

## PRACTICAL EMINENCE AND EXPERIENCE-BASED RECOMMENDATIONS FOR USE OF TNF- $\alpha$ INHIBITORS IN SARCOIDOSIS

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**ABSTRACT.** *Background:* In severe refractory sarcoidosis cases not responding to conventional immunosuppressive treatment, the third-line tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors infliximab and adalimumab might be an alternative. However, appropriate studies to guide the clinician are lacking. The aim of this study was to establish practical recommendations for the use of TNF- $\alpha$  inhibitors in the management of refractory sarcoidosis patients. *Methods:* Based on a literature search and the opinion of sarcoidosis experts worldwide, the recommendations were established. Studies conducted in sarcoidosis were supplemented with data obtained from relevant studies in other inflammatory diseases. A Delphi method of polling, using an online survey addressing 12 clinical questions, was performed amongst 20 of the world's leading sarcoidologists to investigate consensus in case of inadequate data to determine an objective answer. *Results:* Of the 256 papers found, 101 were included. Randomized controlled trial studies about the use of TNF- $\alpha$  inhibitors in sarcoidosis are limited. Ninety-five percent (19 of 20) of the sarcoidologists contacted, completed the questionnaire (Europe 68%, North America 32%). Nine recommendations were formulated concerning general aspects of TNF- $\alpha$  inhibitor use; Specific sarcoidosis related items, including indications, starting and maintenance dosage, interval of treatment, treatment duration, and discontinuation regimen of infliximab and adalimumab, were addressed. *Conclusion:* Based on earlier studies and consensus amongst world's leading sarcoidologists, practical recommendations for the use of TNF- $\alpha$  inhibitors in sarcoidosis were established. These recommendations, with emphasis on indications, dosage and discontinuation regimens, have been developed to support the clinician in the management of refractory sarcoidosis patients. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 91-107)

**KEY WORDS:** Sarcoidosis; Infliximab; Adalimumab; TNF- $\alpha$  inhibitors; Recommendations

### INTRODUCTION

Sarcoidosis is a multiorgan disease of unknown cause, characterized by inflammatory activity with formation of noncaseating granulomas in various organ systems (1). It primarily affects the lungs, but virtually any organ system can be involved (1). The presentation and the course of sarcoidosis are highly variable (1, 2).

Received: 28 November 2013

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Sarcoidosis activity can lead to a wide range of disease severity, varying from an acute disease course with minimal involvement to chronic disease with derangement of organ physiology and functional impairment (1-3). Therefore, especially in severe sarcoidosis cases, a timely implementation of a potent individual treatment regimen is important (1). Since sarcoidosis patients can present to any one of a variety of organ specialists, the therapeutic strategy followed is dependent on the experience of an individual specialist.

When systemic immunosuppressive therapy is indicated, glucocorticosteroids are in general considered the first-line therapy (4-6). However, prolonged use is associated with significant side-effects, making glucocorticosteroids undesirable for chronic disease management (5, 7). In steroid-refractory cases and in the presence of steroid-associated side-effects, second-line disease-modifying antiscaroid drugs (DMASDs), with usually steroid-sparing potency, are available (4, 5, 8, 9). Methotrexate (MTX) is considered the first-choice DMASD (10, 11). Optimized use of these drugs should be pursued (10). Nevertheless, in some sarcoidosis patients the available first- and second-line therapeutics do not provide the optimal result. The potent pro-inflammatory tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) plays a critical role in the immunopathogenesis of sarcoidosis (2, 12-15). In refractory sarcoidosis cases, biological TNF- $\alpha$  inhibitors have been introduced as third-line treatment option (4, 5).

The TNF- $\alpha$  inhibitors infliximab and adalimumab have been widely used for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA) and Crohn's disease (16-18). Until now, only a few studies in sarcoidosis were conducted, demonstrating promising results (12, 19-22). Hence the costs are considerable and substantial side-effects are reported, optimal use of these agents in sarcoidosis is important (23-25). In general, sarcoidosis patients are treated by pulmonologists, who usually have less experience with the use of TNF- $\alpha$  inhibitors. Further complicating the use, evidence-based recommendations for infliximab and adalimumab therapy in sarcoidosis clinical practice are lacking.

The aim of this study was to establish practical recommendations for the use of TNF- $\alpha$  inhibitors in the management of refractory sarcoidosis patients by integrating the evidence obtained through a systematic literature review and the results of a Delphi study amongst sarcoidosis experts worldwide.

## METHODS

The methods used in this study have been described previously by our group (10). The recommendations for the use of TNF- $\alpha$  inhibitors in sarcoidosis were developed in three phases.

### *Systematic review of the literature*

The computerized literature search relied predominantly on PubMed (articles from 1989 to October 2013). The terms 'sarcoidosis' and 'anti-TNF', 'anti-TNF-alpha', 'TNF-alpha inhibitors', 'infliximab' or 'adalimumab' were entered as MeSH terms and free text. Only original research published in English was reviewed. Review papers were used to identify additional studies missed by the database search. Data specifically relating to sarcoidosis were supplemented with the data obtained from relevant studies in other inflammatory diseases, with specific emphasis on rheumatic disorders and inflammatory bowel disease (IBD).

### *Delphi study amongst sarcoidologists worldwide*

As sufficient high-quality studies on the use of infliximab and adalimumab in sarcoidosis are scarce, a Delphi method of polling was used to investigate consensus in situations where there are inadequate data to determine an objective answer. An online web-based questionnaire was sent by e-mail to 20 of the world's leading sarcoidosis experts. The questionnaire addressed some aspects specifically related to sarcoidosis, including indications for use, starting and maintenance dosage, interval of treatment, treatment duration, and discontinuation regimen of infliximab and adalimumab, and general aspects, including work-up and contra-indications prior to the start of the TNF- $\alpha$  inhibitors, use during pregnancy and breast feeding, prevention of antidrug antibody formation, management of infusion reactions, monitoring during use, vaccination and traveling. Questions concerning the experts' clinical experience with both infliximab and adalimumab were addressed as well. Consensus was considered to be achieved when at least 70% of respondents agreed to an answer (26).

### Establishing the recommendations

The information gathered during phases 1 and 2 was combined to formulate the recommendations. They were divided into recommendations for the use of TNF- $\alpha$  inhibitors specifically targeting sarcoidosis and for general use. Proposals were discussed via e-mail, phone and videoconference to reach agreement and finalize each of the recommendations.

