Chapter 7

The role of TNF-α G-308A polymorphisms in the course of pulmonary sarcoidosis

P Wijnen, P Nelemans, J Verschakelen, O Bekers, C Voorter, M Drent

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Abstract

Background
This study was designed to evaluate the relationship between the presence of tumor necrosis factor (TNF) polymorphisms, human leukocyte antigen (HLA)-DRB1*03 linkage and the prognosis of sarcoidosis.

Study design
In a retrospective case-control study, *TNF-α* G-308A, *TNF-α* G-238A, *lymphotoxin-α* (*LTA*) and HLA-DRB1*03 were genotyped in 625 sarcoidosis patients. These patients were classified into 298 patients with persistent disease and 327 patients with non-persistent disease using chest X-ray (CXR) appearances and lung function parameters after at least two years of follow-up.

Results
The *TNF-α* -308A variant allele was observed in 25.5% of patients with persistent disease compared with 44.0% of patients with non-persistent disease. The corresponding odds ratio (OR) was 0.43 with a 95% confidence interval (CI) of 0.30-0.61. A strong linkage was found between *TNF-α* G-308A and HLA-DRB1*03 (OR=0.03, 95% CI: 0.02-0.05). For *TNF-α* G-238A and *LTA NcoI* A252G, there were no statistically significant differences in the distribution of genotypes between the groups with and without persistent disease.

Conclusion
The data indicate that presence of a *TNF-α* -308A variant allele and HLA-DRB1*03 were associated with a favorable prognosis. Because of the strong linkage between *TNF-α* G-308A and HLA-DRB1*03, genotyping of one simple and less expensive TNF-α single nucleotide polymorphism can be used to predict the prognosis of pulmonary sarcoidosis in clinical practice.

Introduction

Sarcoidosis is a multisystem granulomatous disorder with distinct immunopathologic features. The disease is most likely the product of genetic susceptibility and an appropriate environmental antigen.[1-3] The clinical presentation and outcome of sarcoidosis varies considerably. Therapeutic options range from no treatment to a variety of therapeutic agents.
It is well known that the outcome of sarcoidosis varies considerably.[4] The presence of hilar adenopathy alone[5,6] or patients presenting with Löfgren's syndrome more often have a favorable outcome as compared with those with parenchymal lung disease.[7-9] By contrast, the presence of pulmonary fibrosis is associated with chronic disease.[5] Pulmonary disease is the most common manifestation of sarcoidosis, and pulmonary symptoms are the most common reason for treatment.[1,3] It is important to identify the patients who are likely to have a poor prognosis, to ensure the appropriate individual treatment regimen without delay.[10] Genetic polymorphisms contribute to clinical phenotypes.[6,9,11] Association of sarcoidosis and class I and II human leukocyte antigens (HLA) antigens is well known.[3,6,12] Grunewald et al. reported an influence of both HLA class I and class II alleles on the disease course in patients with sarcoidosis. They found that 76.8% of patients with resolving disease, appeared to be HLA-DRB1*03 positive, in contrast to only 9.2% of patients with persistent disease.[6]
Tumor necrosis factor alpha (TNF-α), a potent pro-inflammatory cytokine that plays a pivotal role in inflammatory and immune responses, regulates and sustains granuloma formation in sarcoidosis.[3] TNF-α production is an innate host characteristic that varies between individuals and is associated with certain HLA-D receptor (HLA-DR) alleles.[13] The TNF gene locus, comprising of the *TNF-α*, *lymphotoxin-α* (*LTA*, formerly also referred to as *TNF-β*) and *lymphotoxin-β* genes, is located in the class III region of the major histocompatibility complex (MHC). Genetic analysis has showed a number of polymorphisms in these genes and new polymorphisms with potential functional consequences.[7,14-16] Of genes in the MHC III region, the *TNF-α* polymorphisms have been extensively studied. Several single nucleotide polymorphisms (SNPs) are identified in the *TNF-α* gene. Among these, a common polymorphism in the promoter region, a G to A substitution at position -308, has been associated with variation of TNF-α production. Especially the A-allele of the *TNF-α* G-308A gene is associated with higher TNF-α serum levels and an acute course of sarcoidosis.[17] The existence of a strong linkage disequilibrium between HLA-DRB1*03 and the *TNF-α* -308A variant allele has been shown.[6,9,18] In addition to the *TNF-α G-308A* polymorphism, others found that the *TNF-α* G-238A and *LTA NcoI* A252G SNPs were associated with variations in TNF-α production and suggested a possible role in the course of sarcoidosis.[7,8,11,17]

