysis (Figure 1) [22–27]. Selected characteristics of these six studies are summarized in Table 1. The subject numbers ranged from 32 to 214, and a total of 211 SpA patients (121 AS patients and 90 psoriasis/PsA patients) and 392 IBD patients were included in this meta-analysis. From the aspect of the TNF blockers, infliximab was used alone in three studies, and together with etanercept and adalimumab in the other three studies. The follow-up period ranged from 30 days to 6 years. Five studies detected the association of TNF-α promoter -308 A/G polymorphism with responsiveness to TNF blockers in a total of 131 SpA patients and 392 IBD patients. Only three studies detected the association of TNF-α promoter -857 C/T polymorphism in responsiveness to TNF blockers for a total of 179 SpA patients and 101 IBD patients. One study only showed the alleles rather than genotypes [25].

Association of TNF-α promoter -308 A/G polymorphism & responsiveness of TNF blockers
In addition to G versus A for TNF-α -308 A/G, we also examined genotypes. The following genotype contrasts were included: the G/G versus the (A/A+A/G) genotypes and the (A/G+G/G) versus A/A genotypes. These contrasts correspond to the dominant and recessive effects model of the G allele. The summary of the meta-analysis results of association of TNF-α promoter -308 A/G polymorphism and responsiveness of TNF blockers are shown in Table 2. Publication bias was not detected owing to not enough data being included to draw a funnel plot. Each comparison showed a p-value >0.1 in the test of heterogeneity, which meant there was no heterogeneity among studies, thus fixed model effects were used. We found a significant p-value for G allele versus A allele (OR: 2.14; 95% CI: 1.38–3.33; p = 0.0007) indicating that the G allele reflects better responsiveness than the A allele (Figure 2). In addition, the GG genotype benefited from better responsiveness than (GA+AA) genotypes to the TNF blockers (OR: 2.31; 95% CI: 1.36–3.91; p = 0.002; Figure 3). However, no significant difference was found for (A/G+G/G) versus A/A genotypes (Figure 4).

Association of TNF-α promoter -857 C/T polymorphism & responsiveness of TNF blockers
Similar to TNF-α -308 A/G, we examined the contrasts of the allelic effect of C (common allele) versus T (minor allele), the C/C versus the (C/T+T/T) genotypes and the (C/C+C/T) versus (C/T+T/T) genotypes and the (C/C+C/T) versus (C/T+T/T).
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Disease</th>
<th>DiseasePatient number</th>
<th>TNF inhibitor</th>
<th>Follow-up period</th>
<th>Response criteria</th>
<th>Response criteria</th>
<th>Response criteria</th>
<th>Response criteria</th>
<th>Response criteria</th>
<th>Response criteria</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermeire et al.</td>
<td>2000</td>
<td>Belgium</td>
<td>CD</td>
<td>77</td>
<td>Infliximab</td>
<td>–</td>
<td>CDAI 47</td>
<td>G/G</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[22]</td>
</tr>
<tr>
<td>Louis et al.</td>
<td>2002</td>
<td>Belgium</td>
<td>CD</td>
<td>214</td>
<td>Infliximab</td>
<td>18 weeks</td>
<td>CDAI 116</td>
<td>G/G</td>
<td>35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[23]</td>
</tr>
<tr>
<td>Seitz et al.</td>
<td>2007</td>
<td>Switzerland</td>
<td>AS</td>
<td>22</td>
<td>Infliximab, adalimumab and etanercept</td>
<td>24 weeks</td>
<td>BASDAI 16</td>
<td>G/G</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[24]</td>
</tr>
<tr>
<td>PsA</td>
<td>10</td>
<td>Benjamin</td>
<td>CD</td>
<td>16</td>
<td>Infliximab</td>
<td>30 days</td>
<td>Clinical outcome G 26 A 4</td>
<td>G/A</td>
<td>1</td>
<td>T</td>
<td>0</td>
<td>0</td>
<td>[25]</td>
</tr>
<tr>
<td>Danicova et al.</td>
<td>2009</td>
<td>Denmark</td>
<td>CD</td>
<td>15</td>
<td>Infliximab</td>
<td>6 years</td>
<td>Clinical outcome G 23 A 5</td>
<td>G/A</td>
<td>2</td>
<td>C</td>
<td>28</td>
<td>2</td>
<td>[25]</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>2012</td>
<td>China</td>
<td>AS</td>
<td>99</td>
<td>Infliximab and rhTNFR-Fc</td>
<td>12 weeks</td>
<td>BASDAI 88 A 3</td>
<td>G/G</td>
<td>8</td>
<td>C/C</td>
<td>35</td>
<td>1</td>
<td>[26]</td>
</tr>
<tr>
<td>Vasiopoulou et al.</td>
<td>2012</td>
<td>Greece</td>
<td>PS</td>
<td>80</td>
<td>Infliximab, adalimumab and etanercept</td>
<td>6 months</td>
<td>PASI</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>C/C</td>
<td>41</td>
<td>6</td>
</tr>
</tbody>
</table>