## RESULTS

### Findings of the literature review

The literature search identified 256 citations of potential interest. We screened each title and abstract for relevance resulting in the exclusion of 93 papers, as the TNF- $\alpha$  inhibitors had been used for nonsarcoidosis conditions (24 papers) or the TNF- $\alpha$  inhibitors had been used in a different context (69 papers). Sixty-two studies were review papers, whereas 101 original papers were retrieved and considered further for full review. Checking the references in review papers yielded no additional original studies. Included were four randomized controlled trials (RCTs), two discontinuation studies, one polymorphism study, 12 case series involving 10 or more patients and 82 case reports involving fewer than 10 patients, examining the effectiveness of TNF- $\alpha$  inhibitor treatment in sarcoidosis. Study characteristics and results for the most relevant studies are presented in Appendix 1. Summarizing the available studies, it can be concluded that the number of RCTs supporting the use of TNF- $\alpha$  inhibitors in sarcoidosis is limited and most of the published data were observational case series.

### Findings of Delphi study

A total of 19 of 20 (95%) of the world's leading sarcoidologists completed the questionnaire. Characteristics of the respondents are presented in Table 1. Most experts are working as pulmonologists or rheumatologists in countries in Europe (68% of respondents) and North America (32%). All sarcoidologists have experience with TNF- $\alpha$  inhibitors in the management of refractory sarcoidosis patients, 77% of them prescribing TNF- $\alpha$  inhibitors to five or more sarcoidosis patients a year. Experts reported to prescribe infliximab as an immunosuppressant in 7.2% (mean, range 0-25%) and adalimumab in 4.2% (mean, range 0-25%) of their total sarcoidosis population treated.

Specific sarcoidosis related items gathered from the experts are summarized in Table 2. Seventeen sarcoidologists (89%) had experience with infliximab prescription and 17 experts (89%) with adalimumab. The majority of experienced experts (83%) used an infliximab dosage of 5 mg/kg. All reported to use the 0-2-6 weeks induction regimen and 77% used a maintenance dosing frequency of every 4 or 6 weeks, with a predominance for the 4 weeks interval. The mean response rate for infliximab, reported by the experts, administered every 4 weeks was 78% (range 70-85%), and administered every 6 weeks 68% (range 65-75%). The induction regimen for adalimumab dosing used by the experienced experts was very diverse. However, a preference seemed to be present for a dosage of 40-80 mg in week 0, 40 mg in week 1 and 40 mg in week 2. The majority (71%) of the respondents reported to use a maintenance schedule of adalimumab of 40 mg once every week, whereas most remaining experts used the 40 mg every other week regimen. The mean reported response rate for adalimumab used in a frequency once every week was 63.8% (range 50-75%), where-

**Table 1.** Summary of characteristics of sarcoidosis experts who participated in this study

Number of respondents	19/20 (95.0%)
Pulmonologist/rheumatologist/internist	84.2/10.5/5.3%
Continent: Europe/North America	68.4/31.6%
Working experience: 0-10/10-20/>20 years	26.3/31.6/42.1%
Average number of sarcoidosis patients treated with TNF- $\alpha$ inhibitor: none/1-5/5-25/>25 a year	0/26.3/42.1/31.6%

TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

**Table 2.** Expert opinion amongst sarcoidologists, based on questionnaire answers, for recommendations specifically targeting sarcoidosis

<i>Dosing</i>					
<b>Infliximab</b>		<b>Adalimumab</b>			
Dosage		Induction regimen		Maintenance regimen	
-5 mg/kg body weight	15/18 (83.3%)	Week 0		-40 mg every week	12/17 (70.6%)
-3 mg/kg body weight	2/18 (11.1%)	-120mg	2/17 (11.8%)	-40 mg every 2 weeks	4/17 (23.5%)
-Depending on response	1/18 (5.6%)	-80 mg	6/17 (35.3%)	-Depending on response	1/17 (5.9%)
		-40 mg	9/17 (52.9%)		
Induction regimen		Week 1			
-Week 0, 2, 6	18/18 (100%)	-120 mg	1/17 (5.9%)		
		-80 mg	3/17 (17.6%)		
Maintenance regimen		-40 mg		10/17 (58.8%)	
-Every 4 weeks	7/17 (41.2%)	-0 mg	3/17 (17.6%)		
-Every 6 weeks	6/17 (35.3%)	Week 2			
-Every 8 weeks	3/17 (17.6%)	-80 mg	2/17 (11.8%)		
-Depending on response	1/17 (5.9%)	-40 mg	15/17 (88.2%)		
<i>Treatment duration</i>					
When stable disease before considering discontinuation		When primary effectiveness before considering discontinuation			
-2 years	1/19 (5.3%)	-6 months		13/18 (72.2%)	
-1 years	4/19 (21.1%)	-3 months		2/18 (11.1%)	
-6 months	8/19 (42.1%)	-Other		3/18 (16.7%)	
-No minimum duration	5/19 (26.3%)				
-Other	1/19 (5.3%)				
<i>Discontinuation</i>					
<b>Infliximab</b>		<b>Adalimumab</b>			
-Prolonging interval between 2 doses to 5 weeks, 6 weeks, 8 weeks, and 12 weeks, all during 3 doses, and stop thereafter	12/17 (70.6%)	-Prolonging interval between 2 doses to once every 10 days, once every 2 weeks, all during 3 months, and stop thereafter		5/17 (29.4%)	
-Decreasing dosage without interval change	3/17 (17.6%)	-Prolonging interval between 2 doses to once every 2 weeks during 3 months and stop thereafter		7/17 (41.2%)	
-Other	2/17 (11.7%)	-Decreasing dosage without interval change		2/17 (11.8%)	
		-Stop at once		1/17 (5.9%)	
		-Other		2/17 (11.8%)	

as the mean response rate for an administration frequency of once every 2 weeks was 46.7% (range 30–60%). With regard to the discontinuation regimen of infliximab, the majority of experts (71%) agreed with the gradual prolongation of the dosing interval, while continuing the dosage unchanged. Seventy-one percent applied gradual prolongation of the interval when discontinuing adalimumab, using either a one- or two-step tapering regimen.

Table 3 indicates the questionnaire answers concerning the general items. There was at least

70% agreement amongst experts for most issues in general clinical practice. However, less agreement was found regarding the use of preventive vaccinations, the method of treatment of infusion reactions, and on the consideration of planned pregnancy being a contraindication for TNF- $\alpha$  inhibitor therapy in men. To prevent antidrug antibody formation, MTX was more frequently used compared with glucocorticosteroids.

