



Chapter 7

**Practical eminence and experience-based
recommendations for use of
TNF- α inhibitors in sarcoidosis**

M Drent, J Cremers, T Jansen, R Baughman

Sarcoidosis Vasc Diffuse Lung Dis 2014; accepted for publication

Abstract

Background

In severe refractory sarcoidosis cases not responding to conventional immunosuppressive treatment, the third-line tumor necrosis factor-alpha (TNF- α) 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- α 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- α 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- α 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- α 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.

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} 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- α (TNF- α) plays a critical role in the immunopathogenesis of sarcoidosis.^{2,12-15} In refractory sarcoidosis cases, biological TNF- α inhibitors have been introduced as third-line treatment option.^{4,5}

The TNF- α inhibitors infliximab and adalimumab have been widely used for the treatment of inflammatory diseases, such as rheumatoid arthritis 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- α 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- α 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- α 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- α 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- α 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- α inhibitors had been used for non-sarcoidosis conditions (24 papers) or the TNF- α 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- α inhibitor treatment in sarcoidosis. Study characteristics and results for the most relevant studies are presented in Appendix 3. Summarizing the available studies, it can be concluded that the number of RCTs supporting the use of TNF- α 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 7.1. 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- α inhibitors in the management of refractory sarcoidosis patients, 77% of them prescribing TNF- α 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.

Table 7.1 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- α inhibitor: none/1–5/5–25/>25 a year	0/26.3/42.1/31.6%

TNF- α , tumor necrosis factor- α .

Specific sarcoidosis related items gathered from the experts are summarized in Table 7.2. 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%).

Table 7.2 Expert opinion amongst sarcoidologists, based on questionnaire answers, for recommendations specifically targeting sarcoidosis.

Dosing			
Infliximab		Adalimumab	
Dosage		Induction regimen	
- 5 mg/kg body weight	15/18 (83.3%)	Week 0	Maintenance regimen
- 3 mg/kg body weight	2/18 (11.1%)	- 120mg 2/17 (11.8%)	- 40 mg every 12/17 (70.6%)
- Depending on response	1/18 (5.6%)	- 80 mg 6/17 (35.3%)	week 4/17 (23.5%)
		- 40 mg 9/17 (52.9%)	- 40 mg every 2 weeks 1/17 (5.9%)
Induction regimen			- Depending on response
- Week 0, 2, 6	18/18 (100%)	Week 1	
		- 120 mg 1/17 (5.9%)	
Maintenance regimen		- 80 mg 3/17 (17.6%)	
- Every 4 weeks	7/17 (41.2%)	- 40 mg 10/17 (58.8%)	
- Every 6 weeks	6/17 (35.3%)	- 0 mg 3/17 (17.6%)	
- Every 8 weeks	3/17 (17.6%)		
- Depending on response	1/17 (5.9%)	Week 2	
		- 80 mg 2/17 (11.8%)	
		- 40 mg 15/17 (88.2%)	
Treatment duration			
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%)		
Discontinuation			
Infliximab		Adalimumab	
- 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%)

The induction regimen for adalimumab dosing used by the experienced experts was very divers. 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%), whereas 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 7.3 Expert opinion amongst sarcoidologists, based on questionnaire answers, for the general recommendations.

Pre-administration work-up		Vaccination	
- 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%)		
Contraindications		Treatment infusion reaction	
- 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	12/18 (66.7%)
- Upper airway infection	11/19 (57.9%)	- TNF- α inhibitor	
- Non-healing ulcer of the skin	8/19 (42.1%)	- Premedication for next infusion	11/18 (61.1%)
- Active fungus infection	19/19 (100%)	- Maintenance dosage of GC	2/18 (11.1%)
- 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 ≤ 5 years ago	15/19 (78.9%)		
- Malignancy at present	19/19 (100%)		
Contraindication in (planned) pregnancy		Monitoring	
- 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%)
Prevention of antidrug antibody formation		Traveling abroad	
- 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- α , tumor necrosis factor-alpha.

Table 7.3 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- α inhibitor therapy in men. To prevent antidrug antibody formation, MTX was more frequently used compared with glucocorticosteroids.

