Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis

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ABSTRACT Infliximab is effective as a third-line therapeutic for severe sarcoidosis; however, long-term efficacy is unknown. The aim of this study was to assess the relapse rate after discontinuation of infliximab in sarcoidosis patients and predict relapse by analysis of the activity marker soluble interleukin (IL)-2 receptor (sIL-2R) and maximum standardised uptake value (SUV_{max}) of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET).

In this retrospective cohort study, the proportion of relapse was analysed using the Kaplan–Meier method and predicting factors were studied using Cox regression.

47 sarcoidosis patients who started infliximab therapy were included in the risk analysis. Kaplan–Meier analysis revealed a median time to relapse of 11.1 months and showed that 25% of the cohort relapsed within 4 months. Both mediastinal SUV_{max} $\geqslant$6.0 on FDG PET (hazard ratio 3.77, $p<0.001$) and serum sIL-2R $\geqslant$4000 pg·mL^{-1} (hazard ratio 2.24, $p=0.033$) at start of therapy predicted relapse. In multivariate analysis, a mediastinal SUV_{max} $\geqslant$6.0 at initiation of therapy was an independent predictor of relapse (hazard ratio 4.33, $p<0.001$).

The majority of patients that discontinued infliximab therapy relapsed. High serum sIL-2R and high SUV_{max} on FDG PET at initiation of therapy were significant predictors of relapse. These results suggest close monitoring of patients in this category when they discontinue infliximab treatment.

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For editorial comments see page 337.

Received: March 27 2013 | Accepted after revision: Aug 02 2013 | First published online: Aug 29 2013

Conflict of interest: None declared.

Introduction

Sarcoidosis is a systemic, granulomatous disease that has variable clinical course and can affect multiple organs. This disease can be self-limiting, but can also follow a chronic course in a subgroup of patients [1–3]. When immunosuppressive treatment is indicated, corticosteroids are the first choice drugs [4, 5]. Even though corticosteroids are generally effective, continued use may cause severe side-effects. Second-line therapy therefore usually involves agents with steroid-sparing effects, such as azathioprine or methotrexate [6–11]. However, some patients are resistant to these types of treatment or develop considerable side-effects. Therefore, biologicals have been introduced as new treatment options.

The biological anti-tumour necrosis factor (TNF) drug infliximab (Remicade; Janssen Biotech, Inc., Malvern, PA, USA) has been used widely for treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease and psoriasis [12–14]. Furthermore, it has been the subject of investigation in case series and reports of several manifestations of sarcoidosis. Two randomised controlled trials have investigated short-term infliximab treatment in sarcoidosis and revealed improvement in lung function after 14 weeks of infliximab treatment [15, 16]. *Post hoc* analysis showed positive effects of infliximab treatment on extrapulmonary symptoms [17].

Due to the fact that these studies have focused on treatment outcomes after an induction phase of a maximum of 6 months, long-term outcome after discontinuation of treatment remains largely unknown. Because the optimal treatment duration or best moment to discontinue infliximab treatment have not been studied, in clinical practice, treatment duration is based on the physicians' opinion. However, like most biologicals, infliximab is an expensive drug, which makes excessive or redundant use not desirable in times of rising healthcare costs. Conversely, re-initiation after discontinuation might contribute to anti-infliximab antibody formation, resulting in decreased drug efficacy and sometimes allergic reactions [18].

That relapse of symptoms can occur after discontinuation of infliximab in sarcoidosis was shown in a small series of 14 patients [19]. Prediction of relapse is important to identify patients with a low risk of relapse and possibly shorten therapy duration, because this will reduce the burden of therapy for the patient (long-term safety and efficacy) and lower healthcare costs. Moreover, identifying patients with a high relapse risk after discontinuation would be useful to adjust or even prolong treatment with infliximab in the case of an objectified response.

In Crohn's disease, leukocyte count and C-reactive protein (CRP) levels were found to be predictors of relapse after discontinuation of infliximab therapy [20]. As leukocyte count and CRP are generally within normal limits in sarcoidosis patients, other markers of disease activity in sarcoidosis were also studied: angiotensin-converting enzyme (ACE), soluble interleukin (IL)-2 receptor (sIL-2R) and uptake of ^{18}F-fluorodeoxyglucose (FDG) by positron emission tomography (PET) [21–28].

The aim of this study was to investigate the long-term outcome of infliximab treatment in patients with severe sarcoidosis and to predict which patients will relapse after discontinuation of infliximab therapy.

