Chapter 8

Association of the TNF-α G-308A polymorphism with TNF-inhibitor response in sarcoidosis

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Abstract

Background
Responsiveness to tumor necrosis factor-alpha (TNF-α) inhibitors has been associated with the TNF-α G-308A polymorphism in rheumatoid arthritis. The aim of this study was to examine the association between the presence of this polymorphism and the response to TNF-α inhibitors in patients with refractory sarcoidosis.

Methods
Patients (n=111) who started TNF-α inhibitor treatment (76 infliximab, 35 adalimumab) were followed for at least 1 year. Main symptoms in these patients were fatigue (n=100, 90.1%), small fiber neuropathy (n=91; 82.0%), pulmonary involvement (n=69; 62.2%), and/or uveitis (n=31; 27.9%). Patients were additionally genotyped for the presence of the TNF-α G-308A polymorphism. Treatment response was assessed using clinical outcome measures and questionnaires.

Results
Three-quarters (n=83; 74.8%) of the patients responded well. Of the patients without the variant A-allele 93.6% (73/78; p<0.001) improved, while 30.3% (10/33) of variant A-allele carriers responded favorably to TNF-α inhibitors. For patients with the GG-genotype, the probability of improving compared with remaining stable or deteriorating was three times higher (risk ratio=3.09; 95% confidence interval 1.84-5.20).

Conclusion
Sarcoidosis patients without the TNF-α -308A variant allele (GG-genotype) had a three-fold higher response to TNF-α inhibitors (adalimumab or infliximab). Further research is needed to evaluate the value of genotyping for the TNF-α G-308A polymorphism in order to tailor TNF-α inhibitor treatment.
Introduction

Sarcoidosis is a multisystem disease characterized by inflammatory activity with the formation of noncaseating granulomas that commonly affect the lungs, although other organ systems can also be involved. Clinical presentation and outcome vary greatly and therapeutic options range from no treatment to a variety of pharmacological agents.

Although the exact etiology is still unknown, tumor necrosis factor-alpha (TNF-α) is known to play a crucial role in the granuloma formation. The production of this cytokine by alveolar macrophages is substantially elevated, and TNF-α elevation has been shown to correlate with sarcoid disease activity and progression. In severe sarcoidosis, the release of inflammatory mediators causes derangement of organ physiology and ultimately irreversible organ damage. Timely implementation of an appropriate potent individual treatment regimen is especially important for patients with a severe disease course and poor prognosis.

Glucocorticosteroids are traditionally considered first-line treatment, but their long-term use can be impaired by failure or intolerance, with serious adverse effects such as weight gain/obesity, diabetes or osteoporosis. In case of intolerable side-effects or steroid resistance, second-line treatment options should be considered, such as methotrexate (MTX), azathioprine or leflunomide, but these therapies may also be subject to failure or intolerance. Another option to consider is TNF-α inhibitors, which inhibit the potent pro-inflammatory TNF-α, often a predominant problem in patients with refractory sarcoidosis, and these have shown promising results. However, a drawback of TNF-α inhibitors is considerable treatment costs.

When considering the natural course of sarcoidosis, polymorphisms seem to make an important contribution to the clinical phenotype. Genetic analysis has previously revealed a number of polymorphisms in genes coding for TNF-α, with potential functional consequences. The presence of the TNF-α -308A variant allele, which has been associated with variations in TNF-α production, proved to be associated with a favorable prognosis. In rheumatoid arthritis, the TNF-α G-308A polymorphism has been studied in relation to TNF-α inhibitors. Patients without the TNF-α -308A variant allele were found to be better responders. However, studies assessing such an association in sarcoidosis are currently lacking.