rhTNFR-Fc (Product name: YiSaiPu) is a TNF-α blocker manufactured in China since 2006 that is similar to etanercept [33].

--: Unavailable data; AS: Ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Activity Index; CD: Crohn’s disease; CDAI: Crohn’s Disease Activity Index; DAS28: Disease Activity Score 28; PASI: Psoriasis Area and Severity Index; PS: Psoriasis; PsA: Psoriatic arthritis.
T/T genotypes. Table 3 shows the meta-analysis results. Publication bias was not detected owing to not enough data being included to draw a funnel plot. There was no heterogeneity among studies detecting TNF-α -857 C/T, thus fixed model effects were used. C allele showed better responsiveness than T allele to the TNF blockers (OR: 2.17; 95% CI: 1.17–4.03; p = 0.01; Figure 5). Also, the OR for the T allele carrier state was significantly decreased in the responder group (OR: 3.66; 95% CI: 1.35–9.92; p = 0.01; Figure 6). No significant difference was found for (C/C+C/T) versus T/T genotypes (Figure 7).

Discussion
The TNF-α protein is a potent proinflammatory cytokine and immune modulator of joint destruction, and TNF-α possibly should be considered as a risk factor for the development of SpA and IBD [11]. TNF-α stimulates the expression of adhesion molecules and increases neutrophil activation. The introduction of TNF blocking biologic drugs has constituted the greatest advance in the treatment of SpA and IBD over the past 50 years. The availability of effective anti-TNF treatment has exposed great economic and social value. It is important to be able to identify the predictors for responsiveness to TNF blockers, because the drugs are expensive and can cause serious complications. It has been speculated that the TNF-α -308 and -857 polymorphisms may affect the transcription of TNF-α. However, these studies may show conflicting results owing to small sample sizes and low statistical power. So we aimed to explore whether TNF-α -308 and -857 polymorphisms could be predictors to the responsiveness of TNF blockers.

Our meta-analysis revealed that for both TNF-α -308 or -857 polymorphisms, the common allele (G and C, respectively) showed a better responsiveness to the TNF blockers than the minor allele (A and T, respectively). In addition, it also showed a significant difference between the minor allele carrier (GA+AA and CT+TT) and noncarrier states (GG and CC).

Among the five studies detecting the association of TNF-α promoter -308 A/G polymorphism with responsiveness to TNF blockers, only Seitz et al. demonstrated a positive result as to G allele and GG genotype [24], and Vermeire found a significantly positive association between carriers of allele G and treatment response [22]. The other three studies showed no relevant association of TNF-α promoter -308 A/G polymorphism and therapeutic response [23,25,26]. Among the three studies detecting the association of TNF-α promoter -857 C/T polymorphism with responsiveness to TNF blockers, Tong showed the -857 C/C genotype responded better to therapy [26] and Vasilopoulos revealed carriage of TNF-α -857C was associated with positive response to anti-TNF-α treatment [27]. Our meta-analysis showed quite different results from the studies included. The explanation for this phenomenon may be because we used meta-analysis to combine inconsistent results from several studies to explore a result for SpA and IBD. However, despite belonging to SpA, different diseases such as AS and PsA may have a different mechanism for the response to TNF blockers.

