

Association of rs1568885, rs1813443 and rs4411591 polymorphisms with anti-TNF medication response in Greek patients with Crohn's disease

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Abstract

AIM: To investigate the correlation between rs1568885, rs1813443 and rs4411591 polymorphisms and response to infliximab in a cohort of Greek patients with Crohn's disease (CD).

METHODS: One hundred and twenty-six patients diagnosed with CD based on standard clinical, endoscopic, radiological, and pathological criteria were enrolled in this study at the Gastroenterology Unit of the 2nd Department of Surgery and at the Colorectal Unit of the 1st Department of Propaedeutic Surgery. Infliximab at a dose of 5 mg/kg was administered intravenously at weeks 0, 2, 6 and then every 8 wk. Clinical and serological responses were assessed using the Harvey-Bradshaw Index and serum C-reactive protein (CRP)

levels, respectively, and the endoscopic response was evaluated by ileocolonoscopy performed at baseline and after 12-20 wk of therapy. The changes in endoscopic appearance compared to baseline were classified into four categories, and patients were classified as responders and non-responders. Genomic DNA from whole peripheral blood was extracted and genotyping was performed by allele-specific polymerase chain reactions. χ^2 test with Yate's correction based on the S-Plus was used to compare the genotype frequencies.

RESULTS: Eighty patients (63.49%) were classified as complete and 32 (25.39%) as partial responders to infliximab, while 14 (11.11%) were primary non-responders. No correlation was found between response to infliximab and patients' characteristics such as age, gender and disease duration. There was consistency between Harvey-Bradshaw index scores and serum CRP levels. The TT genotype of the rs1568885 polymorphism was significantly related to partial response ($P = 0.024$) and resistance to infliximab ($P = 0.007$) while the AT genotype was more frequent in partial responders ($P = 0.035$) and in primary non-responders ($P = 0.032$). Regarding rs1813443, the CC genotype was found to be associated with partial response ($P = 0.005$) and primary resistance ($P = 0.002$) to infliximab while no association was found between the rs4411591 polymorphism and the clinical response to infliximab.

CONCLUSION: Based on our results, the rs1568885 and rs1813443 polymorphisms are associated with clinical and biochemical response to infliximab in Greek patients with Crohn's disease.

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Key words: Crohn's disease; Treatment response; Inf-

liximab; Polymorphisms

Core tip: A common treatment for inflammatory bowel disease is the use of tumor necrosis factor (TNF)- α inhibitors such as Infliximab (IFX). The discovery of novel markers of response to anti-TNF agents will provide valuable information for better stratification of these patients which will eventually further improve their clinical course and quality of life. Our results suggest that the rs1568885 and rs1813443 polymorphisms are associated with clinical and biochemical response to IFX in patients with Crohn's disease.

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INTRODUCTION

The use of anti-tumor necrosis factor (TNF) agents such as infliximab (IFX), certolizumab and adalimumab has impressively improved the clinical course of patients with Crohn's disease (CD) during the last decades^[1]. Across these agents, in the pivotal clinical trials, the initial response rate was approximately 60%, while only 30% of these responders maintained remission for as long as one year^[2,3]. Moreover, these medications have numerous reported side effects rendering the benefit to risk ratio narrower^[4]. These conclusions have led to the identification of multiple clinical parameters such as duration of treatment^[5] and disease phenotype^[6], and biological factors such as cytokines^[7] and C-reactive protein (CRP) levels^[8], as predictive markers of response to anti-TNF agents. Despite their utility and easy estimation in the clinical setting, these factors fail to fully predict the response of CD patients to the anti-TNF agents. Therefore, the discovery of novel markers of response to anti-TNF agents will provide valuable information for better stratification of these patients which will eventually further improve their clinical course and quality of life.