The aim of the present study was to assess the association between the presence of the TNF-α G-308A polymorphism and the response to TNF-α inhibitors among patients with refractory sarcoidosis.
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Methods

Study population

Dutch Caucasian patients with refractory sarcoidosis (n=118) with various manifestations despite conventional treatment were started on TNF-α inhibitors during a 4-year period (2007-2011) and followed for at least 1 year. Patients were diagnosed with sarcoidosis in accordance with the guidelines of the World Association of Sarcoidosis and Other Granulomatous diseases, as previously reported.1,18

All patients were given prednisone as a first-line treatment. When this treatment failed or when serious side-effects occurred, a combination of prednisone and MTX was given. Finally, TNF-α inhibitor treatment was started if combination treatment did not achieve clinical improvement. Failure of therapy was determined by a pulmonologist, neurologist and/or ophthalmologist and defined as either clinical or symptomatic progression of disease despite conventional therapy.

If treatment was discontinued within 1 year, patients were regarded as drop-outs. Of the initial 118 patients, seven discontinued treatment within 1 year, leaving 111 for the analyses. Pulmonary and extrapulmonary (i.e. ocular, cutaneous, lymphatic, musculoskeletal, and neurologic) data were collected. Patients were treated with infliximab (n=76) or adalimumab (n=35).

The study was performed in accordance with the Declaration of Helsinki and its amendments. Written informed consent for participation was obtained from all patients and the protocol was approved by the Medical Ethics Board of Maastricht University Medical Centre+, Maastricht, The Netherlands (METC 11-4-116).

Clinical response rate

Responses to TNF-α inhibitors were defined. A patient’s individual clinical response was graded 1 year after starting TNF-α inhibitors, based on documented objective data. Each organ with documented sarcoid involvement or symptoms or inflammation was graded in a systematic manner before and after 1 year of TNF-α inhibitor treatment, as described below. We carefully documented whether a patient improved, was stable or deteriorated.

Improvement was defined as an increase or decrease in at least one of the parameters, values or scores of ≥10% of the original value. Any change, whether an increase or a reduction, of <10% was regarded as stable disease and a decrease or increase, when appropriate, of ≥10% as deterioration.

Evaluation of pulmonary involvement

All chest radiographs were graded, at inclusion and after 1 year of treatment, by a single observer, who was blinded to the genetic test results. Radiographic abnormalities were classified into five stages (0 to IV), as described previously.18
Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusing capacity for carbon monoxide (DLCO) were measured.\textsuperscript{18} Values were expressed as a percentage of the predicted values. The cut-off value for DLCO, FEV1 and FVC was <80% of predicted (≥80% was considered normal).\textsuperscript{21} Respiratory functional impairment (RFI) was defined as DLCO <80%, FVC <80% or FEV1 <80%. Patients without RFI were those for whom all three indices were normal.\textsuperscript{22} Patients with pulmonary sarcoidosis should have RFI and/or abnormal chest radiographs (Stage II or higher; Figure 8.1).

![Figure 8.1](image_url)

Figure 8.1 An example of a patient with respiratory functional impairment with substantial improvement after 1 year of treatment with infliximab. The original value of the diffusing capacity for carbon monoxide improved by ≥10% from 67% to 78% of predicted, while the forced vital capacity changed from 77% to 83%, and the forced expiratory volume in one second from 90% to 92%.

- a. High-resolution computed tomography (HRCT) scan before treatment with infliximab;
- b. HRCT scan after treatment with infliximab showing a decrease of the parenchymal lesions.

Evaluation of uveitis

All patients with eye problems due to sarcoidosis were evaluated by the same ophthalmologist, who was blinded to the genetic test results. The patients were screened for the presence of uveitis, as described previously.\textsuperscript{23} In addition, fluorescein angiography or optical coherence tomography was performed to detect the presence of vasculitis, papillitis, or macular edema, as described previously (Figure 8.2).\textsuperscript{23}

The overall outcome of intraocular inflammatory signs was scored as improvement if at least one of the inflammatory signs scored showed complete clearance or if at least one of the inflammatory signs scored improved in the absence of deterioration of other inflammatory signs. It was scored as stabilization if all inflammatory signs remained unchanged, and as deterioration if at least one of the inflammatory signs increased.\textsuperscript{23}
Evaluation of small fiber neuropathy