Material and methods

Study subjects

Sarcoidosis patients in whom infliximab therapy was initiated at St Antonius Hospital (Nieuwegein, the Netherlands), between August 2004 and October 2010 were included in this retrospective study. St Antonius Hospital serves as a national tertiary referral centre for sarcoidosis. All patients were naïve to infliximab or other anti-TNF therapy. All patients had severe and chronic sarcoidosis. Disease severity was assessed by the treating physician at the moment of initiation, based on clinically significant loss of function (*e.g.* lung function or cardiac function) and severe impairment of quality of life. To be eligible for infliximab therapy, patients needed to be unresponsive to first- and second-line treatment, or experience severe side-effects from these agents or have contraindications (*e.g.* worsening diabetes, psychological deterioration or liver function disorders).

Patients received infliximab intravenously following a standard protocol starting with 5 mg·kg^{-1} bodyweight at weeks 0 and 2 and then every 4 weeks during a period of 6 months. Duration of infliximab therapy after the induction phase of 6 months was based on assessment of the response of symptoms and disease activity by the treating physician. Patients were considered clinically stable at time of treatment cessation. Relapse was defined as the necessity for retreatment due to worsening of symptoms and function in combination with renewed signs of disease activity. Relapse could be of different extent and severity between different patients or the organ systems involved. The moment of initiation of retreatment in previously stable patients was defined as the time point of relapse.

Study parameters

Medical records were reviewed retrospectively for relevant demographic data, disease and treatment characteristics and disease activity parameters (ACE, sIL-2R, CRP and leukocyte count). In the same manner, FDG PET results by maximum standardised uptake value (SUV_{max}) and details of pulmonary function tests were collected. These parameters were recorded at several time points during the treatment period: before infliximab initiation, after 6 months of treatment and when treatment was discontinued in cases of prolonged treatment. For relapsing patients, the clinical and laboratory parameters were again collected, in addition to the type of retreatment and outcome.

Patients were excluded from relapse risk analysis if they had not completed the induction phase of 6 months, because a possible deterioration of symptoms might be due to under-treatment of these patients rather than relapse. All clinical and laboratory tests were performed as part of a standardised protocol and part of clinical practice. The study was approved by the investigational review board of St Antonius Hospital Nieuwegein (registration number LTME/Z-12.33 and acronym ORATS).

Analysis

The proportion of patients who relapsed after discontinuation of therapy was analysed using the Kaplan–Meier method.

Factors associated with time to relapse were studied using a Cox proportional hazards model. Initially, a univariate analysis was performed, selecting variables with $p<0.20$ for multivariate analysis. Appropriate cut-off points were determined using scatter plots.

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences; IBM, Endicott, NY, USA) for Windows, version 19.0. $p<0.05$ was considered significant.

Results

Study subjects

Between August 2004 and October 2010, 56 patients started infliximab therapy at St Antonius Hospital. Four patients did not complete the induction phase of 6 months; three of which developed an allergic

