The −308 tumour necrosis factor-α gene polymorphism predicts therapeutic response to TNFα-blockers in rheumatoid arthritis and spondyloarthritis patients

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Objective. To examine whether the G-to-A polymorphism at position −308 in the promoter of the tumour necrosis factor-α (TNFα) gene influences the therapeutic response to TNFα-blockers in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Methods. A total of 54 patients with RA, 10 with PsA and 22 with AS were genotyped by polymerase chain reaction for the −308 TNFα promoter polymorphism. They were treated with infliximab (n = 63), adalimumab (n = 10) or etanercept (n = 13). Clinical response was assessed after 24 weeks by the Disease Activity Score in 28 joints (DAS28) for RA and PsA, and the Bath Ankylosing Spondylitis Activity Index (BASDAI) for AS patients.

Results. All patients with the A/A genotype (n = 3, all RA) and two patients with the A/G genotype (AS) failed to respond to anti-TNF treatment. Irrespective of the underlying disease, moderate response (n = 44) was predominantly associated with the A/G genotype (A/G 18/22, G/G 4/22), whereas good response (n = 59) was exclusively seen in patients with the G/G genotype. The average improvement in the DAS28 score was 0.83 in the A/A, 1.50 in the A/G and 2.64 in the G/G group of RA and PsA patients (P < 0.0001). The BASDAI score in AS improved on average by 1.21 in the A/G and by 3.30 in the G/G group (P < 0.005).

Conclusions. The data suggest that humans with a TNFα −308 G/G genotype are better responders to anti-TNFα treatment than those with A/A or A/G genotypes independent of the treated rheumatic disease (RA, PsA or AS).

Key words: −308 TNFα promoter polymorphism, Response to TNFα-blockers.

Tumour necrosis factor-α (TNFα)-neutralizing strategies represent a major breakthrough in the treatment of rheumatoid arthritis (RA) [1], ankylosing spondylitis (AS) and psoriatic arthritis (PsA) [2]. However, there is a large heterogeneity in the response to these agents. Therapy with TNFα-blockers is expensive and bears substantial risks. Predictors of treatment response would, therefore, be useful to select the appropriate patients for treatment. Recently, a French study showed that RA patients with the −308 TNFα promoter G/G genotype have a better response to TNFα-blockade with infliximab than those with the −308A allele [3]. In another study, patients with the rare allele of the promoter polymorphism 196 of the p75 TNF receptor showed a poorer response to anti-TNFα therapy [4]. In addition, a recent Swedish study demonstrated that the combination of the diploptypes −308 G/G in the TNFα promoter and of −1087G/G in the interleukin (IL)-10 gene was associated with good responsiveness to etanercept [5]. In the present study, we demonstrate a prognostic impact of the −308 TNFα promoter polymorphism regarding not only the responsiveness of RA patients to infliximab but also to etanercept and adalimumab. In addition, we present data for similar observations in spondyloarthritis patients.

Patients and methods

A total of 54 patients with RA, 10 patients with PsA and 22 patients with AS diagnosed according to the American College of Rheumatology [6] and modified New York criteria [7] required treatment with infliximab (Essex, Luzern CH), adalimumab (Abbott, Baar, CH) or etanercept (Wyeth, Zug, CH). The patients received infusions of infliximab or subcutaneous injections of adalimumab or etanercept according to standard protocols. Fifty-three RA, 10 PsA patients and 11 AS patients continued with s.c. weekly low-dose methotrexate (MTX). One RA patient received leflunomide (20 mg/day), and three AS patients were comedicated with azathioprine (50–150 mg/day). Three AS patients started with MTX after the onset of TNFα-blockade. Approval of the study was obtained from the Local Ethical Committee (Canton of Berne), and informed consent was obtained from all patients.

Response was assessed after 24 weeks of treatment. For RA and PsA patients, the modified disease activity score (DAS28) was used [8–10]. Disease activity of AS patients was assessed using the Bath Ankylosing Spondylitis Activity Index (BASDAI) [11]. We used a detailed categorization of response: in RA and PsA patients moderate response corresponded to a DAS28 improvement of >1.2 and ≤2.2, and good response to an improvement of >2.2 from baseline. Consequently, treatment failure was defined as an improvement in DAS28 <1.2.

In the group of AS patients, a moderate response was defined as an improvement in BASDAI of >20 and ≤50%, and a BASDAI improvement of >50% from baseline corresponded to a good response [11]. Non-responders were defined as having a BASDAI improvement of <20%.