The presence of small fiber neuropathy (SFN) symptoms was assessed using the small fiber neuropathy screenings list (SFNSL). It is a practical, brief and easy to use tool to screen for the presence of SFN-related symptoms with high scores indicating more severe SFN-related symptoms.²⁴

Temperature threshold testing was used to support the presence of SFN. This test was used to assess the function of small caliber sensory fibers by measuring temperature sensation thresholds, as described previously.²⁵

Evaluation of fatigue

One of the most important patient-reported outcome measures is fatigue, which was assessed by means of the fatigue assessment scale (FAS). The FAS contains 10 specific fatigue questions that have been validated for sarcoidosis patients, with high scores indicating more fatigue. The minimal clinically important difference has been established, and a change of ≥4 points or 10% change in FAS score was found to be clinically significant.²⁶
Evaluation of inflammation

Serum levels of angiotensin-converting enzyme (ACE, reference interval: 9–25 U/l; measured by a colorimetric method (cat. no. FU 116; Fujirebio Inc., Tokyo, Japan)) and soluble-interleukin2-receptor (sIL2R, levels considered elevated if >3154 pg/ml; analysed in commercially available Diaclone ELISA kits (Sanquin, Amsterdam, The Netherlands)) were measured according to manufacturer’s instructions.

Other manifestations

Neurosarcoidosis was evaluated by a neurologist based on the results of magnetic resonance imaging scans (Figure 8.3). Photographs of skin lesions prior to and after treatment were used as the main outcome measures for skin lesions.

![Figure 8.3](image_url) Sagittal T2 weighted magnetic resonance images. a. Before treatment showing an extensive spinal cord lesion; b. After 1 year of treatment with infliximab, with only a minor lesion left; c. After 3 years, showing complete remission of the spinal cord lesion.

Evaluation of response rates

The overall response rate was calculated by scoring improvement, stable disease or deterioration of disease manifestations of sarcoidosis. Response was defined as improvement of at least one of the following if it was the main reason for treatment: RFI, SFN symptoms, uveitis, skin lesions or neurosarcoidosis, without deterioration of any other disease manifestation. Stable was defined as no improvement or no deterioration of at least the major reason for treatment without deterioration of any other disease manifestation. Deterioration was defined as deterioration of at least the major disease manifestation.
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Genotyping

DNA was obtained using venous EDTA anti-coagulated blood and isolated, according to the manufacturer’s instructions. All patients were genotyped for the TNF-α G-308A promoter polymorphism using a real-time PCR Fluorescence Resonance Energy Transfer assay (TIB MOLBIOL, Berlin, Germany), as described previously. The person who performed the analyses was blinded to the clinical data and response to therapy.

Statistical analysis

Statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA) for Windows. Cross tables were used to compare the percentages of patients with response according to each genotype. Relative risk (RR) with 95% confidence interval (CI) was calculated to evaluate strength of association. Multivariate logistic regression analyses were used to adjust for relevant baseline differences between genotype groups. The Chi-square test was used to test for statistically significant differences between groups and to calculate deviations from the Hardy-Weinberg equilibrium. A p value of <0.05 (two-sided) was considered to indicate statistical significance.

Results

Characteristics of patients in our sarcoidosis sample and the main reasons for initiating TNF-α inhibitors are summarized in Table 8.1.

Patients suffered from one or more disabling problems: 91 (82.0%) out of 111 suffered from SFN (SFNSL >11), with 38 (34.2%) having severe symptoms (SFNSL >37); 69 (62.2%) out of 111 suffered from pulmonary sarcoidosis (Figure 8.1); 31 (27.9%) out of 111 from uveitis; six (5.4%) out of 111 from skin lesions; one (0.9%) out of 111 from spinal cord involvement; and one (0.9%) out of 111 from kidney failure. In addition, the majority of the patients (100 (90.1%) out of 111) also suffered from fatigue (FAS ≥22), with 59 (59.0%) out of 100 having severe fatigue (FAS >34).