As the first meta-analysis study concerning TNF-α polymorphism and therapeutic response in SpA and IBD patients, we compared our results with other meta-analyses examining RA patients. In 2010, Lee et al. showed that there was no significant difference in the proportions of TNF-α promoter -308 A allele carriers in a group that responded to treatment and a group that did not [30], while Pavy et al. came to the same conclusion [31]. In 2012, Zeng concluded that there was no significant difference between GG and (GA+AA) with responsiveness to the TNF blockers (infliximab, etanercept and adalimumab) [32], which conflicted with our results. Several reasons could be considered: first, SpA and RA are different diseases and may have different mechanisms for the response to TNF blockers. Second, Zeng included 15 studies with a total

Table 2. Association of TNF-α promoter -308 A/G polymorphism and responsiveness of TNF blockers.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Pooled studies</th>
<th>Test of heterogeneity</th>
<th>Effects model</th>
<th>Test of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>G versus A</td>
<td>[22–26]</td>
<td>4.48</td>
<td>p-value</td>
<td>OR</td>
</tr>
<tr>
<td>G versus A</td>
<td>[22–24,26]</td>
<td>4.41</td>
<td>Fixed</td>
<td>2.14</td>
</tr>
<tr>
<td>G+G versus A</td>
<td>[22–24,26]</td>
<td>0.01</td>
<td>Fixed</td>
<td>1.44</td>
</tr>
</tbody>
</table>

Publication bias was not detected owing to not enough data included to draw a funnel plot.

OR: Odds ratio.
of 2127 patients in his meta-analysis, which is a much larger sample size than ours. At the same time, subgroup analysis was performed based on different response criteria (disease activity score 28 [DAS28] and American College of Rheumatology 20% improvement criteria [ACR20]) in his study. Subgroup analysis could explore the source of heterogeneity and reduce the possible influence factor, thus providing more accurate results.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Responder Events</th>
<th>Nonresponder Events</th>
<th>Odds ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duricova 1 [25]</td>
<td>49</td>
<td>3</td>
<td>3.6%</td>
</tr>
<tr>
<td>Duricova 2 [25]</td>
<td>120</td>
<td>1</td>
<td>1.1%</td>
</tr>
<tr>
<td>Louis [23]</td>
<td>271</td>
<td>88</td>
<td>75.7%</td>
</tr>
<tr>
<td>Seitz 1 [24]</td>
<td>36</td>
<td>2</td>
<td>1.5%</td>
</tr>
<tr>
<td>Seitz 2 [24]</td>
<td>20</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Tong [26]</td>
<td>179</td>
<td>16</td>
<td>2.4%</td>
</tr>
<tr>
<td>Vermeire [22]</td>
<td>101</td>
<td>33</td>
<td>15.8%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>864</td>
<td>182</td>
<td>2.14 (1.38–3.33)</td>
</tr>
</tbody>
</table>

Total events 776
Heterogeneity: \( \chi^2 = 4.48; df = 5 \) (\( p = 0.48 \)); \( I^2 = 0\% \)
Test for overall effect: \( Z = 3.38 \) (\( p = 0.0007 \))

Figure 2. Association of TNF-\( \alpha \) promoter-308 A/G polymorphism and responsiveness of TNF blockers (G allele vs A allele). Duricova 1 and Duricova 2 refer to the results of patients from two different countries. Seitz 1 and Seitz 2 refer to the results of two different subsets.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Responder Events</th>
<th>Nonresponder Events</th>
<th>Odds ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis [23]</td>
<td>116</td>
<td>35</td>
<td>80.8%</td>
</tr>
<tr>
<td>Seitz 1 [24]</td>
<td>16</td>
<td>0</td>
<td>1.1%</td>
</tr>
<tr>
<td>Seitz 2 [24]</td>
<td>10</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Tong [26]</td>
<td>88</td>
<td>8</td>
<td>3.5%</td>
</tr>
<tr>
<td>Vermeire [22]</td>
<td>47</td>
<td>12</td>
<td>14.7%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>334</td>
<td>88</td>
<td>2.31 (1.36–3.91)</td>
</tr>
</tbody>
</table>

Total events 277
Heterogeneity: \( \chi^2 = 4.41; df = 3 \) (\( p = 0.22 \)); \( I^2 = 32\% \)
Test for overall effect: \( Z = 3.11 \) (\( p = 0.002 \))