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- α inhibitors in sarcoidosis were established. These recommendations are summarized in Table 7.4 and 7.5 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 rheumatoid arthritis, both infliximab and adalimumab have been proven efficacious in inducing short-term clinical remission.²⁷⁻³² Timely introduction of TNF- α 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 efficacy of TNF- α inhibitor treatment in severe refractory sarcoidosis cases has been proven (Appendix 3).^{12,19-22,34-77} Also in these cases, timely implementation of an effective therapeutic regimen, if necessary consisting of TNF- α 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 rheumatoid arthritis.^{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- α inhibitor treatment.⁴² Future studies are necessary to establish if TNF- α inhibitors are effective by bridging in active disease in order to aim for long-term remission in sarcoidosis as well.

Table 7.4 Recommendations for the use of TNF- α inhibitors specifically targeting sarcoidosis.^a

Recommendation
Dosage
- 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.
Discontinuation
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- α inhibitor for at least 6–12 months, discontinuation should be considered.
- Infliximab: When 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, 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.

^a All recommendations apply to general situations; for every individual case, patient and disease characteristics should be taken into account. TNF- α , tumor necrosis factor-alpha.

Table 7.5 General recommendations for the use of TNF- α inhibitors.

Recommendation
1 Before starting TNF- α 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 ≤ 5 years ago in medical history, and malignancy at present, should be excluded.
2 TNF- α 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- α 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- α inhibitor, a current infection should be excluded. ^a
4 Elective surgeries or interventions and dentist visits should be planned in consultation with the treating physician.
5 To prevent antidrug antibody formation, TNF- α inhibitors should be combined with low doses methotrexate and/or glucocorticosteroids.
6 Mild infusion reactions occurring during treatment with a TNF- α 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- α inhibitor should be considered. To prevent future infusion reactions, premedication for the next infusion is recommended.
7 After the start of TNF- α 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- α therapy; preventive influenza, pneumococcal, and hepatitis B vaccinations before or during TNF- α 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.

^a In case of an infection, the TNF- α 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- α , tumor necrosis factor-alpha.

Indications

The indications for TNF- α 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 DMARDs.⁸⁰ Infliximab is the most widely studied TNF- α 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 marrow⁷³ 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- α may favorably modify the course of heart failure.⁸⁴ However, based on the subsequent findings, heart failure New York Heart Association (NYHA) class III and IV is currently considered a contraindication for the use of TNF- α 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- α 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- α 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- α 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- α 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 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 3).^{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 rheumatoid arthritis.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 3).^{12,19,20,34,36,37,39,42,43,47,50-58,60-70,89} Guidelines and consensus statements in IBD, rheumatoid arthritis, 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 (Appendix 3), whereas three fourth of experts used a dosing frequency of every 4 or 6 weeks.^{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 rheumatoid arthritis, 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- α 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 3).^{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- α 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- α 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 rheumatoid arthritis, it is shown that these patients are less likely to respond to a second TNF- α inhibitor.³² In case of secondary ineffectiveness, switch from one TNF- α 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- α inhibitors. Studies in rheumatoid arthritis 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- α 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 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- α 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 rheumatoid arthritis, 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- α 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- α 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 reinstitution of treatment.⁸⁰ When TNF- α 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 reinstitution 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 rheumatoid arthritis.^{18,30-33,78,92,100} The recommendations presented do not differ from the general attitude towards the use of TNF- α 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- α inhibitor treatment, according to available guidelines.^{18,30-33,92} Discussion exists on the use of preventive vaccinations in patients on TNF- α inhibitors. Two third of sarcoidosis experts stated to prescribe yearly influenza vaccination (killed vaccine) in patients treated with TNF- α 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- α inhibitor, based on age and risk.^{30,32,100}

Other issues

Regular monitoring every 1–3 months after the start of TNF- α 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- α 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- α 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 $\mu\text{g/mL}$ (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- α 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 efforts of the sarcoidosis experts who participated in this study by completing the survey are greatly appreciated. This study was supported by a research grant from the ild care foundation.