Responders were identified based on the following criteria: in 39 (56.5%) out of the 69 patients with RFI at least one lung function test parameter improved by more than 10%. Of the 31 patients with eye involvement, 23 (74.2%) improved substantially according to the criteria used by the ophthalmologist (Figure 8.2). Neurological symptoms improved in 49 (53.8%) out of 91 patients, in 17 of whom this appeared to be the only improving primary endpoint. All six patients with skin lesions responded, as well as the patient suffering from neurosarcoidosis (spinal cord involvement; Figure 8.3) and the patient with kidney problems. Signs of activity and inflammation improved in 75 (67.6%) out of 111 patients, and fatigue improved in 60 (60.0%) out of 100 patients. None of the responders showed deterioration in any of the other manifestations of sarcoidosis that were present.
Overall, 83 (74.8%) of the 111 included patients with refractory sarcoidosis had a positive response. Improvement was achieved in 119 (59.8%) of the 199 organs assessed. The choice of TNF-α inhibitor had no influence on outcome, as both infliximab and adalimumab resulted in 25% non-responders. Allele frequencies were 84.2% for the G-allele and 15.8% for the A-allele. The frequency distribution is in agreement with the Hardy-Weinberg equilibrium. There were no significant differences in TNF-α G-308A polymorphism distribution between the various disease manifestations.

Table 8.1 Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Lung involvement</th>
<th>SFN symptoms</th>
<th>Eye involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>111</td>
<td>69</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45.0 ±10.6</td>
<td>44.5 ±10.8</td>
<td>46.6 ±9.8</td>
<td>43.0 ±11.6</td>
</tr>
<tr>
<td>Female/male</td>
<td>46/65</td>
<td>30/39</td>
<td>10/22</td>
<td>6/4</td>
</tr>
<tr>
<td>CXR stage: O+/II+III+IV</td>
<td>54/43/14</td>
<td>21/34/14*</td>
<td>24/80</td>
<td>9/10</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>85.7 ±24.2</td>
<td>75.2 ±22.7**</td>
<td>104.5 ±12.1</td>
<td>105.4 ±13.4</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>96.6 ±19.2</td>
<td>88.6 ±17.7**</td>
<td>110.6 ±13.1</td>
<td>111.7 ±12.9</td>
</tr>
<tr>
<td>DLCO % predicted</td>
<td>77.1 ±17.2</td>
<td>68.3 ±12.9*</td>
<td>92.2 ±11.8</td>
<td>95.8 ±11.3</td>
</tr>
<tr>
<td>RFI</td>
<td>69 (62.2)</td>
<td>69 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ACE U/l</td>
<td>20.7 ±12.9</td>
<td>21.5 ±14.2</td>
<td>19.0 ±10.1</td>
<td>20.0 ±9.6</td>
</tr>
<tr>
<td>sIL2R pg/ml</td>
<td>3073 ±3120</td>
<td>3530 ±3645</td>
<td>2337 ±1460</td>
<td>1719 ±1190</td>
</tr>
<tr>
<td>FAS</td>
<td>33.0 ±8.5</td>
<td>33.5 ±8.4</td>
<td>33.6 ±17.9</td>
<td>27.6 ±8.1</td>
</tr>
<tr>
<td>Fatigue reported</td>
<td>100 (90.1)</td>
<td>63 (91.3)</td>
<td>29 (90.6)</td>
<td>8 (80.0)</td>
</tr>
<tr>
<td>SFNSL</td>
<td>32.5 ±19.3</td>
<td>32.0 ±20.0</td>
<td>37.6 ±18.0</td>
<td>18.8 ±9.1**</td>
</tr>
<tr>
<td>SFN symptoms</td>
<td>91 (82.0)</td>
<td>54 (78.3)</td>
<td>32 (100)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>31 (27.9)</td>
<td>16 (23.2)*</td>
<td>5 (15.6)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>35</td>
<td>23</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>mg/dose sc</td>
<td>45.9 ±15.5</td>
<td>47.2 ±17.2</td>
<td>48.0 ±17.9</td>
<td>40.0 ±0.0</td>
</tr>
<tr>
<td>dose interval, weeks</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infliximab</td>
<td>76</td>
<td>46</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>mg/dose intravenously</td>
<td>404.1 ±25.5</td>
<td>404.5 ±28.1</td>
<td>403.7 ±19.2</td>
<td>400.0 ±10.0</td>
</tr>
<tr>
<td>dose interval, weeks</td>
<td>4.5 ±0.6</td>
<td>4.5 ±0.5</td>
<td>4.6 ±0.6</td>
<td>4.0 ±0.0</td>
</tr>
<tr>
<td>Co-medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no prednisone, no MTX</td>
<td>40</td>
<td>15</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>prednisone alone</td>
<td>14</td>
<td>10</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>mg/day, orally range</td>
<td>14.3 ±10.7</td>
<td>15.4 ±11.7</td>
<td>15.0 ±0.0</td>
<td>8.8 ±8.8</td>
</tr>
<tr>
<td>prednisone + MTX</td>
<td>28</td>
<td>19</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>pred mg/day, orally</td>
<td>9.3 ±5.2</td>
<td>8.6 ±3.7</td>
<td>12.9 ±8.1</td>
<td>5.0 ±0.0</td>
</tr>
<tr>
<td>MTX mg/week, orally</td>
<td>9.1 ±2.9</td>
<td>9.6 ±3.1</td>
<td>7.9 ±1.0</td>
<td>8.5 ±5.3</td>
</tr>
<tr>
<td>MTX alone</td>
<td>29</td>
<td>18</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>mg/week, orally</td>
<td>7.5 ±1.4</td>
<td>7.5 ±0.8</td>
<td>7.5 ±5.5</td>
<td>7.5 ±0.0</td>
</tr>
</tbody>
</table>

