Efficacy and Safety of TNF Antagonists in Sarcoidosis: Data from the Spanish Registry of Biologics BIOBADASER and a Systematic Review

Jose Ramon Maneiro, MD,* Eva Salgado, MD,*
Juan J. Gomez-Reino, MD, PhD,*,†,[1] Loreto Carmona, MD, PhD,*,‡,[1]
and the BIOBADASER Study Group[2]

Objective: To evaluate the safety, efficacy, and effectiveness of TNF antagonists in patients with sarcoidosis.

Methods: A descriptive study of a case series registered in BIOBADASER and a systematic review was performed. The search strategy of articles published between 1998 and July 2011 in Medline, Embase, and the Cochrane Library included synonyms of sarcoidosis and synonyms of TNF antagonists.

Results: Seven patients treated with infliximab (IFX) and 1 with etanercept (ETN) switched to IFX for inefficacy were registered in BIOBADASER 2.0. In 3, treatment is still ongoing. Reasons for discontinuation were serious adverse events in 2 cases, inefficacy in 2 cases, and complete clinical response in 2 cases. Eight serious adverse events were reported. In the selected 69 of 2262 reports and 1 abstract of the review, 232 patients (89.9%) were treated with IFX and 26 (10.0%) were treated with ETN. In 2 randomized clinical trials, favorable response of the lung disease was reported with IFX. In other randomized clinical trials, no improvement of ocular manifestations was reported with ETN. In the cases series, results were diverse. Mean weighted rates of adverse events, infections, serious infections, and malignancy were 39.9, 22.1, 5.9, and 1.0 per 100 patient-years, respectively.

Conclusions: There is insufficient evidence to ensure the efficacy of TNF antagonists in sarcoidosis. Nevertheless, IFX may be effective in selected manifestations of the disease. Before starting treatment of sarcoidosis with IFX, a careful evaluation of the benefit/risk ratio must be considered on an individual basis.

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Keywords: *sarcoidosis, TNF antagonist, efficacy, effectiveness, safety*

Sarcoidosis is a systemic granulomatous disease of unknown etiology characterized by multiorgan involvement, which usually has a benign course with a high rate of spontaneous remission in the milder cases (1). However, there are progressive or chronic severe forms of the disease with a poor response to the standard therapy with steroids, which require long-term immunosuppressive therapy.

Currently, steroids remain the standard treatment of sarcoidosis. This therapy is limited by long-term side effects, and the existence of steroid-dependent forms. The search for new therapies is still ongoing. Different immunosuppressive drugs have demonstrated generally modest efficacy (2). Among all, methotrexate appears to be the most effective, and it is considered as a possible alternative therapy (3).

*Rheumatology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago, Spain.
†Department Medicine, Medical School, Universidad de Santiago, Santiago, Spain.
‡Health Sciences School, Universidad Camilo José Cela, Madrid, Spain.

[1]These authors contributed equally to this article.

[2]A list of all participants appears in the Appendix.

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Address reprint requests to Jose Ramon Maneiro, Rheumatology Department, Complejo Hospitalario Universitario de Santiago de Compostela, c/Travesía da Choupana s/n, 15701 Santiago de Compostela, Spain. E-mail: joseramon.maneiro.fernandez@sergas.es.

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Table 1 Table of Evidence of Studies on TNF Antagonist for Sarcoidosis: Design and Outcomes