References

1. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizzato G, Rose C, Selroos O, Semenzato G, Sharma OP. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:149-173.
2. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011;305:391-399.
3. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Am J Respir Crit Care Med* 2011;183:573-581.
4. Baughman RP, Nunes H, Sweiss NJ, Lower EE. Established and experimental medical therapy of pulmonary sarcoidosis. *Eur Respir J* 2013;41:1424-1438.
5. Korsten P, Mirsaeidi M, Sweiss NJ. Nonsteroidal therapy of sarcoidosis. *Curr Opin Pulm Med* 2013;19:516-523.
6. Grutters JC, Van den Bosch JM. Corticosteroid treatment in sarcoidosis. *Eur Respir J* 2006;28:627-636.
7. Baughman RP. Pulmonary sarcoidosis. *Clin Chest Med* 2004;25:521-530.vi.
8. Paramothayan S, Lasserson T. Treatments for pulmonary sarcoidosis. *Respir Med* 2008;102:1-9.
9. Paramothayan S, Lasserson TJ, Walters EH. Immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2006:CD003536.
10. Cremers JP, Drent M, Bast A, Shigemitsu H, Baughman RP, Valeyre D, Sweiss NJ, Jansen TL. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. *Curr Opin Pulm Med* 2013;19:545-561.
11. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: a Delphi consensus study. *Respir Med* 2010;104:717-723.
12. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, Albera C, Brutsche M, Davis G, Donohue JF, Muller-Quernheim J, Schlenker-Herzeg R, Flavin S, Lo KH, Oemar B, Barnathan ES. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;174:795-802.
13. Ziegenhagen MW, Rothe ME, Zissel G, Muller-Quernheim J. Exaggerated TNFalpha release of alveolar macrophages in corticosteroid resistant sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;19:185-190.
14. Antoniu SA. Targeting the TNF-alpha pathway in sarcoidosis. *Expert Opin Ther Targets* 2010;14:21-29.
15. Loza MJ, Brodmerkel C, Du Bois RM, Judson MA, Costabel U, Drent M, Kavuru M, Flavin S, Lo KH, Barnathan ES, Baughman RP. Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis. *Clin Vaccine Immunol* 2011;18:931-939.
16. Aaltonen KJ, Virkki LM, Malmivaara A, Kontinen YT, Nordstrom DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PLoS One* 2012;7:e30275.
17. Osterman MT, Haynes K, Delzell E, Zhang J, Bewtra M, Brensinger C, Chen L, Xie F, Curtis JR, Lewis JD. Comparative Effectiveness of Infliximab and Adalimumab for Crohn's Disease. *Clin Gastroenterol Hepatol* 2013;Epub ahead of print.
18. Thomson AB, Gupta M, Freeman HJ. Use of the tumor necrosis factor-blockers for Crohn's disease. *World J Gastroenterol* 2012;18:4823-4854.
19. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, Drent M. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008;31:1189-1196.
20. Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller W, Jr., Sands BE. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23:201-208.
21. Pariser RJ, Paul J, Hirano S, Torosky C, Smith M. A double-blind, randomized, placebo-controlled trial of adalimumab in the treatment of cutaneous sarcoidosis. *J Am Acad Dermatol* 2013;68:765-773.
22. Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2012;250:713-720.

23. Liu Y, Wu EQ, Bensimon AG, Fan CP, Bao Y, Ganguli A, Yang M, Cifaldi M, Mulani P. Cost per responder associated with biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis. *Adv Ther* 2012;29:620-634.
24. Rosenblum H, Amital H. Anti-TNF therapy: safety aspects of taking the risk. *Autoimmun Rev* 2011;10:563-568.
25. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011:CD008794.
26. De Meyrick J. The Delphi method and health research. *Health Educ* 2003;103:7-16.
27. Denmark VK, Mayer L. Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease: an update. *Expert Rev Clin Immunol* 2013;9:77-92.
28. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, De Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgerit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, Van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB, Van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2013;Epub ahead of print.
29. Rubin DT, Panaccione R, Chao J, Robinson AM. A practical, evidence-based guide to the use of adalimumab in Crohn's disease. *Curr Med Res Opin* 2011;27:1803-1813.
30. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL, Jr., Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762-784.
31. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL, Jr., Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64: 625-639.
32. Furst DE, Keystone EC, So AK, Braun J, Breedveld FC, Burmester GR, De Benedetti F, Dörner T, Emery P, Fleischmann R, Gibofsky A, Kalten JR, Kavanaugh A, Kirkham B, Mease P, Rubbert-Roth A, Sieper J, Singer NG, Smolen JS, Van Riel PL, Weisman MH, Winthrop KL. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis* 2013;72 Suppl 2:ii2-34.
33. D'Haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Lofberg R, Quary A, Sands B, Sood A, Watermeyer G, Lashner B, Lemann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011;106:199-212;quiz 213.
34. Wijnen PA, Cremers JP, Nelemans PJ, Erckens RJ, Hoitsma E, Jansen TL, Bekers O, Drent M. Association of the TNF- α G-308A polymorphism with TNF-inhibitor response in sarcoidosis. *Eur Respir J* 2014;In press.
35. Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. *Respiration* 2012;83:218-224.
36. Orum M, Hilberg O, Krag S, Bendstrup E. Beneficial effect of infliximab on refractory sarcoidosis. *Dan Med J* 2012;59:A4535.
37. Keijsers RG, Verzijlbergen JF, Van Diepen DM, Van den Bosch JM, Grutters JC. 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;25:143-149.
38. Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. *Respir Med* 2006;100:2053-2059.
39. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest* 2005;127:1064-1071.