The aim of the present study was to assess the association among *TNF-α* G-308A, *TNF-α* G-238A and *LTA NcoI* A252G variant alleles and clinical outcome in sarcoidosis. In addition, the linkage between *TNF-α* G-308A and HLA-DRB1*03 and its influence on disease course in our population was studied.

Materials and methods

Patients

From January 2000 to July 2008, 625 consecutive Dutch Caucasian sarcoidosis patients, attending the outpatient referral clinic of the Sarcoidosis Management Center of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC) were included in this study. The time since diagnosis to inclusion and/or follow-up for all patients was at least two years. The diagnosis was based on a positive biopsy in 71% of cases. In patients with typical features of Löfgren's syndrome and characteristic features of bronchoalveolar lavage (BAL) fluid analysis results, no biopsy was obtained. This policy is consistent with the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) guidelines.[1]
The study was performed in accordance with the Declaration of Helsinki and its amendments. The protocol was approved by the Medical Ethics Board of the MUMC. Written informed consent for participation in this study was obtained from all subjects.

Collection of clinical data

Clinical course of patients with sarcoidosis was defined using changes in CXR stage and lung function parameters during follow-up. All CXR films were graded by a single observer, who was not aware of the clinical data. Five stages of the radiographical abnormality were recognized: stage 0 (normal CXR), stage I (bilateral hilar lymphadenopathy [BHL]), stage II (BHL and parenchymal abnormalities), stage III (parenchymal abnormalities without BHL) and stage IV (end stage lung fibrosis).
For the main analysis, patients were categorized into groups with and without persistent sarcoidosis. Persistent disease was defined as worsening of the CXR stage to stage II or higher, or remaining at CXR stage II or III, at least two years after diagnosis. Non-persistent disease cases were those who remained at or regressed to stage 0 or I.
At inclusion, the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). The diffusing capacity for carbon monoxide (DLCO) was

measured by the single-breath method (Masterlab). Values were expressed as a percentage of predicted values. The cut-off value for the DLCO, FEV_1 and FVC was <80% of predicted (≥80% is normal).[19]

TNF and HLA typing

TNF

DNA was obtained using venous EDTA anti-coagulated blood and isolated with a High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions.
All patients were genotyped for two *TNF-α* promoter polymorphisms (G-308A and G-238A) and one *LTA* polymorphism (*LTA NcoI* A252G, also known as *lymphotoxin-α*, *LTA_NcoI*, *LTA+252,* or *TNF-β NcoI* A329G).[20,21] For genotyping *TNF-α* G-308A, *TNF-α* G-238A and *LTA NcoI* A252G SNPs, real-time PCR Fluorescence Resonance Energy Transfer (FRET) assays (TIB MOLBIOL, Berlin, Germany) were performed as described by Bestmann et al.[20] on the LightCycler® (Roche Diagnostics). The person who performed the analyses was blinded to the clinical data that were used for the classification of subjects according to disease course.