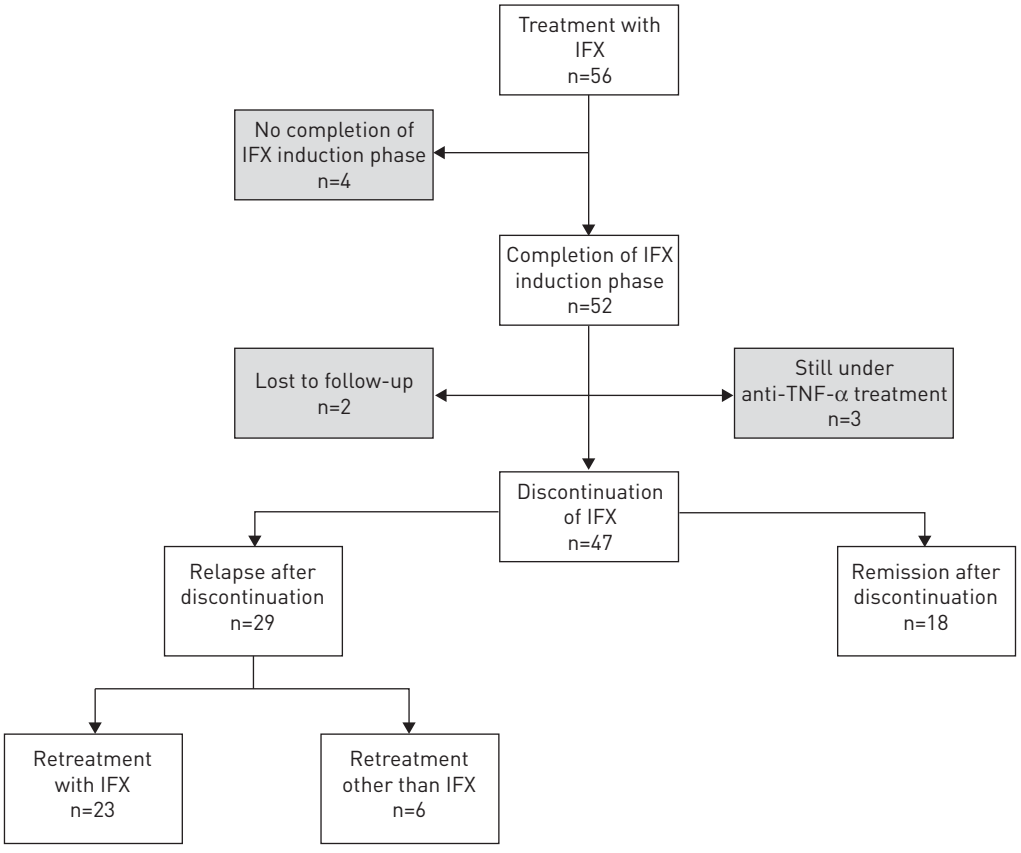

FIGURE 1 Flow diagram of all patients included in the study. Grey boxes indicate exclusion from risk analysis; the induction phase was set at 6 months. IFX: infliximab; TNF: tumour necrosis factor.

DOI: 10.1183/09031936.00055213

TABLE 1 Baseline characteristics of the included patient population at initiation of infliximab therapy

Subjects n	47
Male	26 (55)
Caucasian	36 (77)
Age at initiation of infliximab therapy years	48 (28–71)
Disease duration at initiation of infliximab therapy years	6.3±7.8
Biopsy-proven sarcoidosis	44 (94)
Smoking status[#]	
Never-smokers	25 (58)
Current smokers	7 (16)
Former smokers	11 (26)
Scadding stage	
0	3 (6)
I	5 (11)
II	16 (34)
III	10 (21)
IV	13 (28)
Extrapulmonary involvement	41 (87)
Main treatment indication	
Lungs	30 (64)
Heart	2 (4)
Eye	5 (11)
Central nervous system	3 (6)
Small fibre neuropathy	5 (11)
Spleen	1 (2)
Ear	1 (2)
Medication use prior to initiation of infliximab	
Corticosteroids	10 (21)
Immunomodulation	3 (6)
Corticosteroids and immunomodulation	33 (70)
None	1 (2)
Concomitant medication[¶]	
None	3 (7)
Corticosteroids	13 (28)
Immunomodulation	19 (41)
Corticosteroid and immunomodulation	11 (24)
Duration of infliximab treatment months	8.5±5.8
Disease activity measurements	
SUV_{max} lung parenchyma[+]	4.8±4.1
SUV_{max} mediastinum[+]	5.5±4.3
Angiotensin-converting enzyme $U \cdot L^{-1}$	72.2±42.4
Soluble IL-2 receptor $pg \cdot mL^{-1}$	5649±5020
Vital capacity %	84.7±19.1
FEV_1 %	74.8±22.2
Diffusing capacity of the lung for carbon monoxide[§] %	67.1±17.1

Data are presented as n (%), mean (range) or mean± SD, unless otherwise stated. SUV_{max}: maximum standardised uptake value; IL: interleukin; FEV_1: forced expiratory volume in 1 s. [#]: n=43; [¶]: n=46; [+]: n=42; [§]: n=41.

reaction and one died due to comorbidity. Three patients were still on anti-TNF-α treatment at the moment of inclusion and two patients were lost to follow-up. A total of 47 patients were therefore included in the risk analysis (fig. 1).