First Author	Year	*n*	*N*	Intervention	Follow-Up (mo)	Outcomes	LE
Clinical trial							
Baughman (58)	2006	138	93	Infliximab 3 or 5 mg/kg vs placebo at weeks 0, 2, 6, 12, 18, and 24	13	• Change from baseline in the percent of predicted vital capacity (VC) at week 24 (primary endpoint) • Improvement in Saint George's Respiratory Questionnaire (SGRQ) total score (weeks 24 and 52) • Improvement in 6-min walk distance (6-MWD) (weeks 24 and 52) • Improvement in Borg's CR10 dyspnea score (weeks 24 and 52) • Improvement in chest radiograph R-score (weeks 6 and 24) • Proportion of Lupus Pernio Physician's Global Assessment (LuPGA) responders (60) • Improvement in organs evaluated in the extrapulmonary physician organ severity tool score (ePOST) (week 24)[a] (59) • Safety	2
Baughman (61)	2005	20	9	Etanercept 25 mg/twice a week	6	• Number of treated patients with oral, topical, and periocular injection steroids (primary endpoint) • Improvement in ophthalmology global assessment • Improvement in median poststudy visual acuity (VA) evaluated by an ophthalmologist • Safety	2
Rossman (62)	2006	19	13	Phase I: Infliximab 5 mg/kg vs placebo at week 0 and 2 Phase II: Open-label infusion for all patient at week 6 and 14	9.5	• Mean relative change in VC at week 6 (primary endpoint) • Comparison of the rate of patients achieving a 15% improvement in VC at week 6 • Comparison of the mean Transitional Dyspnea Index stage at week 6 • Comparison of the proportion of patients with improvement in chest X-ray at week 6 • Comparison of the mean change in SF-36 at week 6 • Increase in VC of treated group baseline to week 6 combined with the increase in VC of placebo group week 6 to week 12 • Safety	2
Case series							
Aguiar (63)	2009	10	10	Infliximab 5 mg/kg 0, 2, 6, every 8 weeks	19.2[b]	• Clinical improvement evaluated by a physician • Improvement in VC for pulmonary sarcoidosis • Improvement in thoracic CT scan after treatment for pulmonary sarcoidosis • Improvement in brain MRI after treatment for neurosarcoidosis	4

Table 1 Continued

First Author	Year	*n*	*N*	Intervention	Follow-Up (mo)	Outcomes	LE
						• Improvement in liver enzymes for hepatic sarcoidosis • Safety	
Crouser (64)	2010	5	5	Infliximab 5 mg/kg 0, 2, 6, every 6 to 8 weeks	2	• Increase in $CD4^+$ cell level after treatment • Clinical improvement evaluated by a physician • Improvement >10% in VC after treatment • Improvement ≥10% in ventricular ejection fraction (VEF) • Safety	4 to 5
Doty (65)	2005	10	10	Infliximab (different doses)	13.2[b]	• Clinical improvement evaluated by a physician • Improvement in liver enzymes for hepatic sarcoidosis • Improvement in brain, lower extremity, and spinal MRI • Improvement in ophthalmologic evaluation • Safety	4
Hostettler (66)	2011	16	16	Infliximab 3 mg/kg every 4 to 8 weeks	29	• Clinical improvement evaluated by a physician • Improvement >10% in force vital capacity (FVC) after treatment • Mean improvement in force vital capacity (FVC) • Safety	4
Jounieaux (67)	2010	31	31	Infliximab 3 to 5 mg/kg 0, 2, 6, every 6 weeks	25[c]	• Clinical improvement evaluated by a physician • Improvement in dypsnea and/or FVC after and/or for pulmonary sarcoidosis • Improvement in >50% of skin lesions for cutaneous sarcoidosis • Improvement in brain MRI and/or clinical improvement for neurosarcoidosis • Improvement in cardiac MRI for cardiac sarcoidosis • Improvement in liver enzymes for hepatic sarcoidosis • Improvement in ophthalmologic evaluation for ocular sarcoidosis • Improvement in creatinine for renal sarcoidosis • Safety	4
Keijsers (68)	2008	12	12	Infliximab 5 mg/kg 0, 2, 6, every 6 weeks	NR	• Clinical improvement evaluated by a physician • Improvement in chest radiograph • Improvement in FVC (mean of improvement) • Improvement in ^{18}F-FDG PET: normalized, improvement or not changes	4
Moravan (69)	2009	7	7	Infliximab 5 mg/kg 0, 2, 6, every 6 to 8 weeks	31.5[c]	• Clinical improvement evaluated by a physician • Improvement in brain MRI	4