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Genomic DNA was extracted from whole blood using a commercially available kit (Qiagen, Hilden, Germany). Genotypes were determined with the use of fluorogenic allele-specific oligonucleotide probes (TaqMan assay I). Primer pairs were designed to match the −308G or −308A allele, resulting in amplification of the target sequence. Genotype calling was carried out with the allelic discrimination analysis module of the ABI PRISM® 7700 SDS (software version 1.7).

Patients, characteristics and quantitative measures are presented as mean ± s.d. compared with Students, two-tailed t-test. A P-value < 0.05 was regarded as statistically significant. Association analyses of treatment response with −308 TNFα promoter diplotype (A/A, A/G, G/G), the allelic status (−308A absent or present), or the anti-TNF agents used in this study were done by χ² test. All statistics were done with the software package SPSS® version 12.0 (SPSS Munich, Germany).

Results

In Table 1, basis demographics, disease status and drug treatment of RA and AS patients were compared according with their −308 genotype (A/A, A/G, G/G). RA patients with the A/A and A/G genotypes tended to be younger than those with the G/G genotype. There were no significant differences in prednisolone and DMARD comedication at study entry. About 61.1% of RA patients received infliximab, 22.2% etanercept and 16.7% were treated with adalimumab.

Mean disease duration of AS patients was somehow longer in those with the A/G genotype compared with their G/G-positive counterparts (16.8 vs 9.5 yr; P < 0.025). The vast majority of AS patients was treated with infliximab (94.1%), and only one patient with adalimumab.

Table 2 demonstrates the division of RA, PsA and AS patients according to the −308 genotype that resulted in groups of comparable disease activity at baseline. RA patients and PsA patients were compared with infliximab, adalimumab or etanercept, were followed up. We examined whether the clinical response at 24 weeks could be predicted by the TNFα promoter genotype at position −308. Our analysis supports previous findings [3] on the importance of the −308 TNF promoter polymorphism for the response to infliximab of RA patients. In addition, our results provide evidence for similar associations in other inflammatory conditions.
and for the other two currently available TNF-blocking agents, etanercept and adalimumab.

When we analysed patients according to their clinical response (moderate and good responses), carriers of the G/G genotype by far outweighed patients with the A/G genotype in the group of good responders. In contrast, A/G carriers had a 14-fold higher probability of achieving only a moderate response compared with patients with the G/G genotype. The rare A/A genotype was strongly associated with non-response in our RA patients. In fact, we calculated a 10-fold higher probability of non-response in this group of patients compared with patients with the A/G genotype.

This is the first study reporting the importance of a TNFα polymorphism predicting response to TNFα-blocking agents not only in RA but also in PsA and AS. A previous study in Crohn’s disease did not find any influence of −308 TNFα gene polymorphism on the response to infliximab [12], and a Swedish group found that only a combination of the G/G genotype of the −308 TNFα promoter and the −1087 G/G genotype of IL-10 was associated with good responsiveness to etanercept in RA patients [5]. Our patients were comparable with regard to age and disease duration, but in contrast to the Swedish study, our RA patients were all on parenteral MTX, which is known to have a higher bioavailability compared with oral MTX [13]. One can argue that the more intensive MTX comedication had an impact on baseline inflammatory cytokine levels before starting with TNFα-blockers, rendering patients more sensitive to TNFα neutralization. This hypothesis is supported by our own studies on the effect of MTX on the IL-1 pathway [14]. It suggests a synergistic role of the two therapeutic strategies regarding the proinflammatory cytokine network. Another explanation is the inhibitory effect of MTX on the production of neutralizing antibodies to the TNFα-blocking molecules. Furthermore, it has previously been reported that MTX reduces the clearance of TNFα-blocking antibodies and thereby increases the bioactivity and the clinical response [15]. These mechanisms could also explain the substantially higher response rate of our RA patients with A/G or G/G genotypes compared with a French cohort of patients [3].

Our data furthermore support the previous observation [16] that a rapid CRP reduction upon TNFα-blockade was associated with the clinical response in RA patients (data not shown).

The results of clinical studies [16, 17] showing that some patients not responding to one TNFα-blocker may respond to the treatment with another TNFα-blocking agent, however, are not supported and cannot be explained by our data. Whether it is the locus investigated here, the presence of distinct TNFα haplotypes or MHC genes linked to −308 A/G as discussed elsewhere remains to be elucidated [3, 18, 19]. Similar results in RA and SpA, diseases of completely different genetic background, give rise to the assumption that the TNFα gene, rather than the class I or class II MHC genes, is of importance for the response to TNFα-blockade.

Collectively, the presented results illustrate that the TNFα promoter is important determinant of treatment response irrespective of genetic associations of the underlying diseases.

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References