Demographics, clinical characteristics and disease activity parameters at baseline are summarised in table 1. The most common reason for initiating treatment was a pulmonary treatment indication (30 (64%) patients); however, of the total cohort, 41 (87%) patients suffered from extrapulmonary manifestations of sarcoidosis. Most patients (46 out of 47) were treated with prednisone and/or methotrexate before infliximab was initiated. In the four patients who did not use prednisone, the most common contraindications were obesity and diabetes. The majority of patients received additional immunosuppressive or immunomodulatory agents while being treated with infliximab to prevent formation of anti-infliximab antibodies; only three patients were not on any type of concomitant medication due to

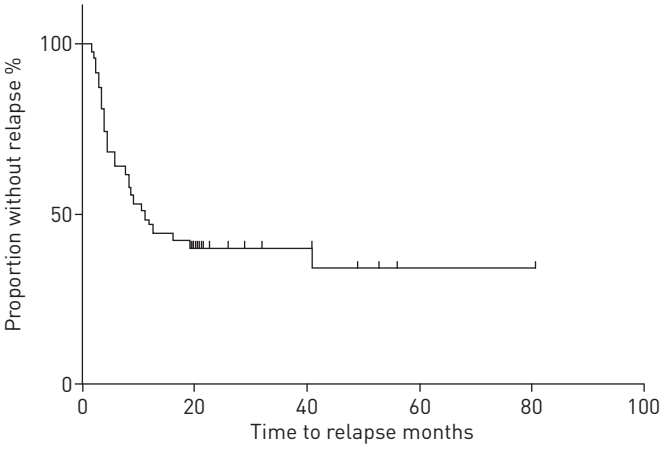

FIGURE 2 Kaplan–Meier analysis of time to relapse after discontinuation of infliximab therapy. The median time to relapse in the total cohort was 11 months. In total, 29 (62%) out of 47 patients experienced relapse.

intolerance. The mean±SD treatment duration was 8.5±5.8 months. After treatment discontinuation, the mean±SD overall follow-up time was 36.6±22.6 months.

Relapse

Kaplan–Meier analysis revealed a median±SE time to relapse of 11.1±2.57 months after discontinuation of infliximab treatment and showed that 25% of the total cohort relapsed within 4 months (fig. 2). Out of 47 included patients, 29 (62%) experienced relapse after a mean±SD time of 7.8±7.7 months. Relapse occurred within the first 10 months in 20 out of 29 relapsing patients. Moreover, only two out of 29 relapsing patients did so after a period of 20 months. Relapse in most patients was a severe deterioration of symptoms requiring retreatment, with some patients being as ill as they were before treatment with infliximab.

The majority of patients who experienced relapse were retreated with infliximab (23 out of 29 patients). Three of those 23 patients developed an allergic response to infliximab and switched to alternative medication. Six patients were retreated with agents other than infliximab due to varying reasons, including pregnancy, previous adverse events during infliximab treatment and the degree of relapse severity. Of these six patients, one was treated with prednisone, two were treated with azathioprine and another two were treated with hydroxychloroquine. One patient was enrolled in a clinical trial for an experimental drug.

Predictive factors of relapse

The results of univariate analysis for predictive factors of relapse are shown in table 2. At time of initiation of infliximab therapy, two factors were found to be predictors of relapse. Patients with mediastinal SUV_{max} scores $\geqslant$6.0 have a significantly higher chance of relapse than patients with SUV_{max} scores $<$6.0 (hazard ratio 3.77, $p<0.001$). Moreover, a serum sIL-2R concentration $\geqslant$4000 pg·mL^{-1} at the start of therapy was found to predict relapse (hazard ratio 2.24, $p=0.033$). None of the factors analysed at the time of treatment discontinuation were found to predict relapse.

In multivariate analysis, mediastinal SUV_{max} scores $\geqslant$6.0 at initiation of treatment were found to be an independent predictor of relapse ($p<0.001$; hazard ratio corrected for ethnicity=4.33). It must be noted that levels of sIL-2R and mediastinal SUV_{max} scores correlate significantly ($p=0.005$; Pearson's $R=0.446$) (table 3). Duration of treatment as such was not found to be a predictor of relapse.

Discussion

In this study we found a high proportion of relapse (62%) after discontinuation of infliximab therapy in sarcoidosis patients, after a mean time of 8 months. These relapse episodes were characterised by recurrence of sarcoidosis symptoms with need for therapeutic intervention. Both a high mediastinal SUV_{max} score on FDG PET and a high serum sIL-2R concentration at the initiation of therapy were found to significantly predict the chance of relapse in sarcoidosis patients.