* p<0.001 lung involvement versus SFN and eye involvement. ** p<0.01 eye involvement versus lung involvement and SFN. * All values presented are absolute numbers with percentages in parentheses if applicable and means ±SD if appropriate. ACE, angiotensin-converting enzyme (reference range: 9.0–25.0 U/l); CXR, chest radiograph; DLCO, carbon monoxide diffusing capacity; FAS, fatigue assessment scale; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MTX, methotrexate; RFI, respiratory functional impairment defined as DLCO <80%, FVC <80% or FEV1 <80% (percentage of predicted); sc, subcutaneous; SFN, small fiber neuropathy; SFNSL, small fiber neuropathy screenings list; sIL2R, soluble interleukin2-receptor (reference range: <3154 pg/ml); y, years.
Of the patients without the A-allele, 73 (93.6%) out of 78 \( (p<0.001) \) had a positive response to TNF-\( \alpha \) inhibitors, compared with 10 (30.3%) out of the 33 patients with the variant A-allele. For patients possessing the GG-genotype, the probability of improving was three times higher than that of remaining stable or deteriorating (RR=3.09; 95% CI 1.84–5.20), as shown in Table 8.2.

Table 8.2 Disease course in relation to TNF-\( \alpha \) G-308A polymorphism.\(^a\)

<table>
<thead>
<tr>
<th>TNF-308</th>
<th>Total</th>
<th>Improved</th>
<th>Stabilized/worsened</th>
<th>RR (95% CI)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>78</td>
<td>73 (93.6)</td>
<td>5 (6.4)</td>
<td>3.09 (1.84–5.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA</td>
<td>31</td>
<td>9 (29.0)</td>
<td>22 (71.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>2</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Absolute numbers with percentages or range in parentheses. 95% CI, 95% confidence interval; RR, relative risk; TNF-308, TNF-\( \alpha \) G-308A genotype; GG, wild type; GA, heterozygote; AA, homozygote variant.

The different genotype groups (GG 70.3%, GA 27.9%, and AA 1.8%) were similar with respect to distribution of therapy (infliximab versus adalimumab) and co-medication, but the group with the GG-genotype had a higher mean age and proportion of female patients (Table 8.3). Multivariate logistic regression analysis to adjust for baseline differences in age and gender between the genotype groups resulted in an adjusted odds ratio of 39.7 (95% CI 11.1–142.3), which was slightly higher than the unadjusted odds ratio of 33.6 (95% CI 10.4–108.3).