Recent studies highlight the potential effect of the individual's genetic background on the response to anti-TNF treatment. Taylor *et al.*^[9] demonstrated that patients homozygous for a TNF-polymorphism (LTA NcoI-TNFC-aa13L-aa26 1-1-1-1 haplotype) were poor responders to IFX while Pierik *et al.*^[10] found that the biological response to IFX was lower in patients carrying the TNFR1 36G mutation in the *TNFR1* gene. Additionally, López-Hernández *et al.*^[11] recently also maintained that particular TNF- α genotypes may be involved in the different responses to TNF- α inhibitor treatment in Spanish patients with inflammatory bowel diseases (IBD). How-

ever, other reports have failed to confirm the correlation between polymorphisms in the *TNF* genes and clinical response to this agent^[8,12]. Moreover, according to Niess *et al.*^[13], p.Arg702Trp, p.Gly908Arg and p.Leu1007fsX1008 polymorphisms in the *NOD2/CARD15* gene are related to poorer response to anti-TNF agents, while Weiss *et al.*^[14] found that *NOD2/CARD15* mutations did not have any impact on the response to IFX which was consistent with previous reports^[15]. Finally, the rs1143634 C allele was found to be correlated with higher serum IL1 β concentrations and lower response to IFX treatment in CD patients^[16].

Umicevic-Mirkov *et al.*^[17], in a recent report, performed a genome-wide association analysis in a cohort of 882 patients with rheumatoid arthritis and evaluated the association between single nucleotide polymorphisms and response to anti-TNF therapy. Three genetic loci (rs1568885, rs1813443 and rs4411591) with improved *P* value in the overall meta-analysis showed directional consistency over all four cohorts studied by the authors. The rs4411591 polymorphism is located in the *Loc100130480*, encoding a hypothetical protein, while the rs1813443 maps in the intronic region of contactin 5 (*CNTN5*) which is a member of the immunoglobulin superfamily and contactin family and mediates cell surface interactions during nervous system development^[18]. According to our knowledge, these genes have not been yet implicated in the development and progression of IBD. However, the correlation of these polymorphisms with the response to anti-TNF in patients with a systemic inflammatory disease such as rheumatoid arthritis suggests that they can be evaluated as potential biomarkers of the response of patients with CD to an anti-TNF agent such as IFX.

The aim of this study was to determine whether these reported loci (rs1568885, rs1813443 and rs4411591) reflect an association with response to IFX in patients with CD.

MATERIALS AND METHODS

Patients

One hundred and twenty six patients diagnosed with CD attending the IBD Clinic at the Gastroenterology Unit of the 2nd Department of Surgery, "Aretaieio" Hospital, and at the Colorectal Unit of the 1st Department of Propaedeutic Surgery, "Hippokrateio" Hospital, Athens, Greece, were enrolled in this case-control study. The diagnosis of CD was based on standard clinical, endoscopic, radiological, and pathological criteria^[19,20]. Patients with inflammatory (luminal) disease who were naïve to IFX were eligible for the study.

IFX was administered intravenously at a dose of 5 mg/kg at week 0, 2, 6 and then every 8 wk. Clinical and serological responses were assessed using the Harvey-Bradshaw Index (HBI)^[21] and serum levels of CRP, respectively, at baseline (before the 1st infusion of IFX), the day before each subsequent IFX infusion, and after 12 wk

Table 1 Demographic, clinical and biological characteristics of the study population *n* (%)

Characteristics	Complete responders	Partial responders	Primary non-responders	<i>P</i> value
Age (yr, mean ± SD)	80 (63.49) 28.42 ± 12.85	32 (25.39) 26.65 ± 14.21	14 (11.11) 27.32 ± 13.88	0.807
Gender (%)				
Male	62 (77.5)	19 (58.37)	8 (57.14)	0.082
Female	18 (22.5)	13 (40.63)	6 (42.86)	
CRP levels (mg/dL, mean ± SD)				
Pre-treatment (0 wk)	3.47 ± 0.85	5.62 ± 3.44	4.48 ± 2.15	< 0.0001
Post-treatment (12 wk)	1.07 ± 0.72	3.55 ± 1.49	1.61 ± 1.4	< 0.0001
ΔCRP levels (%)	75.27 ± 36.23	81.03 ± 32.05	63.91 ± 32.73	0.311
Disease years	8 ± 6.48	7.47 ± 5.11	8.18 ± 4.32	0.987
Infliximab dosing (mg/kg)	5	5	5	1.000
Localization (%)				
Colitis	26 (32.5)	4 (12.5)	2 (14.28)	0.295
Ileocolitis	50 (62.5)	27 (84.75)	12 (85.72)	
Upper gastroenteric	4 (5)	1 (2.75)	0	
Behaviour (%)				
Inflammatory	34 (42.5)	10 (31.25)	5 (35.71)	0.016
Stricturing	14 (17.5)	9 (28.13)	2 (14.29)	
Penetrating	32 (40)	13 (40.62)	7 (50)	