**Table 3.** Expert opinion amongst sarcoidologists, based on questionnaire answers, for the general recommendations

<i>Pre-administration work-up</i>		<i>Vaccination</i>	
-IGRA test	19/19 (100%)	-Vaccines made of live, attenuated microorganisms discouraged	17/18 (94.4%)
-Chest radiograph	19/19 (100%)	-Influenza vaccination	12/18 (66.7%)
-Treatment TB after positive screening	14/19 (73.7%)	-Pneumococcal vaccination	8/18 (44.4%)
-Hepatitis B serology	16/19 (84.2%)	-Hepatitis B vaccination	5/18 (27.8%)
-Hepatitis C serology	12/19 (63.2%)		
-HIV serology	7/19 (36.8%)		
-Malignancy screening	7/19 (36.8%)		
<i>Contraindications</i>		<i>Treatment infusion reaction</i>	
-TB infection	16/19 (84.2%)	-Mild: decreasing infusion velocity	14/18 (77.7%)
-Opportunistic infection	18/19 (94.7%)	-Hydrocortisone, paracetamol/ acetaminophen, clemastine, and when indicated adrenaline	10/18 (55.6%)
-Serious bacterial infection or treated with antibiotics	19/19 (100%)	-Permanent discontinuation TNF- $\alpha$ inhibitor	12/18 (66.7%)
-Upper airway infection	11/19 (57.9%)	-Premedication for next infusion	11/18 (61.1%)
-Non-healing ulcer of the skin	8/19 (42.1%)	-Maintenance dosage of GC	2/18 (11.1%)
-Active fungus infection	19/19 (100%)		
-Active Herpes Zoster infection	18/19 (94.7%)		
-Hepatitis B	15/19 (78.9%)		
-Hepatitis C	13/19 (68.4%)		
-Heart failure NYHA class III/IV	15/19 (78.9%)		
-Malignancy $\leq 5$ years ago	15/19 (78.9%)		
-Malignancy at present	19/19 (100%)		
<i>Contraindication in (planned) pregnancy</i>		<i>Monitoring</i>	
-In women	18/19 (94.7%)	-Every 1-3 months after start	18/18 (100%)
-In men	10/19 (52.6%)	-Every 3-6 months thereafter	15/18 (83.3%)
<i>Prevention of antidrug antibody formation</i>		<i>Traveling abroad</i>	
-Use of MTX	17/18 (94.4%)	-Discouraged to countries without medical/sanitary supplies	16/18 (88.9%)
-Use of GC	9/18 (50.0%)		

GC, glucocorticosteroids; IGRA, interferon- $\gamma$  release assay; MTX, methotrexate; NYHA, New York Heart Association; TB, mycobacterium tuberculosis; TNF- $\alpha$ , tumor necrosis factor- $\alpha$

## DISCUSSION

Based on earlier studies and the results of a Delphi study amongst the world's leading sarcoidologists, practical recommendations for the use of TNF- $\alpha$  inhibitors in sarcoidosis were established. These recommendations are summarized in tables 4 and 5 and have been developed to support the clinician in the management of refractory sarcoidosis patients.

## RECOMMENDATIONS WITH AN APPROACH SPECIFIC FOR SARCOIDOSIS

### *Effectiveness*

In Crohn's disease and RA, both infliximab and adalimumab have been proven efficacious in inducing short-term clinical remission (27-32). Timely introduction of TNF- $\alpha$  inhibitor treatment can lead to a greater likelihood of control of symptoms and prevention of serious organ damage resulting in a more favorable outcome (27-29, 33). The short term effi-

**Table 4.** Recommendations for the use of TNF- $\alpha$  inhibitors specifically targeting sarcoidosis<sup>a</sup>

Recommendation
<i>Dosage</i>
- Infliximab: Intravenous infusion of a dosage of 5 mg/kg at week 0, 2, 6 and every 4 weeks thereafter is recommended; consider other maintenance dosages depending on disease activity.
- Adalimumab: Subcutaneous administration at a dosage of 80-160 mg at week 0, 40 mg at week 1, and 40 mg once every week thereafter, is recommended; consider other maintenance dosages depending on disease activity.
<i>Discontinuation</i>
In case of severe uncontrolled side-effects; primary ineffectiveness during 3-6 months of treatment; secondary ineffectiveness due to antibody formation; or stable disease during treatment with a TNF- $\alpha$ inhibitor for at least 6-12 months, discontinuation should be considered.
- Infliximab: Discontinuing infliximab because of stable sarcoidosis, gradually prolonging the interval between 2 doses to 5 weeks (during 3 doses), 6 weeks (during 3 doses), 8 weeks (during 3 doses), 12 weeks (during 3 doses) and stop thereafter, while continuing the dosage unchanged, is recommended.
- Adalimumab: When discontinuing adalimumab because of stable sarcoidosis for prolonged period, prolonging the interval between 2 doses to once in every 10 days (during 3 months), once in every 2 weeks (during 3 months), and stop thereafter, while continuing the dosage unchanged, is recommended.
<sup>a</sup> All recommendations apply to general situations; for every individual case, patient and disease characteristics should be taken into account. TNF- $\alpha$ , tumor necrosis factor- $\alpha$