HLA

Genomic DNA was isolated with QIA-AMP kits following the supplier's protocol (Qiagen, Westburg, Leusden, The Netherlands). Concentration and purity of DNA samples were measured at 260 nm and 260/280 nm.
Low-resolution typing of HLA-DRB1 was obtained by Luminex reverse SSO, using bead kits from One Lambda (One Lambda, Bethesda, MD) or by PCR-SSP using 45 in-house primer mixes as described previously.[22]

Statistical analysis

Statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL) for Windows.
Cross tables were used to compare the observed percentages with each genotype between groups of patients differing in prognosis. The chi-square test was used to test for statistical significant differences between groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were also derived from these tables to evaluate the strength of associations between genotypes and the course of sarcoidosis. Multivariate logistic regression models were used to adjust for differences in baseline characteristics between compared groups. A p-value of <0.05 (two sided) was considered to indicate statistical significance. Deviations from the Hardy–Weinberg equilibrium were analysed using the chi-square test.

Results

Patient characteristics of the studied total population and within groups of patients with and without persistent sarcoidosis are summarized in Table 7.1. Patients with persistent disease more often were male, smoked less often and were more frequently treated with corticosteroids. At diagnosis, the percentage with CXR stage 0 or I was much lower in patients with persistent disease than in the patients with non-persistent disease. Persistent disease was also associated with lower mean values of DCLO, FEV_1 and FVC at diagnosis.

Table 7.1 Patient characteristics for the total population and sorted by disease persistence.

		Total population (n=625)	Non-persistent (n=327)	Persistent (n=298)	p[a] value
Gender	Female	280 (44.8)	178 (54.4)	102 (34.2)	
	Male	345 (55.2)	149 (45.6)	196 (65.8)	<0.001
Age at diagnosis	Year±SD	40.2±11.7	40.5±12.6	39.8±10.6	
	(range)	(12-84)	(17-84)	(12-76)	
	<40 year	353 (56.5)	185 (56.6)	168 (56.4)	
	≥40 year	272 (43.5)	142 (43.4)	130 (43.6)	1.00
Smoking	No	556 (89.1)	282 (86.2)	275 (92.3)	
	Yes	68 (10.9)	45 (13.8)	23 (7.7)	0.020
Time since diagnosis	<5 year	154 (24.6)	82 (25.1)	72 (24.2)	
	≥5 year	471 (75.4)	245 (74.9)	226 (75.8)	0.78
Corticosteroid use	No	281 (45.0)	185 (56.6)	96 (32.2)	
	Yes	344 (55.0)	142 (43.4)	202 (67.8)	<0.001
CXR at diagnosis	0	59 (9.4)	59 (18.1)	0	
	I	188 (30.1)	178 (54.4)	10 (3.4)	
	II	244 (39.1)	65 (19.9)	179 (60.1)	
	III	134 (21.4)	25 (7.6)	109 (36.5)	<0.001[c]
CXR at follow-up	0	270 (43.2)	270 (82.6)	0	
	I	57 (9.1)	57 (17.4)	0	
	II	142 (22.7)	0	142 (47.7)	
	III	74 (11.9)	0	74 (24.8)	
	IV	82 (13.1)	0	82 (27.5)	<0.001[d]
DLCO[b]	Mean ± SD	81.2±17.3	86.9±15.1	75.0±17.5	
	(range)	(23-129)	(37-129)	(23-121)	
	≥80%	341 (56.0)	228 (71.9)	113 (38.7)	
	<80%	268 (44.0)	89 (28.1)	179 (61.3)	<0.001
FEV_1[b]	Mean ± SD	89.8±21.5	99.8±15.6	78.7±21.7	
	(range)	(23-140)	(54-140)	(23-128)	
	≥80%	439 (72.4)	289 (91.2)	150 (51.9)	
	<80%	167 (27.6)	28 (8.8)	139 (48.1)	<0.001
FVC[b]	Mean ± SD	98.7±19.1	106.0±15.5	90.5±19.4	
	(range)	(25-152)	(66-152)	(25-148)	
	≥80%	509 (84.8)	301 (95.3)	208 (73.2)	
	<80%	91 (15.2)	15 (4.7)	76 (26.8)	<0.001

[a] Non-persistent versus persistent. [b] % of predicted (<80% is abnormal). [c] CXR 0+I versus II+III. [d] CXR IV versus 0+I+II+III. n=number, SD=standard deviation, CXR=chest X-ray, DLCO=diffusing capacity of carbon monoxide, FEV_1=forced expiratory volume in 1 s, FVC=forced vital capacity. Missing: 16/19/25 for DLCO/FEV_1/FVC, respectively. All values presented are absolute numbers with percentages in parentheses unless otherwise specified.