Figure 3. Association of TNF-\( \alpha \) promoter -308 A/G polymorphism and responsiveness of TNF blockers (G/G vs [G/A+A/A] genotypes). Seitz 1 and Seitz 2 refer to the results of two different subsets.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Responder Events</th>
<th>Nonresponder Events</th>
<th>Odds ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis [23]</td>
<td>155</td>
<td>53</td>
<td>73.1%</td>
</tr>
<tr>
<td>Seitz 1 [24]</td>
<td>20</td>
<td>2</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Seitz 2 [24]</td>
<td>10</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Tong [26]</td>
<td>91</td>
<td>8</td>
<td>26.9%</td>
</tr>
<tr>
<td>Vermeire [22]</td>
<td>54</td>
<td>21</td>
<td>2.57 (0.15–43.02)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>334</td>
<td>88</td>
<td>2.83 (0.69–11.60)</td>
</tr>
</tbody>
</table>

Total events 330
Heterogeneity: \( \chi^2 = 0.01; df = 1 \) (\( p = 0.94 \)); \( I^2 = 0\% \)
Test for overall effect: \( Z = 1.44 \) (\( p = 0.15 \))

Figure 4. Association of TNF-\( \alpha \) promoter -308 A/G polymorphism and responsiveness of TNF blockers ([A/G+G/G] vs A/A genotypes). Seitz 1 and Seitz 2 refer to the results of two different subsets.
There are still several limitations of our present study. First, owing to the fact that only six studies met the criteria and were included in this meta-analysis, we could not rule out the existence of publication bias, which may affect the results. More studies are needed to detect the association of TNF-α polymorphism and responsiveness to TNF blockers. Second, amidst the limitations, we can conclude that the TNF-α promoter -857 C/T polymorphism significantly affects the responsiveness to TNF blockers.

### Table 3. Association of TNF-α promoter -857 C/T polymorphism and responsiveness of TNF blockers.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Pooled studies</th>
<th>Test of heterogeneity</th>
<th>Effects model</th>
<th>Test of association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q</td>
<td>p-value</td>
<td>I² (%)</td>
</tr>
<tr>
<td>C versus T</td>
<td>[25–27]</td>
<td>2.61</td>
<td>0.27</td>
<td>23</td>
</tr>
<tr>
<td>CC versus CT+TT</td>
<td>[26,27]</td>
<td>0.04</td>
<td>0.84</td>
<td>0</td>
</tr>
<tr>
<td>CC+CT versus TT</td>
<td>[26,27]</td>
<td>0.05</td>
<td>0.82</td>
<td>0</td>
</tr>
</tbody>
</table>

Publication bias was not detected owing to not enough data included to draw a funnel plot.

### Figure 5. Association of TNF-α promoter -857 C/T polymorphism and responsiveness of TNF blockers (C allele vs T allele).

Duricova 1 and Duricova 2 refer to the results of patients from two different countries.

### Figure 6. Association of TNF-α promoter -857 C/T polymorphism and responsiveness of TNF blockers (C/C vs [C/T+T/T] genotypes).

### Figure 7. Association of TNF-α promoter -857 C/T polymorphism and responsiveness of TNF blockers ([C/T+C/C] vs T/T genotypes).
TNF-α gene polymorphisms at -308 and -857 positions could predict therapeutic response with TNF-α blockers in SpA and IBD. Individuals with the G allele and C allele showed better anti-TNF-α treatment responses than those with the A allele and T allele. The -308 G/G genotype (p = 0.002) and -857 C/C genotype (p = 0.01) are predictors of good response. In the future, presence or absence of the -308 G/G genotype and/or -857 C/C genotype could help us to determine which patients will benefit more from anti-TNF-α therapy.

Future perspective
Although the present meta-analysis suggests that TNF-α gene polymorphisms at the -308 and -857 positions could predict therapeutic response with TNF-α blockers, several clinical aspects remain to be clarified. Only six studies met the criteria and were included in this meta-analysis, more studies of different ethnic populations are needed to detect the association.

Conclusion
In conclusion, this meta-analysis showed that TNF-α gene polymorphisms at the -308 and -857 positions could predict therapeutic response with TNF-α blockers in SpA and IBD. Individuals with the G allele and C allele showed better anti-TNF-α treatment responses than those with the A allele and T allele. The -308 G/G genotype (p = 0.002) and -857 C/C genotype (p = 0.01) are predictors of good response. In the future, presence or absence of the -308 G/G genotype and/or -857 C/C genotype could help us to determine which patients will benefit more from anti-TNF-α therapy.