**Table 5.** General recommendations for the use of TNF- $\alpha$  inhibitors

Recommendation
<i>Dosage</i>
1 Before starting TNF- $\alpha$ inhibitors, active or latent TB infection (positive IGRA test), serious opportunistic infections, serious bacterial infections, infections treated with antibiotics, upper airway infections with fever, active fungus infection, active herpes zoster infection, hepatitis B/C infection, heart failure NYHA class III/IV, malignancy $\leq 5$ years ago in medical history, and malignancy at present, should be excluded.
2 TNF- $\alpha$ inhibitors should not be used by women for at least 2-3 months before planned pregnancy; a recommendation for the use by men is not possible because of lack of evidence. TNF- $\alpha$ inhibitors should not be used during pregnancy or breast feeding; in individual cases, use during pregnancy can be considered.
3 Before every administration of the TNF- $\alpha$ inhibitor, a current infection should be excluded <sup>a</sup>
4 Elective surgeries or interventions and dentist visits should be planned in consultation with the treating physician.
5 To prevent antidrug antibody formation, TNF- $\alpha$ inhibitors should be combined with low doses methotrexate and/or glucocorticosteroids.
6 Mild infusion reactions occurring during treatment with a TNF- $\alpha$ inhibitor should be treated by decreasing the infusion velocity; serious infusion reactions with hydrocortisone, paracetamol/ acetaminophen, clemastine, and when indicated adrenaline; permanent discontinuation of the TNF- $\alpha$ inhibitors should be considered. To prevent future infusion reactions, premedication for the next infusion is recommended.
7 After the start of TNF- $\alpha$ inhibitors, regular monitoring is recommended every 1-3 months and once the dosage is stable every 3-6 months.
8 The use of vaccines made of live, attenuated microorganisms is discouraged, but vaccines made of killed microorganisms can be used safely during anti-TNF- $\alpha$ therapy; preventive influenza, pneumococcal, and hepatitis B vaccinations before or during the use of TNF- $\alpha$ inhibitors can be considered.
9 In general, traveling to countries without decent medical and sanitary supplies or for which administration of vaccines made of live, attenuated microorganisms is necessary, is discouraged. When traveling to countries without sufficient medical supplies, the patient should take antibiotics along. During travel, adalimumab should be transported and preserved in a cooled environment.
<sup>a</sup> In case of an infection, the TNF- $\alpha$ inhibitor should at least temporarily be discontinued until all signs of the infection have disappeared. IGRA, interferon-gamma release assay; NYHA, New York Heart Association; TB, mycobacterium tuberculosis; TNF- $\alpha$ , tumor necrosis factor- $\alpha$

cacy of TNF- $\alpha$  inhibitor treatment in severe refractory sarcoidosis cases has been proven (Appendix 1) (12, 19-22, 34-77). Also in these cases, timely implementation of an effective therapeutic regimen, if necessary consisting of TNF- $\alpha$  inhibitors, should be pursued to obtain low disease activity and a better outcome. Effectiveness of infliximab and adalimumab in maintaining long-term clinical remission has been shown in Crohn's disease and RA (27, 28, 32, 78). One study in sarcoidosis showed maintained efficacy with prolonged infliximab treatment (mean treatment duration 46 months) (79). However, another study found only 10 of 25 patients with sarcoid eyes involvement successfully maintained on long-term TNF- $\alpha$  inhibitor treatment (42). Future studies are necessary to establish if TNF- $\alpha$  inhibitors are effective by bridging in active disease in order to aim for long-term remission in sarcoidosis as well.

### *Indications*

The indications for TNF- $\alpha$  inhibitor treatment in sarcoidosis consist of its use as a third-line treatment option in refractory cases with inadequate response to or in the presence of unacceptable side-effects from first-line glucocorticosteroids and second-line DMASDs (80). Infliximab is the most widely studied TNF- $\alpha$  inhibitor in sarcoidosis. It is shown to be effective in pulmonary sarcoidosis (12, 20, 35-38, 79), but its use has also been described for skin (19, 36, 38, 39, 47, 49, 79), neurological (19, 39, 45, 48, 51-55, 57, 60, 61, 64, 66-68, 70, 79), liver (19, 38, 39, 75, 79), kidney (19, 76, 77, 79), muscle (19, 39, 79), bone (19, 38, 39, 74, 79), and eye (uveitis) (19, 36, 38, 42, 58, 59, 65, 69, 79) involvement, hypercalcaemia (50), small fiber neuropathy (46, 63), and extreme devastating fatigue (43). Its value in cardiac sarcoidosis is also shown in case reports (19, 35, 56, 62, 69).

The use of adalimumab has especially been shown for eye involvement (consisting of uveitis, choroidal involvement, papillitis and macula edema) (22, 71). Beneficial effects have been described for patients with symptomatic lung (22), skin (21), bone (74), and bone marrow (73) involvement and sarcoidosis associated fatigue (22, 43, 72).

To date, etanercept is not used in sarcoidosis disease management. In an open label trial of pulmonary sarcoidosis, etanercept was associated with treatment failure (81). Furthermore, the drug failed

in an RCT investigating patients with refractory sarcoidosis uveitis (82). These results are in line with observations in Crohn's disease (83).

### *Cardiac sarcoidosis*

Initial observations suggested that inhibition of TNF- $\alpha$  may favorably modify the course of heart failure (84). However, based on the subsequent findings, heart failure NYHA class III and IV is currently considered a contraindication for the use of TNF- $\alpha$  inhibitors (30, 31), which is supported by almost 80% of the participating sarcoidosis experts. Chung et al. (85) evaluated the efficacy and safety of infliximab in 150 patients with stable NYHA class III or IV heart failure and showed that TNF- $\alpha$  inhibition adversely affected the clinical condition of these patients. Mann et al. (86) ruled out a positive effect of etanercept on death or hospitalization due to chronic heart failure (NYHA class II-IV). Furthermore, the occurrence of symptomatic cardiac arrhythmias associated with the use of infliximab has been reported (87, 88).

What to do with TNF- $\alpha$  inhibitors in patients with cardiac sarcoidosis, either with or without consequent heart failure? In the presence of active cardiac sarcoidosis without signs of heart failure class III or IV and without responsiveness to conventional treatment, we recommend considering infliximab. In case reports, infliximab is demonstrated to have beneficial effects in cardiac sarcoidosis (19, 35, 56, 62, 69). Furthermore, 84% of sarcoidosis experts stated to use TNF- $\alpha$  inhibitors in selected cases of cardiac involvement. In the presence of active cardiac sarcoidosis with heart failure NYHA class III or IV, more caution is warranted. The decision to either implement or refrain from TNF- $\alpha$  inhibitors should be based on the patients' individual circumstances. If cardiac sarcoidosis activity is the only cause for heart failure, infliximab can be considered (for instance young sarcoidosis patient without relevant comorbidity or co-medication). If besides cardiac sarcoidosis activity other causes for heart failure are present, infliximab should be considered contraindicated.