Table 8.3 Demographic and medication characteristics of the sarcoidosis sample according to genotype.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>GG</th>
<th>GA/AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>male</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>year ±SD</td>
<td>45.7±10.3</td>
<td>42.6±10.8</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infliximab (n=76)</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>adalimumab (n=35)</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Co-medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>prednisone</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>prednisone + MTX</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>MTX</td>
<td>21</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Absolute numbers, percentages in parentheses and mean ±SD if appropriate. GG, TNF-\( \alpha \) G-308A wild type; GA, heterozygote; AA, homozygote variant; MTX, methotrexate; n, number; SD, standard deviation.
Nine (8.1%) patients formed antibodies against infliximab and were switched to adalimumab (n=4) or had to discontinue the TNF-α inhibitor treatment (n=5). None of the patients developed antibodies against adalimumab. Adverse events were seen in 14 (12.6%) out of 111 patients treated with TNF-α inhibitors. Documented adverse events were minor infections (n=11), sepsis (n=1), and the occurrence of herpes zoster infection (n=5). Two patients suffered from an infusion reaction, after the fifth and eighth infliximab administrations, respectively. However, after adjustment of the infusion time no further problems emerged and the treatment was continued.

Discussion

To the best of our knowledge, this is the first study to demonstrate an association between the TNF-α G-308A polymorphism and responsiveness to TNF-α inhibitor treatment in sarcoidosis. Efficacy of TNF-α inhibitors was found in 75% of our sample of patients with refractory sarcoidosis who had failed to respond to conventional treatment. TNF-α inhibitor treatment was well tolerated. Patients without the TNF-α -308A variant allele (GG-genotype) responded better to TNF-α inhibitors (93.6% versus only 30.3%), having a three-fold higher probability of improving compared with variant allele carriers (RR 3.09, 95% CI 1.84–5.20). This suggests that this variant allele (GA/AA-genotypes) negatively affects TNF-α inhibitor treatment response. However, since the study population was relatively small, the associations should be interpreted with some caution.

It is well known that the clinical course and prognosis of sarcoidosis varies considerably, and research suggests that polymorphisms coding for TNF-α production might play a role. The TNF-α -308A variant allele is associated with higher TNF-α production, and several studies have found the variant allele to be more frequently observed in patients with Löfgren’s syndrome, who often showed spontaneous remission. The presence of the TNF-α -308A variant allele has been found to have a more favorable impact on clinical outcome. By contrast, the GG-genotype has been associated with an unfavorable prognosis, with a significantly higher risk of developing persistent sarcoidosis and progression to more severe pulmonary involvement.

In the present study, sarcoidosis patients with the TNF-α G-308A GG-genotype appeared to be more likely to be TNF-α inhibitor responders. The GA- or AA-genotype was found in 29.7% of our 111 patients, whereas in other studies these genotypes were found in about 35–40% of general sarcoidosis populations and/or healthy controls. The slightly lower frequency of the AA- and GA-genotypes in our study population could be the result of selection bias, as more severe sarcoidosis cases tend to undergo TNF-α inhibitor therapy. The GG-genotype is more likely to be present in these cases, since this genotype has been associated with a more unfavorable sarcoidosis prognosis.
The association between the \( \text{TNF-\( \alpha \) G-308A polymorphism} \) and \( \text{TNF-\( \alpha \) inhibitor} \) therapy has been more extensively studied in rheumatoid arthritis. In line with our results, rheumatoid arthritis patients with the GG-genotype had a better overall response rate.\(^{15,20,28}\) There have been no previous studies in sarcoidosis demonstrating this association. It was previously shown that patients with a severe disease course were more likely to respond to \( \text{TNF-\( \alpha \) inhibitor} \) treatment.\(^{11,29}\) It is tempting to speculate that these patients most likely did not possess the variant A-allele. Since GG-genotype carriers are more likely to have an unfavorable outcome and to achieve a good response to \( \text{TNF-\( \alpha \) inhibitor} \) treatment, the decision whether or not to start \( \text{TNF-\( \alpha \) inhibitors} \) in these patients seems rather easy. In contrast, patients suffering from sarcoidosis with the variant A-allele are more likely to have a favorable prognosis with spontaneous resolution of the disease. In the present study, approximately 70% (23 out of 33) of these patients did not respond to \( \text{TNF-\( \alpha \) inhibitors} \). Nevertheless, a considerable proportion of the variant allele carriers showed stabilization of disease. Although stabilization was not considered a ‘response’ in the present study, in specific cases it might be regarded as a desirable aim. To date, too little evidence is available to decide whether these patients should not be given \( \text{TNF-\( \alpha \) inhibitor} \) treatment.