40. Milman N, Graudal N, Loft A, Mortensen J, Larsen J, Baslund B. Effect of the TNF-alpha inhibitor adalimumab in patients with recalcitrant sarcoidosis: a prospective observational study using FDG-PET. *Clin Respir J* 2012;6:238-247.
41. Banse C, Bisson-Vaivre A, Kozyreff-Meurice M, Vittecoq O, Goeb V. No impact of tumor necrosis-factor antagonists on the joint manifestations of sarcoidosis. *Int J Gen Med* 2013;6:605-611.
42. Baughman RP, Lower EE, Ingledue R, Kaufman AH. Management of ocular sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:26-33.
43. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. *Respiration* 2010;80:212-219.
44. Baughman R. Tumor necrosis factor inhibition in treating sarcoidosis: the American experience. *Rev Port de Pneumologia* 2007;8:S47-S50.
45. Goenka N, Venna N. Teaching NeurolImages: Sarcoidosis presenting as longitudinally extensive myelitis: Excellent response to infliximab. *Neurology* 2013;81:e61.
46. Vorselaars AD, Sjogren EV, Van Moorsel CH, Grutters JC. Bilateral Vocal Cord Carcinoma in a Sarcoidosis Patient during Infliximab Therapy. *Case Rep Pulmonol* 2013;2013:308092.
47. Tu J, Chan J. Cutaneous sarcoidosis and infliximab: evidence for efficacy in refractory disease. *Australas J Dermatol* 2013;Epub ahead of print.
48. O'Reilly MW, Sexton DJ, Denny MC, Counihan TJ, Finucane FM, O'Brien T, O'Regan AW. Radiological remission and recovery of thirst appreciation after infliximab therapy in adipsic diabetes insipidus secondary to neurosarcoidosis. *Qjm* 2013;Epub ahead of print.
49. Vorselaars AD, Keijsers RG, Grutters JC. Earlobe sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:55-57.
50. Huffstutter JG, Huffstutter JE. Hypercalcemia from sarcoidosis successfully treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:51-52.
51. Chintamaneni S, Patel AM, Pegram SB, Patel H, Roppelt H. Dramatic response to infliximab in refractory neurosarcoidosis. *Ann Indian Acad Neurol* 2010;13:207-210.
52. Pereira J, Anderson NE, McAuley D, Bergin P, Kilfoyle D, Fink J. Medically refractory neurosarcoidosis treated with infliximab. *Intern Med J* 2011;41:354-357.
53. Santos E, Shaunak S, Renowden S, Scolding NJ. Treatment of refractory neurosarcoidosis with Infliximab. *J Neurol Neurosurg Psychiatry* 2010;81:241-246.
54. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology* 2009;72:337-340.
55. Sodhi M, Pearson K, White ES, Culver DA. Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. *Respir Med* 2009;103:268-273.
56. Barnabe C, McMeekin J, Howarth A, Martin L. Successful treatment of cardiac sarcoidosis with infliximab. *J Rheumatol* 2008;35:1686-1687.
57. Dolhun R, Sriram S. Neurosarcoidosis presenting as longitudinally extensive transverse myelitis. *J Clin Neurosci* 2009;16:595-597.
58. Petropoulos IK, Vaudaux JD, Guex-Crosier Y. Anti-TNF-alpha therapy in patients with chronic non-infectious uveitis: the experience of Jules Gonin Eye Hospital. *Klin Monbl Augenheilkd* 2008;225:457-461.
59. Baughman RP, Bradley DA, Lower EE. Infliximab in chronic ocular inflammation. *Int J Clin Pharmacol Ther* 2005;43:7-11.
60. Kumar G, Kang CA, Giannini C. Neurosarcoidosis presenting as a cerebellar mass. *J Gen Intern Med* 2007;22:1373-1376.
61. Toth C, Martin L, Morrish W, Coutts S, Parney I. Dramatic MRI improvement with refractory neurosarcoidosis treated with infliximab. *Acta Neurol Scand* 2007;116:259-262.
62. Uthman I, Touma Z, Khoury M. Cardiac sarcoidosis responding to monotherapy with infliximab. *Clin Rheumatol* 2007;26:2001-2003.
63. Hoitsma E, Faber CG, Van Santen-Hoeufft M, De Vries J, Reulen JP, Drent M. Improvement of small fiber neuropathy in a sarcoidosis patient after treatment with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23:73-77.
64. Salama B, Gicquel JJ, Lenoble P, Dighiero PL. Optic neuropathy in refractory neurosarcoidosis treated with TNF-alpha antagonist. *Can J Ophthalmol* 2006;41:766-768.