of treatment. Ileocolonoscopy was performed by a single endoscopist at baseline and after 12-20 wk of therapy to evaluate the presence of mucosal bleeding. The changes in endoscopic appearance compared to baseline were classified in four categories and patients were classified based on their response to IFX therapy with standard criteria as previously described^[22-24]. The ethical committee of the participating hospitals approved the study, and written informed consent was obtained in advance from each patient.

Genotyping

Genomic DNA from whole peripheral blood containing EDTA was extracted using validated techniques (NucleoSpin Blood kit; Macherey-Nagel, Germany). The genotyping was performed by allele-specific polymerase chain reactions (PCRs). Primer sequences for the rs1568885 polymorphism were forward 5'-TA-AAATACCAAGAAGCATGA-3', reverse T 5'-CTGAT-CAATCCTTTTTAA-3', and reverse A 5'-CTGAT-CAATCCTTTTTTAT-3'; for the rs1813443, reverse 5'-CATTAAATCTCACTGTCCTTTGC-3', forward G 5'-TTTCTCCAGCTGTGTTAACTG-3' and forward C 5'-TTTCTCCAGCTGTGTTAACTC-3'; for the rs4411591, reverse 5'-GACTCCATCTCCCTCATC-CA-3', forward G 5'-CACTCAACTCCAGTCCA-CAAG-3' and forward C 5'-CACTCAACTCCAGTCCA-CAAC-3'. The PCR products were then subjected to 3% agarose-gel electrophoresis.

Statistical analysis

Genotype frequencies were compared with the χ^2 test with Yate's correction using S-Plus (v.6.2Insightful, Seattle, WA). Odds ratios (OR) and 95%CI were obtained with GraphPad (v.300, GraphPad Software, San Diego, CA). The *P* values are all two-sided. *P* values of < 0.05 were considered to be significant.

RESULTS

Patients' demographic and clinical characteristics are presented in Table 1. Eighty patients (63.49%) were classified as complete, and 32 (25.39%) as partial responders to IFX, while 14 (11.11%) patients were primary non-responders in this study. There were no statistically significant differences between complete or partial responders and primary non-responders in terms of mean age, gender, disease duration, location and behavior and smoking habits. There was consistency between HBI scores and serum CRP levels classifying patients as complete or partial responders and primary non-responders.

Regarding the rs1568885 polymorphism, the AT genotype was more frequent in partial responders (*P* = 0.035) and in primary non-responders (*P* = 0.032) (Table 2). The TT genotype was also more frequent in partial responders (*P* = 0.024) and primary non-responders (*P* = 0.007) (Table 2). Based on these data, patients with AT genotype have 2.71 and 4.75 times increased risk of presenting partial response and primary resistance, respectively, compared to patients with AA genotype. Finally, patients with TT genotype have 8.14 and 21.37 times increased risk of presenting partial response and primary resistance, respectively, compared to patients with AA genotype. These results suggest that the carriers of the rs1568885T allele are more likely to fail the IFX treatment.

As far as the rs1813443 polymorphism is concerned, partial responders (*P* = 0.005) and primary non-responders (*P* = 0.002) present higher frequency of the CC genotype (Table 2). This result can be translated to the conclusion that the presence of the CC genotype is associated with 6.13 times increased risk of partial response and 11.5 times increased risk of primary resistance to IFX compared to the presence of GG genotype.