Table 7.2 shows the distribution of polymorphisms for *TNF-α* G-308A, *TNF-α* G-238A, *LTA* and HLA-DRB1*03 in patients with and without persistent disease. The *TNF-α* -308A variant allele was more often present in the patients with non-persistent disease (44.0%) when compared with patients having persistent disease (25.5%). This difference was statistically significant ($p<0.001$). HLA-DRB1*03 was comparable with the *TNF-α* G-308A with 34.9% of patients with non-persistent disease being DRB1*03 positive and of the patients with persistent sarcoidosis 13.4% having DRB1*03, see Table 7.2.

Table 7.2 Genotype distributions for the total population and sorted by disease persistence.

	Genotype	Total population (n=625)	Non-persistent (n=327)	Persistent (n=298)	p[a] value
TNF-308	GG	405 (64.8)	183 (56.0)	222 (74.5)	
	GA	200 (32.0)	129 (39.4)	71 (23.8)	<0.001[b]
	AA	20 (3.2)	15 (4.6)	5 (1.7)	
TNF-238	GG	562 (89.9)	290 (88.7)	272 (91.3)	
	GA	63 (10.1)	37 (11.3)	26 (8.7)	0.29[b]
	AA	0	0	0	
LTA	AA	281 (45.0)	130 (39.8)	151 (50.7)	
	AG	279 (44.7)	158 (48.3)	121 (40.6)	0.09[b]
	GG	65 (10.3)	39 (11.9)	26 (8.7)	
DRB1*03	Neg	471 (75.4)	213 (65.1)	258 (86.6)	
	Pos	154 (24.6)	114 (34.9)	40 (13.4)	<0.001

[a] Non-persistent versus persistent. [b] No variant allele versus variant allele. TNF-308=*TNF-α* G-308A, TNF-238=*TNF-α* G-238A, LTA=*LTA NcoI* A252G, DRB1*03=HLA-DRB1*03, GG=wild type for TNF-308 and TNF-238, for LTA wild type=AA. All values presented are absolute numbers with percentages in parentheses unless otherwise specified.

For *TNF-α* G-238A and *LTA* there were no statistically significant differences in the distribution of genotypes between the groups with and without persistent disease; therefore, these polymorphisms were not used for further analysis. However, for the *LTA* there was a trend towards a higher G-allele percentage in the group with non-persistent disease (60.2%) compared with the group with a persistent course (49.3%).
In Table 7.3, patients were classified according to genotype distribution and next to persistent versus non-persistent disease outcome or HLA-DRB1*03 presence, alternative clinical parameters for clinical course, such as CXR stage and lung function test results are shown. Patients with poor prognosis were compared with patients with good prognosis with respect to the distribution of the *TNF-α* -308A variant allele. Those with CXR stage 0 and lung function parameters ≥80% represented the group with good prognosis and were used as reference. The ORs with 95% CIs were consistently and in most comparisons significantly lower than 1, indicating a protective effect of the presence of a *TNF-α* -308A variant allele. Presence of the *TNF-α* -308A variant

allele is associated with good prognosis: in the groups with favorable clinical outcome this allele was observed significantly more often than in the groups with a less favorable clinical outcome. The OR was 0.43 with 95% CI: 0.31-0.61. After adjustment for age, gender, corticosteroid use and smoking, the odds ratio remained the same: OR=0.43 (95% CI: 0.30-0.61).

Table 7.3 Prognosis by genotype distribution of the *TNF-α* G-308A variant.