### *Dosing*

No guidelines are available concerning dosing of infliximab or adalimumab in sarcoidosis. Only one

Appendix 1. Summary of characteristics and results of studies describing infliximab and adalimumab use in sarcoidosis

Authors	Drug	Study goal	Patients treated (n)	Outcome	Drop-outs (n)	Organ involvement	Combi/monotherapy	Dosage	Adverse effects
Baughman et al. (2006) (12)	Infliximab	To assess the efficacy of infliximab in pulmonary sarcoidosis, multicentre study	138 (46 infliximab 3 mg/kg, 47 infliximab 5 mg/kg, 45 placebo)	Significantly higher increase in FVC% from baseline to week 24 in infliximab group (3 and 5 mg/kg) compared to placebo (p=0.038); no improvement in dyspnea, 6MWD, skin abnormalities (LuPGA); patients with more severe disease tended to benefit more from infliximab	2 in infliximab 3 mg/kg group, 2 in infliximab 5 mg/kg group, 1 in placebo group. Reasons: withdrawal of consent, unable to draw blood, lost to follow-up	Lungs, skin, eye	Combination with GC n=70, immunomodulation n=10, GC/immunomodulation n=58. No difference between groups.	3 or 5 mg/kg iv at 0, 2, 6, 12, 18, and 24 weeks and were followed through week 52	Pneumonia n=4, squamous cell carcinoma n=1, epithelioid sarcoma n=1. Infusion reactions 2.3%. Other side-effects not different for placebo and infliximab groups.
Judson et al. (2008)(19)	Infliximab	To assess the efficacy of infliximab in extrapulmonary sarcoidosis, multicentre study (secondary endpoint of study)	138 (62 combined infliximab 3 mg/kg or 5 mg/kg, 30 placebo)	Extrapulmonary organ severity was determined by a novel severity tool (ePOST) with an adjustment for the number of organs involved (ePOSTadj). The change from baseline to week 24 in ePOST as well as the improvement in ePOSTadj was greater for the combined infliximab group compared with placebo (p<0.05).	2 in infliximab 3 mg/kg group, because study drug was not received	17 extrapulmonary organs, among others peripheral lymph nodes, skin, bone, joints, liver, eyes	See Baughman et al. (12) No difference between groups.	3 or 5 mg/kg iv at 0, 2, 6, 12, 18, and 24 weeks and were followed through week 52	See Baughman et al. (12)
Rossmann et al. (2006) (20)	Infliximab	To assess the safety, tolerability and efficacy of infliximab in pulmonary sarcoidosis, multicentre study	19 (13 infliximab, 6 placebo at weeks 0 and 2 and open-label infliximab for all subjects at weeks 6 and 14)	At 6 weeks the mean relative change in VC $\pm$ SD compared to baseline was 15.22 $\pm$ 9.91% for infliximab and 8.39 $\pm$ 3.33% for placebo (p=0.65)	None	Lungs (radiographic stage II, III and IV)	-	5mg/kg iv at 0, 2, 6 and 14 weeks	Decreased WBC and elevated CK n=1, pneumonia n=1, cellulitis, acute renal failure, pulmonary embolus with consequent death n=1, and visual field defect n=1
Pariser et al. (2013)(21)	Adalimumab	To assess the effectiveness and safety of adalimumab in cutaneous sarcoidosis	16 (10 adalimumab, 6 placebo)	Improvement in target lesion area (p=0.0063), target lesion volume (p=0.0225), and Dermatology Life Quality Index score (p=0.0034); no significant changes in pulmonary function tests, radiographic findings, or laboratory studies	3 in adalimumab, 1 in placebo group. Reasons: did not receive allocation treatment, unable to be contact, unable to arrange transportation	Skin	Monotherapy	Adalimumab group 80 mg sc at week 0 and 40 mg once a week thereafter during 12 weeks, both groups 40 mg once a week during 12 weeks thereafter	Pneumonia (n=1), other adverse effects mild.

*Discontinuation and polymorphism studies*

Authors	Drug	Study goal	Patients followed (n)	Outcome	Predictive factors of relapse	Organ involvement	Mean duration of treatment with infliximab	Dosage	Combi/monotherapy	Adverse effects
Vorselaers et al. (2013) (89)	Infliximab	To assess the relapse rate and predict relapse after discontinuation of infliximab	47	29 (62%) had relapse after infliximab discontinuation; mean follow-up time 36.6 $\pm$ 22.6 months, median time to relapse 11.1 $\pm$ 2.57 months	Mediastinal SUVmax scores $\geq$ 6.0 and serum sIL2R $\geq$ 4000 pg/mL at the start of therapy	Pulmonary n=30, extrapulmonary involvement n=41	8.5 $\pm$ 5.8 months	5 mg/kg iv at 0, 2 and 6 weeks, and every 4 weeks thereafter	Monotherapy n=3, combination with GC n=13, immunomodulation n=19, GC/immunomodulation n=11	Allergic reaction n=3 in patients not included
Panselinas et al. (2012) (98)	Infliximab	To assess the course of sarcoidosis after discontinuation of infliximab	14	12 (86%) had deteriorated as compared with their status at the time of discontinuation, mean follow-up time 12 months, 50% deteriorated within 3 months after discontinuation	-	CNS, skin	4.4 months	5 mg/kg iv at 0, 2 and 6 weeks, and every 6 weeks thereafter	Combination with GC n=7, MTX n=2, GC/MTX n=2, GC/AZA n=1, GC/cyclophosphamide n=1	Not described
Wijnen et al. (2013) (34)	Infliximab/Adalimumab	To assess association TNF- $\alpha$ G-308A polymorphism and response to TNF- $\alpha$ inhibitors after 1 year	111 (76 Infliximab, 35 adalimumab)	83 (75%) responded well; of patients without the variant A-allele 93.6% (p<0.001) improved, while 30.3% of variant A-allele carriers improved	-	Lungs n=69, eyes n=31, SFN n=91, skin n=6, spinal cord n=1, kidney n=1	At least 1 year	Infliximab 5 mg/kg iv at 0, 2 and 6 weeks, and every 4 weeks thereafter/ Adalimumab 40 mg sc once a week	Combination with GC n=14, MTX n=29, GC/MTX n=28	Minor infections n=11, sepsis n=1, herpes zoster infection n=5, antibody formation infliximab n=9

*Large case series*

Authors	Drug	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/monotherapy	Dosage	Effect of therapy	Adverse effects (n)
Russell et al. (2013)(79)	Infliximab	53 organs of 42 patients	31 organs	Lungs, skin, lymph nodes, CNS	Combination with GC n=24, MTX n=20, HCO n=23, etanercept n=1	Unknown, average treatment duration 46.2 months, up to a maximum of 85 months	Complete remission n=2; discontinuation of other therapeutic agents during infliximab n=13; symptom and clinical resolution or improvement; small improvement in FVC, FEV1, TLC (not significant)	Adverse events in 57%, discontinuation because of toxicity n=3
Hostettler et al. (2012) (35)	Infliximab	16 (treatment for 12 months)	14	Predominant pulmonary n=5, extrapulmonary n=11 (CNS, lupus pernio, heart)	Combination with GC n=6, GC/immunomodulator n=7	3 mg/kg iv in 4/6/8 weekly intervals	Improvement of FVC 0-10% in 4/5 with predominant pulmonary involvement; complete or partial improvement in 10/11 with extrapulmonary involvement	After 4 years of therapy symptomatic bradyarrhythmia 6h after infliximab infusion, which lead to temporary discontinuation of infliximab n=1