Table 1 Continued

First Author	Year	*n*	*N*	Intervention	Follow-Up (mo)	Outcomes	LE
Panselinas (70)	2009	14	14	Infliximab 5 mg/kg 0, 2, 6, every 6 weeks	12[d]	• Safety • Clinical deterioration after discontinuation of drug • Mean time (mo) of deterioration after discontinuation of drug • Clinical improvement evaluated by a physician • Improvement in brain or spinal MRI • Improvement in muscle MRI	4
Pritchard (71)	2004	5	5	Infliximab 3 mg/kg 0,2, 6, every 4 to 8 weeks	NR	• Clinical improvement evaluated by a physician • Improvement in spinal MRI • Improvement in thoracic TC scan • Safety	4
Saleh (72)	2006	12	12	Infliximab 2, 6, 10, 14, every 8 weeks	36	• Clinical improvement evaluated by a physician • Improvement in brain MRI or TC scan • Improvement in bone scan • Improvement in FVC • Improvement in liver enzymes for hepatic sarcoidosis • Safety	4
Santos (73)	2010	4	4	Infliximab 3 to 5 mg/kg 0, 2, 6, every 8 weeks	20	• Clinical improvement evaluated by a physician • Improvement in brain MRI • Safety	4
Utz (74)	2003	17	17	Etanercept 25 mg/twice a week	15	• Improvement in at least 2 of following parameters: measures of pulmonary function, chest radiograph and/or dypsnea level at 12 mo (primary endpoint) • Improvement in SF-36 composited (physical and mental) scores at 12 mo • Safety	3to4
BIOBADASER	2011	8	8	Infliximab (different doses)[e]	66	• Safety	4

n, number of patients included in studies; *N*, number of patients treated with TNF antagonists; LE, level evidence; NR, not reported; MRI, magnetic resonance imaging; CT, computed tomography.
[a]Data published in other report (Judson et al).
[b]Data obtained from treatment regimen and doses of TNF antagonist.
[c]Data obtained from duration of treatment with TNF antagonist.
[d]Follow-up after discontinuation of TNF antagonist.
[e]One patient previously received ETN.

The role of tumor necrosis factor (TNF) in granulomatous conditions is well recognized (4-6). Nonetheless, its role in sarcoidosis remains unknown. High levels of this cytokine in broncoalveolar lavage of patients with active disease (7,8) and a decrease of these high levels following treatment have been published (9-11). These findings suggest that targeting TNF may be useful in the treatment of sarcoidosis. Currently, these biologics that antagonize TNF have been used for the treatment of sarcoidosis, and conflicting results are reported. Off-label use of medications on sound bases may be a reasonable approach for the treatment of uncommon conditions; however, the definition of their efficacy and safety needs continuous scrutiny. In this article, we have analyzed a case series (CS) of patients with sarcoidosis treated with TNF antagonists and performed a systematic review to evaluate the efficacy and safety in sarcoidosis.

MATERIALS AND METHODS

Descriptive Study

We studied all cases of sarcoidosis confirmed by pathology and treated with TNF antagonists in the Spanish registry of biological therapies BIOBADASER from February 2000 to July 2011. A description of BIOBADASER 2.0 has been

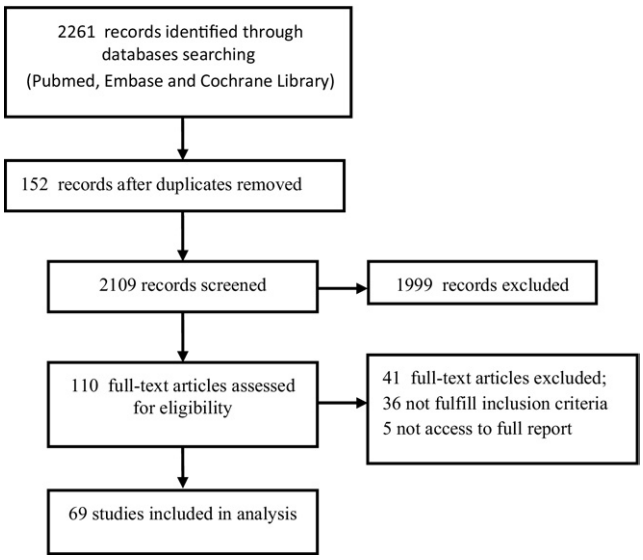

Figure 1 Results of the literature search.