Disease relapse after infliximab discontinuation in sarcoidosis patients was first noted in a study of 14 patients by PANSELINAS *et al.* [19]. The relapse rate in this cohort was even higher (86%) than in our cohort. Based on the natural history of disease, patients with a longer duration of disease could be more prone to relapse after discontinuation of infliximab. However, as the time from diagnosis to infliximab initiation was longer in our cohort (6.3 *versus* 4.7 years), this is unlikely to be the cause of the lower relapse incidence found in our cohort. Patients in our cohort were treated for a longer period of time; in the study by PANSELINAS

DOI: 10.1183/09031936.00055213

TABLE 2 All factors investigated in primary univariate analysis

	p-value	Hazard ratio (95% CI)
Treatment duration	0.670	1.01 (0.95–1.08)
Age at treatment initiation	0.361	0.98 (0.94–1.02)
Female	0.875	0.94 (0.45–1.98)
Non-Caucasian	0.090#	2.03 (0.90–4.60)
Extrapulmonary involvement	0.964	1.03 (0.36–2.96
Biomarkers at start of therapy		
SUV_{max}		
Total	0.033#	1.10 (1.00–1.20)
Lungs	0.703	1.02 (0.93–1.11)
Mediastinum	0.001#	1.16 (1.06–1.26)
ACE	0.925	1.00 (0.99–1.01)
CRP	0.712	1.17 (0.52–2.63)
sIL-2R	0.103#	1.00 (1.00–1.00)
VC %	0.410	0.99 (0.97–1.01)
FVC %	0.367	0.99 (0.97–1.01)
FEV_1 %	0.648	1.00 (0.98–1.02)
Tiffeneau index	0.967	1.00 (0.97–1.03)
D_{LCO} %	0.255	0.99 (0.96–1.01)
Biomarkers after 6 months of treatment		
SUV_{max}		
Total	0.312	1.12 (0.90–1.41)
Lungs	0.758	1.08 (0.66–1.78)
Mediastinum	0.226	1.14 (0.92–1.41)
ACE	0.816	1.00 (0.99–1.02)
CRP	0.637	1.25 (0.50–3.09)
sIL-2R	0.957	1.00 (1.00–1.00)
Leukocytes	0.941	0.99 (0.84–1.12)
Biomarkers at end of therapy		
ACE	0.917	1.00 (0.98–1.02)
CRP	0.343	1.50 (0.65–3.43)
sIL-2R	0.841	1.00 (1.00–1.00)
Leukocytes	0.750	1.03 (0.86–1.24)
VC %	0.406	0.99 (0.96–1.01)
FEV_1 %	0.839	1.00 (0.98–1.02)
Tiffeneau index	0.762	1.01 (0.98–1.04)
D_{LCO} %	0.542	0.99 (0.97–1.02)
Change in biomarkers		
ACE %	0.671	0.67 (0.99–1.00)
sIL-2R %	0.374	1.00 (0.99–1.00)
VC %	0.815	1.00 (0.95–1.04)
FEV_1 %	0.649	1.01 (0.97–1.05)

SUV_{max}: maximum standardised uptake value; ACE: angiotensin-converting enzyme; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor; VC: vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusion capacity of the lung for carbon monoxide. #: all factors having $p<0.2$ were selected for further analysis in multivariate analysis.

et al. [19] nine out of 14 patients had been treated with fewer than six infusions. It is not known whether a more intensive infliximab treatment regimen can prevent relapse or change the course of the disease.

No studies have focused on predicting relapse after discontinuation of infliximab therapy in sarcoidosis patients. In Crohn's disease, leukocyte count and CRP levels were found to be predictors of relapse after discontinuation of infliximab therapy [20]. However, CRP levels and leukocyte count were not predictors of relapse in our sarcoidosis cohort, as in this disease their levels are mostly within the normal range.

In this study, mediastinal SUV_{max} score on FDG PET and a high serum sIL-2R concentration at the start of therapy were identified as predictors of relapse. FDG PET has previously been demonstrated to be a predictor for decline in lung function in untreated patients and is more sensitive than ^{67}gallium imaging in the assessment of sarcoidosis activity in mediastinal and pulmonary areas [26, 27]. In previous studies, serum sIL-2R levels at disease presentation were correlated with parenchymal infiltration in pulmonary sarcoidosis and were possible prognostic markers at diagnosis [29, 30].