## Large case series

Orum et al. (2012)(36)	Infliximab	12	12	Lungs n=9, eyes n=2, skin n=2, oesofagus n=1, bone marrow n=1, kidney n=1, nose n=1	Not described	3 mg/kg iv at 0, 2 and 6 weeks, and every 8 weeks thereafter	Increase in FEV1, FVC, DLCO and TLC n=9; ACE and sIL2R in patients with raised values pretreatment decreased to values within the reference interval n=6; steroid-sparing effect on ocular sarcoidosis n=2, effect on cutaneous sarcoidosis n=2, all patients had reduced organ involvement and subjective improvement in symptoms	None
Keijzers et al. (2008) (37)	Infliximab	12	11	Lungs, eyes, muscle, skin	Combination with GC n=9, MTX n=10, HCQ n=1	5 mg/kg iv at 0, 2, 6, 12, 18 and 24 weeks	ACE decreased with an average of 39% (p<0.01); sIL2R with 47% (p<0.01); VC increased with 5,4% (p<0.01); DLCO with 3,3% (p<0.05); SUVmax decreased with 55% ±35 (p<0.01)	Not described
Saleh et al. (2006)(38)	Infliximab	12	12	Lungs n=2, skin n=3, neurologic n=2, eyes n=1, bone n=1, liver n=1, lymph nodes n=2, hypercalcaemia n=1	Combination with GC and/or MTX	3 mg/kg iv at weeks 2, 4, 6, 10 and 14, and every 8 weeks thereafter	All 12 patients improved significantly; lung function, skin lesions, MR imaging, CT, vision, bone scan and liver tests improved.	Mild allergic drug reaction responsive to antihistamine n=1
Doty et al. (2005)(39)	Infliximab	10	10	Lupus pernio n=5, skin non-lupus n=1, bone n=1, CNS n=1, liver n=1, muscle n=1	Combination with GC n=6, MTX n=2, HCQ n=2	5 mg/kg iv at 0, 2 and 6 weeks, and every 8 weeks thereafter	Reduction of GC dose in 5 of 6, improvement of symptoms n=9; objective improvement on physical examination, laboratory studies, or imaging studies n=10	Drug reaction n=1, oral candidiasis n=1, angioimmunoblastic lymphoma n=1
Ercikens et al. (2012) (22)	Adalimumab	26	26	Eye (refractory posterior uveitis), lungs	Combination with oral GC n=26, MTX n=18	40 mg sc once a week	Improvement of eye disease in 22 (85%) and stabilization in 4 (15%); improvement of ACE and CRP (p<0.01); improvement of fatigue in 67% (p<0.01) and of DLCO in 88% (p<0.01); tapering down of GC (p<0.01) and MTX (p<0.05) after 6 and 12 months of treatment	Development of solid mass at injection site n=1, minor local skin reactions n=4
Milman et al. (2012) (40)	Adalimumab	10	9	Intrathoracic n=9, extrathoracic n=4	Combination with GC n=8, MTX n=7, AZA n=1	40 mg sc once in 2 weeks	FDG PET uptake decreased in 9 (p=0.01) and increased in 1 patient; SUVmax fell from median 14.1 to 7.0 (p<0.03), and mean SUV fell from median 6.5 to 2.9 (p<0.02); no effect on pulmonary function tests, serum ACE and blood lymphocyte concentrations; physiological component summary score of SF-36 increased (p=0.07)	Pneumonia n=1, vaginal candidiasis n=1

*Large case series*

Banase et al. (2013)(41)	Infliximab/Adalimumab	14	19 prescriptions in 10 patients (8 infliximab, 8 adalimumab, 3 etanercept)	25 (19 infliximab, 6 adalimumab)	25 initial	Eyes	Articular sarcoidosis involvement n=19, pulmonary n=9, ocular n=2	Monotherapy n=10, combination with MTX n=9, NSAID n=12, GC n=5	Infliximab 5 mg/kg iv per 6 weeks, adalimumab 40 mg sc once in 2 weeks, etanercept 50 mg sc once a week	At 3 months, moderate or satisfactory efficacy on DAS28 (14/19, 73.7%); after 1 year no significant effect on articular manifestations, DAS28 with ESR or CRP, global VAS score, extra-articular involvement; no impact on MTX or NSAID use; they were significant GC-sparing (prednisone 6.3 before versus 3.2 mg/day after therapy)	Mild infections n=2, toxiderma n=1 with resolution after discontinuation
Baughman et al. (2012) (42)	Infliximab/Adalimumab	25 (19 infliximab, 6 adalimumab)	25 (19 infliximab, 6 adalimumab)	25 initial	Eyes			Monotherapy n=1, combination with MTX n=14, AZA n=10, LEF n=3	Infliximab 3-5 mg/kg iv at week 0, 2 and every 4 weeks thereafter, adalimumab 40 mg sc once in 1-2 weeks	Initial response to TNF- $\alpha$ inhibitor n=25, successful long-term therapy (ongoing treatment or remission) n=10 (7 infliximab, 3 adalimumab)	Anaphylaxis n=2, arthralgia and rash n=7, infections n=2, toxicity leading to discontinuation infliximab n=8, adalimumab n=3
Elferich et al. (2010) (43)	Infliximab/Adalimumab	42 (31 infliximab, 11 adalimumab)	42 (31 infliximab, 11 adalimumab)	-		Cognitive failure, fatigue		Combination with GC and/or MTX	Infliximab 5 mg/kg iv at 0, 2 and 6 weeks and every 4 weeks thereafter, adalimumab 40 mg sc once a week	Significant higher improvement in CFQ and FAS compared to without TNF- $\alpha$ inhibitor (p<0.0001)	None
Baughman (2007) (44)	Infliximab/Adalimumab	122 (82 infliximab, 27 adalimumab, 13 etanercept)	74 (58 infliximab, 13 adalimumab, 3 etanercept)	74 (58 infliximab, 13 adalimumab, 3 etanercept)	Not described	Not described	Not described	Not described	Not described	Clinical status of one or more organs improved or reduction concurrent medications	Adalimumab: infection n=2, reaction injection site n=3; infliximab: anaphylactic reaction n=2, hypotension n=2, allergic reactions n=5, gastrointestinal bleeding n=3, alopecia n=1, skin cancer n=2