Finally, the evaluation of the rs4411591 polymorphism in our cohort showed that there was no associa-

Table 2 Distribution of genotypes in patients and controls *n* (%)

Genotype	Complete responders (<i>n</i> = 80)	Partial responders (<i>n</i> = 32)	<i>P</i> value; OR (95%CI)	Non-responders (<i>n</i> = 14)	<i>P</i> value; OR (95%CI)
rs1568885					
AA	57 (71.25)	14 (43.75)	1.0 (reference)	4 (28.57)	1.0 (reference)
AT	21 (26.25)	14 (43.75)	0.035; 2.71 (1.11-6.64)	7 (50)	0.032; 4.75 (1.26-17.9)
TT	2 (2.5)	4 (12.5)	0.024; 8.14 (1.3549.05)	3 (21.43)	0.007; 21.37 (2.73-167.2)
rs1813443					
GG	46 (57.5)	10 (31.25)	1.0 (reference)	4 (28.57)	1.0 (reference)
GC	28 (35)	14 (43.75)	0.09; 2.3 (0.9-5.87)	4 (28.57)	0.7; 1.64 (0.38-7.1)
CC	6 (7.5)	8 (25)	0.005; 6.13 (1.74-21.63)	6 (42.86)	0.002; 11.5 (2.5-52.84)
rs4411591					
GG	54 (67.5)	17 (53.12)	1.0 (reference)	10 (71.43)	1.0 (reference)
GA	24 (30)	12 (37.5)	0.34; 1.58 (0.66-3.84)	4 (28.57)	1; 0.9 (0.26-3.16)
AA	2 (2.5)	3 (9.37)	0.11; 4.76 (0.73-30.94)	0	1; 1.04 (0.05-23.23)

tion between any of the genotypes and response to IFX (Table 2).

DISCUSSION

IFX has been widely adopted for the treatment of Crohn's disease that is refractory to corticosteroids and immunosuppressive therapy, such as azathioprine and methotrexate. Recently, IFX has been used in combination with immunosuppression earlier during disease progression showing better initial control and improved long-term mucosal healing^[25]. Despite the obvious benefits in patients' quality of life^[26], the response rates differ between different studies and different populations^[2,3,27]. Data from induction trials in patients with moderate-to-severe CD resistant to conventional therapies showed that between 21% and 44% more patients achieved remission with IFX than with placebo. Moreover, according to two large maintenance trials, between 14% and 24% more patients achieved remission with IFX^[28]. The variability of the response rates between different individuals clearly decreases the efficacy of this agent in the treated patients, suggesting that the identification of predictive biomarkers is critical to improve patient outcomes.

The widely used clinical parameters such as disease location and biological factors such as cytokines can only partially predict the response to IFX^[29], while recent reports have evaluated the predictive value of gene polymorphisms^[26,30], fecal markers^[31] and gene expression profiles^[32]. According to a recent study, genome-wide association analysis in patients with rheumatoid arthritis discovered that three genetic loci (rs1568885, rs1813443 and rs4411591) showed directional consistency over all cohorts studied^[17]. Rheumatoid arthritis, as a systemic inflammatory disease with significant implication of T cell induced immunity, shares important characteristics with CD and it is reasonable to suggest that these polymorphisms may serve as good candidates for prediction of response. To our knowledge, this is the first study evaluating the predictive value of these polymorphisms regarding the response to IFX in patients with CD.

The efficacy of IFX was assessed with clinical, serological and endoscopic parameters. Clinical response to

IFX was evaluated using the HBI, which has shown good correlation with the CD activity index in clinical trials^[33]. Serologic evaluation of response to IFX was based on serum CRP alterations, which have been shown to be correlated with clinical course and inflammatory activity^[34,35]. Finally, the patients underwent ileocolonoscopy 12-20 wk after the initiation of therapy to obtain an objective view of the intestinal mucosa.