		GG (n=405)	GA (n=200)	AA (n=20)	OR[a] (95%CI) carriage -308A	p[a] value
Persistence	No	183 (56.0)	129 (39.4)	15 (4.6)	1	
	Yes	222 (74.5)	71 (23.8)	5 (1.7)	0.43 (0.30-0.61)	<0.001
DRB1*03	Pos	18 (11.7)	118 (76.6)	18 (11.7)	1	
	Neg	387 (82.2)	82 (17.4)	2 (0.4)	0.03 (0.02-0.05)	<0.001
CXR stage	0	150 (55.6)	109 (40.4)	11 (4.0)	1	
	I	33 (57.9)	20 (35.1)	4 (7.0)	0.91 (0.51-1.63)	0.75
	II	105 (74.0)	34 (23.9)	3 (2.1)	0.45 (0.28-0.68)	<0.001
	III	47 (63.5)	25 (33.8)	2 (2.7)	0.72 (0.41-1.23)	0.23
	IV	70 (85.4)	12 (14.6)	0	0.19 (0.09-0.38)	<0.001
CXR improving	No	286 (70.1)	111 (27.2)	11 (2.7)	1	
	Yes	119 54.8)	89 (41.0)	9 (4.2)	1.93 (1.37-2.72)	<0.001
CXR stable	No	197 (63.8)	103 (33.3)	9 (2.9)	1	
	Yes	208 (65.8)	97 (30.7)	11 (3.5)	0.91 (0.66-1.27)	0.62
CXR worsening	No	327 (61.3)	186 (34.9)	20 (3.8)	1	
	Yes	78 (84.8)	14 (15.2)	0	0.28 (0.16-0.52)	<0.001
DLCO[b]	Mean±SD	80.3±17.0	82.2±18.1	89.2±14.9		
	(range)	(37-128)	(23-129)	(57-121)		
	≥80%	208 (61.0)	116 (34.0)	17 (5.0)	1	
	<80%	188 (70.2)	77 (28.7)	3 (1.1)	0.68 (0.48-0.97)	0.031
FEV_1[b]	Mean±SD	87.6±21.7	93.0±20.9	100.4±16.1		
	(range)	(26-140)	(23-136)	(71-128)		
	≥80%	272 (62.0)	149 (33.9)	18 (4.1)	1	
	<80%	122 (73.1)	43 (25.7)	2 (1.2)	0.61 (0.40-0.93)	0.020
FVC[b]	Mean±SD	97.2±18.9	100.6±19.3	109.1±15.6		
	(range)	(33-152)	(25-147)	(83-148)		
	≥80%	320 (62.9)	170 (33.4)	19 (3.7)	1	
	<80%	69 (75.8)	22 (24.2)	0	0.56 (0.33-0.95)	0.031

[a] No variant allele versus variant allele. [b] % of predicted (<80% is abnormal). n=number, OR=Odds ratio corrected for age, gender, corticosteroid use and smoking, SD=standard deviation, DRB1*03=HLA-DRB1*03, CXR=chest X-ray, DLCO=carbon monoxide diffusing capacity, FEV_1=forced expiratory volume in 1 s, FVC=forced vital capacity, -308A=*TNF-α* -308A variant allele, GG=wild type, GA=heterozygote, AA=homozygote variant. Missing: 16/19/25 for DLCO/FEV_1/FVC, respectively. All values are absolute numbers with percentages in parentheses unless otherwise specified.

The OR for the HLA-DRB1*03 positive versus negative cases compared with the presence of a *TNF-α* -308A variant allele was 0.03 (95% CI: 0.02-0.05) indicating a strong association.