*ePOST, extrapulmonary physician organ severity tool, a novel severity tool to examine the state of sarcoidosis extrapulmonary organ involvement in 17 extrapulmonary organs in which each organ has to be scored on a scale from 0 (not affected) to 6 (very severely affected); ePOSTadj score, ePOST score divided by the number of extrapulmonary organs involved; LuPGA, Lupus Pernio Physician's Global Assessment, semiquantitative rating scale representing the physician's assessment of the patient's lupus pernio status relative to baseline. ACE, angiotensin-converting enzyme; AZA, azathioprine; CFQ, cognitive failure questionnaire; CK, creatine kinase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography, DAS28, disease activity score in 28 joints; DLCO, diffusing capacity for carbon monoxide; ESR, erythrocyte sedimentation rate; FAS, fatigue assessment scale; 18F-FDG PET, fluorine18-fluorodeoxyglucose positron emission tomography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GC, glucocorticosteroids; HCQ, hydroxychloroquine; iv, intravenous; LEF, leflunomide; MR, magnetic resonance imaging; MTX, methotrexate; 6MWD, 6-minute walk distance; n, number; NSAID, nonsteroidal anti-inflammatory drug; sc, subcutaneous, SD, standard deviation; SF-36, short form-36; SFN, small fiber neuropathy; sLL2R, soluble-inter-leukin2-receptor; SUVmax, maximum standardized uptake value of 18F-fluorodeoxyglucose positron emission tomography; TLC, total lung capacity; TNF-, tumor necrosis factor- $\alpha$ ; VAS, visual analog scale; VC, vital capacity; WBC, white blood cell.*

randomized controlled trial compared different dosages of intravenous infliximab in sarcoidosis (placebo vs. 3 mg/kg body weight vs. 5 mg/kg, n=138) (12). No significant difference in the change from baseline in the percentage of predicted forced vital capacity (FVC%) between the 3 mg/kg and 5 mg/kg group was found, whereas the combined infliximab group had a significant increase in the FVC% compared with no change in placebo-treated patients ( $p=0.038$ ). Other studies and case series used either dosages of 5 mg/kg or 3 mg/kg, but a preference for infliximab 5 mg/kg seemed to be present (Appendix 1) (20, 34-39, 41-43, 45-47, 49-70, 74-77, 89, 90). The majority of sarcoidosis experts reported using an infliximab dosage of 5 mg/kg. Guidelines and consensus statements recommend an infliximab dosage of 5 mg/kg in IBD, ankylosing spondylitis, psoriatic arthritis and psoriasis, and of 3 mg/kg in RA (91). Combining the available evidence, infliximab infusion using a dosage of 5 mg/kg is recommended in sarcoidosis.

The induction regimen most frequently used in sarcoidosis literature consisted of infliximab administration in week 0, 2 and 6, which was also supported by all sarcoidosis experts (Appendix 1) (12, 19, 20, 34, 36, 37, 39, 42, 43, 47, 50-58, 60-70, 89). Guidelines and consensus statements in IBD, RA, ankylosing spondylitis, psoriatic arthritis and psoriasis, all recommended a 0-2-6-weeks induction regimen (91). Maintenance dosages used in the literature varied from every 4 to 8 weeks, whereas three fourth of experts used a dosing frequency of every 4 or 6 weeks (Appendix 1) (12, 19, 20, 34-39, 41-43, 45-70, 74-77, 89, 90). A predominance for the 4 weeks interval was present. The mean reported response rate for infliximab administered every 4 weeks was higher when compared to the 6 weeks interval. In IBD and RA, a maintenance dosing every 8 weeks is advised, whereas in ankylosing spondylitis, psoriatic arthritis and psoriasis maintenance treatment every 6-8 weeks is recommended (91). Given the better reported results in sarcoidosis when using the 4 weeks maintenance interval, an infliximab induction regime at week 0, 2, 6, followed by maintenance dosing every 4 weeks is recommended (3).

The induction regimen used in week 0 until 2 for subcutaneous adalimumab was very diverse, but most sarcoidosis experts were in favor of weekly dosing of relatively low dosages. In Crohn's disease a

loading dose of 160/80 mg was advised at week 0/week 2 to achieve early disease control, whereas in rheumatic inflammatory diseases a loading dose was not advised (18, 29, 32). Results in Crohn's disease show that initiating TNF- $\alpha$  inhibitors early in the disease course at sufficient dosage levels, might prevent serious organ damage and result in a more favorable outcome (33, 92). Following the experience in Crohn's disease, loading dosages of 80-160 mg at week 0, with at least 40 mg at week 1 and 2, respectively, should be considered in sarcoidosis.

The number of sarcoidosis studies using an adalimumab maintenance dosage of 40 mg every week versus every other week is equal (Appendix 1) (21, 22, 34, 40-43, 72-74). Experienced sarcoidosis experts were more likely to use the weekly dosing interval. The mean reported response rate was in favor of the weekly administration compared to the every other week administration. This was also reported in an expert review on TNF- $\alpha$  inhibitor use in sarcoidosis (80). Guidelines in Crohn's disease, recommending the 40 mg every other week maintenance therapy regimen, are difficult to compare with sarcoidosis, given the higher induction dosages used (29). In accordance with infliximab practice and given the opinion of experienced sarcoidologists, we suggest using an adalimumab maintenance dosage of 40 mg once a week in sarcoidosis. To create a better evidence-based foundation for dosing recommendations, future research is necessary.

### *Discontinuation*

In case of supposedly primary ineffectiveness, TNF- $\alpha$  inhibitors should be continued for at least 3-6 months before discontinuation can be considered, which is supported by more than 80% of sarcoidosis experts. In rheumatic inflammatory diseases and IBD, response is most frequently seen in the first month of treatment, but it can also be achieved after longer treatment duration (29, 32). In primary non-responding patients, adjustment of dosage or administration interval or a biological agent with another mode of action should be considered (91). In RA, it is shown that these patients are less likely to respond to a second TNF- $\alpha$  inhibitor (32). In case of secondary ineffectiveness, switch from one TNF- $\alpha$  inhibitor to another or a biological agent from another class can be successful (32). In sarcoidosis,

promising results have been shown for rituximab, a chimeric monoclonal antibody that targets CD-20 cells with reduction of circulating mature B lymphocytes (93, 94).