65. Benitez-del-Castillo JM, Martinez-de-la-Casa JM, Pato-Cour E, Mendez-Fernandez R, Lopez-Abad C, Matilla M, Garcia-Sanchez J. Long-term treatment of refractory posterior uveitis with anti-TNF α (infliximab). *Eye (Lond)* 2005;19:841-845.
66. Carter JD, Valeriano J, Vasey FB, Bognar B. Refractory neurosarcoidosis: a dramatic response to infliximab. *Am J Med* 2004;117:277-279.
67. Sollberger M, Fluri F, Baumann T, Sonnet S, Tamm M, Steck AJ, Brutsche M. Successful treatment of steroid-refractory neurosarcoidosis with infliximab. *J Neurol* 2004;251:760-761.
68. Katz JM, Bruno MK, Winterkorn JM, Nealon N. The pathogenesis and treatment of optic disc swelling in neurosarcoidosis: a unique therapeutic response to infliximab. *Arch Neurol* 2003;60:426-430.
69. Roberts SD, Wilkes DS, Burgett RA, Knox KS. Refractory sarcoidosis responding to infliximab. *Chest* 2003;124:2028-2031.
70. Pettersen JA, Zochodne DW, Bell RB, Martin L, Hill MD. Refractory neurosarcoidosis responding to infliximab. *Neurology* 2002;59:1660-1661.
71. Dragnev D, Barr D, Kulshrestha M, Shanmugalingam S. Sarcoid panuveitis associated with etanercept treatment, resolving with adalimumab. *BMJ Case Rep* 2013;Epub ahead of print.
72. Kamphuis LS, Lam-Tse WK, Dik WA, Van Daele PL, Van Biezen P, Kwekkeboom DJ, Kuipers RW, Hooijkaas H, Van Laar JA, Bastiaans J, Baarsma GS, Van Hagen PM. Efficacy of adalimumab in chronically active and symptomatic patients with sarcoidosis. *Am J Respir Crit Care Med* 2011;184:1214-1216.
73. Patel SR. Systemic sarcoidosis with bone marrow involvement responding to therapy with adalimumab: a case report. *J Med Case Rep* 2009;3:8573.
74. Hasni SA, Kunz D, Finzel K, Gruber BL. Osseous sarcoidosis treated with tumor necrosis factor-inhibitors: case report and review of the literature. *Spine (Phila Pa 1976)* 2010;35:E904-907.
75. Te HS, Campbell L, Chohan S. Infliximab therapy for hepatic and intestinal sarcoidosis. *Gastroenterol Hepatol (N Y)* 2007;3:447-452.
76. Ahmed MM, Mubashir E, Dossabhoy NR. Isolated renal sarcoidosis: a rare presentation of a rare disease treated with infliximab. *Clin Rheumatol* 2007;26:1346-1349.
77. Thumfart J, Muller D, Rudolph B, Zimmering M, Querfeld U, Haffner D. Isolated sarcoid granulomatous interstitial nephritis responding to infliximab therapy. *Am J Kidney Dis* 2005;45: 411-414.
78. Hommes DW, Oldenburg B, Van Bodegraven AA, Van Hogezaand RA, De Jong DJ, Romberg-Camps MJ, Van der Woude J, Dijkstra G. Guidelines for treatment with infliximab for Crohn's disease. *Neth J Med* 2006;64:219-229.
79. Russell E, Luk F, Manocha S, Ho T, O'Connor C, Hussain H. Long term follow-up of infliximab efficacy in pulmonary and extra-pulmonary sarcoidosis refractory to conventional therapy. *Semin Arthritis Rheum* 2013;43:119-124.
80. Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;25:76-89.
81. Utz JP, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, Schroeder DR. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 2003;124:177-185.
82. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest* 2005;128:1062-1047.
83. Osterman MT, Lichtenstein GR. Current and Future Anti-TNF Therapy for Inflammatory Bowel Disease. *Curr Treat Options Gastroenterol* 2007;10:195-207.
84. Bozkurt B, Torre-Amione G, Warren MS, Whitmore J, Soran OZ, Feldman AM, Mann DL. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation* 2001;103:1044-1047.
85. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- α , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133-3140.
86. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, Van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, Fleming T. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004;109: 1594-1602.