Table 7.3 also shows an increase in mean values of lung function test result parameters as the number of A-alleles in the *TNF-α* G-308A genotype increases (e.g. mean % DCLO GG=80.3 < GA=82.2 < AA=89.2).
In the total population the proportions of patients without or with a *TNF-α* G-308A variant allele were 64.8% (GG) and 35.2% (32.0% GA and 3.2% AA), respectively (chi2=0.61, p=0.74). These findings were in accordance with the Hardy-Weinberg equilibrium. The observed allele frequencies for all 625 patients were 80.8% for the *TNF-α* G-308 and 19.2% for the *TNF-α* -308A allele (p=0.18). The frequency distribution is similar to the distribution reported in healthy Dutch controls (75.0% for the G-allele and 25.0% for the A-allele) from the literature.[23]

Discussion

In this study, we observed that the presence of a *TNF-α* -308A variant allele had a favorable impact on radiologic evolution and prognosis in sarcoidosis. Patients without a *TNF-α* -308A variant allele had a significantly higher risk of developing persistent sarcoidosis with progression to a higher CXR stage and worsening of lung function, particularly the DLCO and FVC. Furthermore, the existence of a strong linkage disequilibrium between the *TNF-α* -308A variant allele and the presence of HLA-DRB1*03 was confirmed.
In our current study, the presence of a *TNF-α* -308A variant allele was associated with a lower risk of worsening of the disease. No association between the *TNF-α* G-308A polymorphism and sarcoidosis in general was found as all genotype and allele frequencies of the 625 studied sarcoidosis patients were in Hardy-Weinberg equilibrium, similar to control populations in literature and in concurrence with findings from earlier studies.[8,11,23,24] In a meta-analysis by Medica et al., it was concluded that the presence of the *TNF-α* -308A variant allele increased the susceptibility to and risk of sarcoidosis by as much as 47%, and it was suggested that the polymorphism could be involved in the clinical presentation of sarcoidosis.[17]
When sorting the sarcoidosis patients into persistent and non-persistent categories a clear association did emerge between the absence of the *TNF-α* -308A variant allele and sarcoidosis persistence (OR=0.43, p<0.001). In earlier studies, it was found that carriers of the *TNF-α* -308A variant allele were more prone to go through the more acute form (i.e. Löfgren's syndrome) of sarcoidosis with frequent spontaneous remission.[8,9,11] This is accordance with our finding that presence of the *TNF-α* -308A variant allele is more prevalent in the non-persistent group.
Categorizing the patients according alternative parameters for clinical course, instead of grouping them into patients with persistent and non-persistent

disease, also showed strong associations with the distribution of the *TNF-α G*-308A genotype. Looking at the results from this perspective revealed that the *TNF-α* -308A variant allele was absent in the large majority of patients who had evolved to CXR stage IV at the end of follow-up (OR=0.19, p<0.001). Previous studies are hard to compare with our data as not only sample size and characteristics of the participants (ethnicity) displayed significant heterogeneity, but sarcoidosis patients were almost always only categorized into Löfgren and non-Löfgren patients, and not according to the different CXR stages. Therefore, previously no conclusions could be drawn about associations or differences in genotype distribution between the various CXR stages.[6,8,11] The categorization according to alternative parameters of clinical outcome also showed that the mean lung function test results were worse in the wild type (*TNF-308* GG) category (Table 7.3). The finding that presence of the variant A-allele is strongly and consistently associated with a more favorable prognosis, irrespective of the definition of good prognosis, lends support to the validity of this association. Moreover, the large sample size in this study also makes it very unlikely that the findings are due to chance.

When examining the selected TNF polymorphisms, only the *TNF-α* G-308A SNP showed significant association with disease progression. The *TNF-α* G-238A polymorphism did not show a different distribution for the non-persistent and persistent disease groups. In accordance to others, we observed that presence of the *LTA NcoI* 252G variant allele only tended to be higher in patients who did not progress, ruling it out as a prognostic factor.[25] In a Japanese population, however, as studied by Yamaguchi et al., the A-allele of the *LTA NcoI* A252G polymorphism was found to be a marker for prolonged clinical course.[26] This is an important reminder of the fact that populations of different ethnicity, as in this case Japanese versus Caucasian, can display different associations to the same polymorphisms. However, in line with Mrazek et al., we also found a slight increased but not statistically significant *LTA NcoI* 252G variant allele presence (34.6%; chi2=1.52, p=0.22) in CXR stage I at diagnosis compared with CXR stages 0, II and III.[7]