An issue clinicians are struggling with is in which sarcoidosis patients and after what treatment duration, maintenance of clinical remission is likely when tapering off TNF- $\alpha$  inhibitors. Studies in RA have been investigating this issue aiming 'biological free remission' (BFR), i.e. sustainability of remission after a biological agent is discontinued (95, 96). The first difficulty is the identification of patients with stabilization of sarcoidosis disease, i.e. patients who might be possible candidates for sustained BFR after tapering down TNF- $\alpha$  inhibitor treatment. To identify these patients, a definition of response is needed (97). Since sarcoidosis is a disease which can affect almost every organ system and which has a fluctuating disease course, defining exact response criteria is difficult. Wijnen et al. (34) made a first attempt how to define treatment response in sarcoidosis and assessed possible predictors of response. Other studies did not use standardized criteria, but determined treatment effect based on evaluation by the treating physician. Prospective studies are really needed to establish criteria for the identification of responders and non-responders when evaluating pharmacological treatment. Another question is: which period is long enough before successful withdrawal of TNF- $\alpha$  inhibitors is reasonable and which indicators can be used to establish this period? Vorselaars et al. (89) showed that the majority of sarcoidosis patients (29 of 47 patients, 62%) relapsed after discontinuation of infliximab after a mean treatment duration of 8.5 months with a median time to relapse of 11.1 months. Panselinas et al. (98) showed deterioration in 12 of 14 patients (86%) after discontinuation of infliximab after a mean treatment duration of 4.4 months. These results suggest that successful discontinuation only is probable after stable disease has been reached. Sixty-three percent of sarcoidosis experts reported that stable disease has to be present for at least 6 to 12 months of treatment before they considered discontinuation. In RA, recommendations suggest that a discontinuation attempt should be considered in case of low disease activity or remission for at least 6 months (99). Future research is necessary to establish in which sarcoidosis patients and after what optimal TNF- $\alpha$  inhibitor

treatment duration, sustained BFR can be achieved.

In sarcoidosis or other chronic inflammatory diseases, no recommendations are available for the best stepwise discontinuation regimen of TNF- $\alpha$  inhibitors. When discontinuing infliximab in stable sarcoidosis disease, we recommend, based on the expert opinion, gradually prolonging of the interval between 2 doses to 5 weeks (during 3 doses), 6 weeks (during 3 doses), 8 weeks (during 3 doses), 12 weeks (during 3 doses) and stop thereafter, while continuing the dosage unchanged. When discontinuing adalimumab, prolonging the interval between 2 doses to once in every 10 days (during 3 months), once in every 2 weeks (during 3 months), and stop thereafter, while continuing the dosage unchanged, is recommended. There is a risk of relapse after discontinuation, often necessitating reinstatement of treatment (80). When TNF- $\alpha$  inhibitor treatment is resumed, the risk of antidrug antibody formation is possibly higher, with consequent higher risk for loss of response and allergic reactions during infusion (80). A careful tapering method might trace a threatening relapse while gradually prolonging the interval. Prompt reinstatement of the original dosing regimen can avoid the occurrence of a relapse in most cases.

## GENERAL RECOMMENDATIONS

The general recommendations are based on guidelines and consensus statements in other chronic inflammatory diseases, mainly IBD and RA (18, 30-33, 78, 92, 100). The recommendations presented do not differ from the general attitude towards the use of TNF- $\alpha$  inhibitors and are according to the clinical practice already followed by the participating experts.

### *Infection prevention*

Every patient should be screened for the possibility of (latent) TB (31, 32, 92, 101). The use of live attenuated vaccines is contraindicated during TNF- $\alpha$  inhibitor treatment, according to available guidelines (18, 30-33, 92). Discussion exists on the use of preventive vaccinations in patients on TNF- $\alpha$  inhibitors. Two third of sarcoidosis experts stated to prescribe yearly influenza vaccination (killed vaccine) in pa-

tients treated with TNF- $\alpha$  inhibitors. However, only 44% indicated that they routinely administer pneumococcal vaccinations (killed vaccine) and 28% reported the completion of hepatitis B series (killed vaccine) in patients at risk. Rheumatology and IBD guidelines recommended annual influenza vaccination and periodic pneumococcal vaccination for all patients receiving biological agents (30-33, 92). The immune response to influenza and pneumococcal vaccinations in patients receiving biologic therapies may be attenuated, although serological protection is adequate in most cases (30-32). The completion of hepatitis B vaccination series was also recommended in case of risk factors, such as a history of intravenous drug abuse or in healthcare professionals (30-32). Some recently updated guidelines also advise vaccination for human papillomavirus (recombinant vaccine) before or during biological therapy and herpes zoster vaccination (live vaccine) before starting a TNF- $\alpha$  inhibitor, based on age and risk (30, 32, 100).

#### *Other issues*

Regular monitoring every 1-3 months after the start of TNF- $\alpha$  inhibitors is recommended; and once the use is stable every 3-6 months. Given the risk of rare instances of pancytopenia, aplastic anaemia or abnormal liver transaminases during TNF- $\alpha$  inhibitor use, monitoring of complete blood count and liver transaminases is recommended (30, 32). The frequency should be established by the patient's concomitant drugs use, conditions and risk factors. To prevent antidrug antibody formation during TNF-inhibitor treatment, concomitant immunosuppressive therapy (MTX, azathioprine or glucocorticosteroids) is recommended (91).

A recent study in RA shows that adalimumab levels are influenced by concomitant MTX use: patients on adalimumab monotherapy had a median adalimumab level of 4.1  $\mu\text{g/mL}$  (IQR 1.3-7.7), whereas patients concomitantly taking MTX had a median level of 7.4  $\text{mg/mL}$  (IQR 5.3-10.6,  $p < 0.001$ ) (102). A better clinical response was present for patients using both adalimumab and MTX (102). A possible explanation is that patients with concomitant MTX are less prone to antibody formation (102).

## CONCLUSION

Based on earlier studies and the results of a Delphi study amongst world's leading sarcoidologists, practical recommendations for the use of TNF- $\alpha$  inhibitors in sarcoidosis were established. These recommendations with emphasis on indications, dosage and discontinuation regimens have been developed to support the clinician in the management of refractory sarcoidosis patients.

## ACKNOWLEDGEMENTS

The authors greatly appreciate the efforts of all the participating sarcoidosis experts who completed the survey.

## FUNDING

This study was supported by an educational grant from the ild care foundation.

## CONFLICTS OF INTEREST STATEMENT

There are no conflicts of interest.

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