87. Sood A, Midha V. Symptomatic sinus bradycardia with infliximab. *Indian J Gastroenterol* 2004;23: 118-119.
88. Sote Y, Green S, Maddison P. Complete heart block after infliximab therapy. *Rheumatology (Oxford)* 2008;47:227-228.
89. Vorselaars AD, Verwoerd A, Van Moorsel CH, Keijsers RG, Rijkers GT, Grutters JC. Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis. *Eur Respir J* 2013;Epub ahead of print.
90. Dasilva V, Breuil V, Chevallier P, Euler-Ziegler L. Relapse of severe sarcoidosis with an uncommon peritoneal location after TNFalpha blockade. Efficacy of rituximab, report of a single case. *Joint Bone Spine* 2010;77:82-83.
91. De Vries HS, Van Oijen MG, Driessen RJ, De Jong EM, Creemers MC, Kievit W, De Jong DJ. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists. *Br J Clin Pharmacol* 2011;71:7-19.
92. Orlando A, Armuzzi A, Papi C, Annese V, Ardizzone S, Biancone L, Bortoli A, Castiglione F, D'Inca R, Gionchetti P, Kohn A, Poggioli G, Rizzello F, Vecchi M, Cottone M. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. *Dig Liver Dis* 2011;43:1-20.
93. Lower EE, Baughman RP, Kaufman AH. Rituximab for refractory granulomatous eye disease. *Clin Ophthalmol* 2012;6:1613-1618.
94. Beccastrini E, Vannozzi L, Bacherini D, Squatrito D, Emmi L. Successful treatment of ocular sarcoidosis with rituximab. *Ocul Immunol Inflamm* 2013;21:244-246.
95. Kavanaugh A, Smolen JS. The when and how of biologic agent withdrawal in rheumatoid arthritis: learning from large randomised controlled trials. *Clin Exp Rheumatol* 2013;31:S19-21.
96. Tanaka Y, Hirata S, Saleem B, Emery P. Discontinuation of biologics in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2013;31:S22-27.
97. Baughman RP, Drent M, Culver DA, Grutters JC, Handa T, Humbert M, Judson MA, Lower EE, Mana J, Pereira CA, Prasse A, Sulica R, Valyere D, Vucinic V, Wells AU. Endpoints for clinical trials of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:90-98.
98. Panselinas E, Rodgers JK, Judson MA. Clinical outcomes in sarcoidosis after cessation of infliximab treatment. *Respirology* 2009;14:522-528.
99. Van den Broek M, Lems WF, Allaart CF. Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis? *Clin Exp Rheumatol* 2012;30:S21-26.
100. Papa A, Mocci G, Bonizzi M, Felice C, Andrisani G, De Vitis I, Guidi L, Gasbarrini A. Use of infliximab in particular clinical settings: management based on current evidence. *Am J Gastroenterol* 2009;104: 1575-1586.
101. Redelman-Sidi G, Sepkowitz KA. IFN-gamma release assays in the diagnosis of latent tuberculosis infection among immunocompromised adults. *Am J Respir Crit Care Med* 2013;188:422-431.
102. Pouw MF, Krieckaert CL, Nurmohamed MT, Van der Kleij D, Aarden L, Rispens T, Wolbink G. Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis* 2013;Epub ahead of print.