Executive summary

Objectives
- Spondyloarthritis (SpA) and inflammatory bowel disease (IBD) are two homologous diseases. Several studies have examined the potential contribution of TNF-α promoter -308 A/G and -857 C/T polymorphisms to responsiveness to TNF blockers in SpA and IBD.
- However, the results of these studies remain inconsistent owing to small sample sizes and low statistical power. The present study aims to explore whether TNF-α promoter -308 A/G and -857 C/T polymorphisms have association with responsiveness to TNF blockers in SpA and IBD.

Methods
- We examined the association of the TNF-α polymorphisms with responsiveness to TNF blockers with SpA and IBD patients within the electronic databases PubMed and Elsevier Science Direct up to February 2013.
- Statistical manipulations were undertaken using the program RevMan 5.0 (Cochrane Collaboration).
- A meta-analysis was performed. Pooled odds ratios (ORs) and 95% CIs were calculated by both dominant and recessive genetic models.

Results
- Six relevant studies with a total of 211 SpA patients (121 ankylosing spondylitis patients and 90 psoriasis/pсорiatic arthritis patients) and 392 IBD patients were included in this meta-analysis.
- We found a significant p-value for G versus A allele (OR: 2.14; 95% CI: 1.38–3.33; p = 0.0007) indicating that the G allele reflects better responsiveness than the A allele.
- The G/G genotype benefited from better responsiveness than (GA+AA) genotypes to TNF blockers (OR: 2.31; 95% CI: 1.36–3.91; p = 0.002).
- No significant difference was found for (A/G+G/G) versus A/A genotypes (OR: 1.44; 95% CI: 0.69–11.6; p = 0.15).
- The C allele showed better responsiveness than T allele to TNF blockers (OR: 2.17; 95% CI: 1.17–4.03; p = 0.01).
- The OR for the T allele carrier state was significantly decreased in the responder group (OR: 3.66; 95% CI: 1.35–9.92; p = 0.01).
- No significant difference was found for (C/C+C/T) versus T/T genotypes (OR: 3.38; 95% CI: 1.00–11.48; p = 0.05).

Conclusion
- TNF-α gene polymorphisms at -308 and -857 positions could predict therapeutic response to TNF-α blockers.
- Individuals with the G allele and C allele showed better anti-TNF-α treatment responses than those with the A allele and T allele.
- The -308 G/G genotype and -857 C/C genotype are predictors of good response.
between TNF-α polymorphisms and responsiveness to TNF blockers. More studies about cofunction of TNF-α -308, -857 and other genes with response to anti-TNF therapy are required. In the future, pharmacogenomics will be widely utilized in SpA and IBD with TNF-α blockers for personalized medication. The -308 G/G genotype and/or -857 C/C genotype could guide us to select appropriate patients for anti-TNF-α therapy.

Acknowledgements
The authors would like to extend their gratitude to Shanghai Scientific Committee Basic Research Fund for their financial support. The authors would like to thank P Bajracharya from Shree Birendra Military hospital, Nepal for her help in revising the article. The authors would like to thank Director H Jia from the Department of Statistics for her support in their analysis. Finally, the authors wish to acknowledge all the colleagues in their department for their assistance and encouragement.

Financial & competing interests disclosure
This study has been supported by grants from Shanghai Scientific Committee Basic Research Fund (08JC1406300, 08JC1406200). This study was also supported by grants from National Natural Science Foundation of China (NSFC; H1008,81302580) and National Key Basic Research Program of China (973 Program (2014CB541804). The authors have no other relevant affiliations or financial involvement in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References
Papers of special note have been highlighted as:
* of interest
** of considerable interest
**Research Article**

Tong, Zhao, Qian et al.

---


26 Tong Q, Zhao DB, Bajracharya P et al. TNF-α -857 C>T and -308 G>A polymorphisms were found, which is in contrast to the findings of our study.


---

**Websites**


102 RevMan 5 download and installation. [http://ims.cochrane.org/revman/download](http://ims.cochrane.org/revman/download)