The results of our study are in line with other case series demonstrating an efficacy of infliximab in 64–100% of sarcoidosis patients treated.\(^{12,30,31}\) In the present study, uveitis demonstrated the best response rate (74%), followed by RFI (57%), and SFN (54%). These response rates are in line with previous research.\(^{11,23,29,31,32}\) It is probable that the higher response rate for uveitis is influenced by the shorter time between diagnosis and initiating \( \text{TNF-\( \alpha \) inhibitors} \) (4.5 ±4.3 years for uveitis, compared with 6.3 ±5.6 years for SFN and 6.8 ±5.6 years for RFI, \( p=0.05 \)). These results suggest that initiating \( \text{TNF-\( \alpha \) inhibitors} \) early in the course of the disease might prevent serious organ damage and result in a more favorable outcome. This is in agreement with results in Crohn’s disease.\(^{33,34}\)

The \( \text{TNF-\( \alpha \) inhibitors} \) adalimumab and infliximab were both generally well tolerated in our study, in agreement with data from other studies.\(^{35,36}\) Adverse events were observed in 12.6% of patients and a 4.5% discontinuation rate due to antibody formation was seen during at least 1 year of \( \text{TNF-\( \alpha \) inhibitor} \) treatment. Outcome or adverse effects did not differ between infliximab and adalimumab, similar to findings for other chronic inflammatory diseases.\(^{34,37,38}\)

Refractory uveitis is a registered indication for adalimumab treatment in The Netherlands, whereas patients with pulmonary and/or neurological symptoms have mainly been treated with infliximab. The choice between adalimumab and infliximab was, therefore, mainly based on insurance reimbursement issues.

Despite the overall efficacy of \( \text{TNF-\( \alpha \) inhibitors} \), there are limitations to the use of \( \text{TNF-\( \alpha \) inhibitor} \) treatment for every sarcoidosis patient. In addition to the side-effects, another drawback of \( \text{TNF-\( \alpha \) inhibitors} \) is the considerable treatment cost.\(^{15}\) It is, therefore, important to tailor treatment. The present study provides a step forward in identifying sarcoidosis patients who might be at risk of developing a more severe
manifestation of the disease and in selecting those most likely to have a good response to TNF-α inhibitor treatment. It might help to start an appropriate individual treatment regimen and, thus, avoid irreversible damage at an early stage. It is useful to know beforehand whether a patient is highly likely to respond to TNF-α inhibitor treatment, as this can be of great clinical and economic benefit. A better understanding may help achieve personalized, cost-effective treatment regimens. However, to date, too little evidence is available to decide whether TNF-α inhibitors should be withheld from sarcoidosis patients carrying the variant A-allele. For these patients there might be better alternative options. Prospective randomized controlled trials, with a sufficiently large study population, are needed to address the effect of TNF-α inhibitors in patients with the variant A-allele, compared with placebo and/or conventional therapy.

In conclusion, our results show that sarcoidosis patients without the TNF-α -308A variant allele (GG-genotype) had a three-fold higher response to TNF-α inhibitor treatment than A-allele carriers. We also found that TNF-α inhibitors were efficacious in the treatment of refractory sarcoidosis (75% response rate) and were well tolerated. Further research is needed to evaluate whether individualized treatment can be improved by basing decisions on the TNF-α G-308A polymorphism of sarcoidosis patients in whom conventional therapy has failed or proved intolerable.

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Chapter 8

References