According to our results, the TT and AT genotypes of the rs1568885 polymorphism are significantly associated with partial and non-response to IFX. Interestingly, Umićević Mirkov *et al*^[17] showed that the presence of the A allele is related to good response to anti-TNF agents in patients with rheumatoid arthritis, supporting our data, despite the absence of any known pathophysiological mechanism connecting this genetic locus with the inflammatory pathways. This particular polymorphism has not yet been associated with the pathogenesis and progression of CD, and further studies are needed to evaluate its role in the development and progression of inflammatory bowel diseases.

Furthermore, only the CC genotype of the rs1813443 polymorphism was associated with partial response and initial resistance to IFX based on the above presented clinical, serologic and endoscopic criteria. Umićević Mirkov *et al*^[17] found that the presence of the C allele predicts for poor response to anti-TNF in patients with rheumatoid arthritis, which is in agreement with our results. This polymorphism, as mentioned above, is located in the intronic region of *CNTN5* which is implicated in the development of the nervous system^[18]. Interestingly, antibodies against the CNTN1/CASPR1 complex occur in a subset of patients with chronic inflammatory demyelinating polyradiculoneuropathy who share common clinical features^[34] and CNTN2 is known to be targeted by T cells and autoantibodies during the development of the inflammatory process in multiple sclerosis^[35]. These results suggest that members of the contactin superfamily have already been implicated in T cell mediated autoimmune diseases of the nervous system, supporting their potential role in the development of autoimmune inflammatory processes in other organs such as joints and intestine.

Finally, our data suggest that different genotypes of

the rs4411591 genetic locus do not have any impact on the response to IFX. The marker rs4411591 maps the Loc100130480, encoding a hypothetical protein and, according to Umicević Mirkov *et al.*¹⁷, the presence of the C allele is associated with good response to anti-TNF agents in patients with rheumatoid arthritis. The absence of any correlation in our study may be attributed to the relatively small population of patients, and further studies are needed to evaluate any potential impact of this genetic locus on the response of CD patients to IFX.

It is known that the basic mechanisms of inflammation are similar among different autoimmune diseases. The efficacy of IFX is associated with the role of TNF in the development and progression of inflammation within a particular genetic background for each individual. It could be hypothesized that genetic alterations and variations may alter the response to an anti-TNF agent such as IFX in various autoimmune diseases. According to our data, two genetic loci which are known predictive biomarkers for response to anti-TNF agents in patients with rheumatoid arthritis do predict the response to IFX in a cohort of patients with CD. This conclusion supports the concept of a strong genetic implication in autoimmune inflammation which may be similar among different autoimmune diseases, especially when they share common features such as the critical role of T cells. Finally, the predictive value of these polymorphisms regarding the response to IFX provides us with novel tools for patient stratification to improve the efficacy of this widely used anti-TNF agent.

COMMENTS

Background

A common treatment for inflammatory bowel diseases is the use of tumor necrosis factor (TNF)- α inhibitors such as Infliximab (IFX). The discovery of novel markers of response to anti-TNF agents will provide valuable information for better stratification of these patients which will eventually further improve their clinical course and quality of life.

Research frontiers

Recent studies highlight the potential effect of the individual's genetic background on the response to anti-TNF treatment.

Innovations and breakthroughs

Umicević Mirkov *et al.* recently reported identifying genetic factors predicting anti-TNF treatment outcome in patients with RA using a genome-wide association approach. Eight genetic loci showed improved *p* value in the overall meta-analysis compared with the first stage, three of which (rs1568885, rs1813443 and rs4411591) showed directional consistency over all four cohorts studied. In accordance with our results, they suggest genetic loci are associated with response to anti-TNF treatment.

Applications

The predictive value of genetic polymorphisms regarding the response to IFX provides us with novel tools for patient stratification to improve the efficacy of this widely used anti-TNF agent.

Peer review

This is a good descriptive study in which authors analyze the predictive effect of different genetic loci regarding response to anti-TNF treatment.

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