TABLE 3 Factors associated with time to relapse in univariate and multivariate analysis

	p-value	Hazard ratio (95% CI)
Univariate analysis		
Non-Caucasian ethnicity	0.090	2.03 (0.90–4.60)
SUV_{max} mediastinum $\geqslant$6.0	0.001¶	3.77 (1.71–8.33)
SUV_{max} total# $\geqslant$6.0	0.076	2.06 (0.93–4.57)
sIL-2R $\geqslant$4000 pg·mL^{-1}	0.033¶	2.24 (1.07–4.68)
Multivariate analysis		
SUV_{max} mediastinum $\geqslant$6.0+	<0.001¶	4.33 (1.92–9.81)

Maximum standardised uptake value (SUV_{max}) and soluble interleukin-2 receptor (sIL-2R) measurements were taken at start of therapy. #: maximum score of mediastinum and lung parenchyma; ¶: significant values; +: corrected for ethnicity.

In our cohort, patients with SUV_{max} scores $\geqslant$6.0 were found to be four times more likely to experience relapse than patients with SUV_{max} <6.0. In addition, we showed that patients with serum levels of sIL-2R $\geqslant$4000 pg·mL^{-1} were more than twice as likely to relapse than those with lower serum sIL-2R levels. However, this does not mean that patients with normal sIL-2R at start of therapy will not relapse.

FDG PET results were found to be more adequate predictors of relapse than serum levels of sIL-2R, although it must be acknowledged that FDG PET should not be performed repeatedly, because of radiation exposure and associated healthcare costs. Furthermore, not all treatment centres may have access to FDG PET and qualified nuclear physicians with specific knowledge in the field of sarcoidosis. Therefore, serum levels of sIL-2R, when measured in a standardised fashion, can still serve as indicators of relapse risk.

Although in our opinion sIL-2R is a parameter suited to guide infliximab therapy, and a normal sIL-2R level might be required before infliximab therapy is tapered off, we could not prove this in our study. In our cohort, infliximab treatment was sometimes prolonged when clinically indicated. These patients could have elevated sIL-2R levels. In fact, at the moment of discontinuation, only seven patients had elevated sIL-2R levels (>4000 pg·mL^{-1}). Our study might therefore underestimate the guiding effect of sIL-2R in tapering infliximab treatment.

Besides the finding that the incidence of relapse was high in our cohort, the median time to relapse in the total cohort was 11 months. Interestingly, 93% of relapsing patients did so within the first 20 months, making relapse unlikely in patients who are still in remission after this period of time. In clinical practice, follow-up of these patients can probably be performed at longer time intervals.

A limitation of this study is the retrospective nature of the design, because nonstandardisation of follow-up necessarily occurs in a retrospective study. For instance, patients differed in terms of treatment indications and conditions, especially regarding the type and dose of concomitant and consolidation treatment used. While this may be considered a limitation, this variation does reflect clinical practice.

From this study, it appears that patients with high disease activity at the start of therapy, reflected by high sIL-2R or mediastinal SUV_{max} on FDG PET, have an increased chance of relapse after discontinuation of treatment. A possible explanation could be that these patients, suffering from severe active disease, need a more intensive treatment regimen, either in dose or duration. No study has focused on the optimal duration of infliximab therapy in sarcoidosis after the 6-month induction phase. It might be worthwhile to investigate whether the risk of relapse would be lower if infliximab administration was continued for a longer period or at a higher dosage schedule than the standard 5 mg·kg^{-1} in selected patients. For now, close monitoring of patients with high SUV_{max} scores and serum sIL-2R levels at the start of treatment is warranted.

The high relapse rate of 55% 1 year after discontinuation of infliximab therapy found in this study underlines the importance of additional research in this field and the need for new therapeutic approaches. The relapse rate in sarcoidosis after discontinuation of infliximab appears to be higher than described in inflammatory bowel disease, with a relapse rate of 25% after 1 year for ulcerative colitis and of 39–44% for Crohn's disease [20, 31]. Even though most sarcoidosis patients benefit from infliximab therapy initially, neither infliximab nor any of the currently available drugs can actually cure the disease.

In conclusion, this study provides evidence for a high relapse rate after discontinuation of infliximab therapy in sarcoidosis patients. For the first time it was shown that both high serum sIL-2R level and high SUV_{max} on FDG PET at initiation of therapy are valuable predictors of relapse after infliximab discontinuation. Close monitoring of patients in this category who discontinue treatment is therefore

DOI: 10.1183/09031936.00055213

indicated. In addition, the results suggest that longer duration of infliximab treatment might be needed in these patients, but prospective trials are needed to prove the clinical benefit of such a practice.

Acknowledgements

We would like to thank Ellen Tromp, statistician at St Antonius Hospital (Nieuwegein, the Netherlands) for expert statistical assistance.

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