In the current study, it was also found that smoking appeared to protect against progressing to persistent sarcoidosis, for fewer smokers were present in the persistent disease group. This was in accordance with findings from earlier studies.[27-30]

Interestingly, in our population, men more often showed progression to persistent sarcoidosis. It is tempting to speculate that this might be explained by the fact that males were more frequently exposed to occupational and/or environmental antigenic triggers than females (67.4% versus 31.2%, respectively). It is known that these triggers, beside genetic factors, are involved in the pathogenic concept of sarcoidosis.[3,31,32]

The frequency of use of systemic corticosteroids was higher in patients with persistent disease and may be a confounder for clinical course. However, after adjustment for differences in baseline characteristics between the groups with persistent and non-persistent disease using multivariate logistic regression, the OR associated with the presence of the *TNF-α* -308A variant allele did not change and was still indicative of a halving of the risk of persistent disease.
In the clinical management of sarcoidosis patients, it is important to identify those cases that might have a chance to develop a more severe manifestation of sarcoidosis. In those particular cases, treatment aimed at avoiding irreversible damage should be started early.[33] Corticosteroids are still the first drug of choice to treat sarcoidosis in most cases, but it is well known that long-term use is associated with significant toxicity.[33] Since a few years anti-TNF-α agents are being used more frequently, especially in chronic cases.[10,34] Failure of patient response to conventional therapy or the presence of unacceptable side effects from other available drugs, especially prednisone, constitute the most common reasons for prescribing an anti-TNF-α agent for sarcoidosis.[34] When considering anti-TNF-α treatment it can be very important to have information that might be helpful in predicting whether a patient will be a responder or non-responder. Studies into responders and non-responders to anti-TNF-α therapy have been carried out, e.g. in rheumatoid arthritis (RA) patients by Mugnier et al.[35] They found that patients without a *TNF-α* G-308A allelic variant were the overall better responders. As shown in the present study, patients without a *TNF-α* -308A variant allele were also more prone to develop the persistent form of sarcoidosis. Interestingly, in the infliximab trial by Baughman et al., it was found that the patients with a more severe or longer duration of (i.e. persistent) pulmonary disease including reduced FVC, severe dyspnoea as well as a more impaired quality of life were more likely to respond to anti-TNF-α treatment.[36] This might suggest that they were most likely cases without a variant allele. In accordance to experiences with RA patients, it seems to be practical and helpful to monitor sarcoidosis patients without a *TNF-α* G-308A allelic variant early and initiate treatment accordingly. So it appears that one simple and less expensive SNP test prior to treatment could not only render very useful information about progression. Given that this was beyond the scope of this study, future study should evaluate whether a single SNP test (*TNF-α* G-308A) might also be helpful in deciding to start anti-TNF-α treatment or not. Moreover, when anti-TNF-α treatment is considered genotyping *TNF-α* G-308A may be a useful tool to differentiate between responders and non-responders of anti-TNF-α treatment in sarcoidosis.

Conclusion

Our results clearly show that genotyping for the *TNF-α* G-308A polymorphism is helpful in predicting prognosis in sarcoidosis patients. The risk of progressing to a more severe pulmonary involvement is higher in the absence of a *TNF-α* G-308A allelic variant and HLA-DRB1*03. Because of the strong linkage between *TNF-α* G-308A and HLA-DRB1*03 genotyping of one simple *TNF-α* SNP is useful in predicting the prognosis of pulmonary sarcoidosis. The findings in this study can be used as a base for further clinical validation of the use of *TNF-α* G-308A genotyping to predict the clinical course of sarcoidosis in individual patients. Research must continue to depict the role of *TNF* genes in the immunogenetics and clinical management of sarcoidosis.

References

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