published elsewhere (12-15) and its protocol is available in English at its web page (https://biobadaser.ser.es/biobadaser/eng/index.html). In brief, BIOBADASER 2.0 is a national drug safety registry of patients with rheumatic diseases starting treatment with any biologic and followed thereafter. The registry was established in February 2000 and includes data from 14 large public hospitals throughout Spain. Patients entering the registry are followed prospectively and evaluated at the time of adverse events or when a change in the biological therapy occurs. Data are collected online by participating physicians. The following items are included systematically: gender, date of birth, diagnosis, date of diagnosis, comorbidities, types of biologics, dates of initiation and of discontinuation, concomitant treatment, date of AE occurrence, severity, type, and classification of AE according to the MedDRA dictionary (http://www.meddramsso.com/).

For assessment of the consistency and quality, the database is constantly monitored online. Additionally, a random sample of patients is selected and audited in site in all 14 centers annually. The study was approved by the Ethics Review Committee of the Hospital Ramon y Cajal, Madrid, acting as reference committee. Starting January 2008, all patients sign an informed consent to comply with the Spanish regulations for data protection and research.

A descriptive analysis of the sample was performed.

Systematic Review

We performed a systematic literature review to identify all publications including sarcoidosis patients exposed to TNF antagonists. The protocol of the review is available online as supplementary material, available at http://www.semarthritisrheumatism.com.

The clinical question was formulated according to the PICO (Patient, Intervention, Comparator, and Outcome) approach (16). Patients were defined as sarcoidosis confirmed by histology; intervention was the treatment with any TNF antagonist. There was no comparator for review design, and finally, outcome was defined as any aspect of efficacy or safety of these therapies. The final search question was formulated as, "Are the TNF antagonists effective and/or safe in sarcoidosis?"

Table 2 Excluded Articles from the Review of Sarcoidosis Treated with TNF Antagonists and Reason for Exclusion

Reason for Exclusion	First Author (yr)
Abstracts with full version of article published	Baughman (2002) (17) Baughman (2005) (56) Baughman (2006) (19) Judson (2006) (20) Rossman (2005) (21) Yee (2001) (22)
Characteristics of the publication (review)	Wells (2008) (23)
Characteristics of the publication (commentary of prior reports)	Cook (2002) (24) Corbett (2009) (25) Kahler (2007) (26) Morcos (2003) (27) O'Connor (2002) (28)
No data about histology	Chintamaneni (2010) (29) Cufi-Benet (2010) (30) Dhingra (2009) (31) Elffericht (2010) (32) Jonker (2007) (33) Lindstedt (2005) (34) Malaviya (2010) (35) Marnane (2009) (36) Menon (2004) (37) Migliore (2008) (38) Saurenmann (2006) (39) Simonini (2011) (40) Thielen (2009) (41)
Diagnosis of sarcoidosis during treatment with TNF antagonists	Suzuki (2009) (57)
No access to full report	Baughman (2005) (18) Baughman (2001) (42) Hoitsma (2006) (43) Petropoulos (2008) (44) Tuchinda (2006) (45)
No fulfilling inclusion criteria	Sorrentino (2004) (46)
Difficult to extract data about treatment with TNF antagonists	Stagaki (2009) (47)
Not value on efficacy or safety	Baughman (2009) (48) Drent (2006) (49) Loza (2011) (50) Sweiss (2010) (51)
Patients not treated with TNF antagonists	Evrard (2008) (52) Gallagher (2007) (53) Maña (2010) (54) Markert (2007) (55)

Table 3 Characteristics of Patients with Sarcoidosis Included in Clinical Trials and Case Series of Sarcoidosis Treated with TNF Antagonists

First Author	Year	*N*	% Women	Age	Time of Disease (mo)
Clinical trial					
Baughman (58)	2006	93	55.9	47.8	82.8
Baughman (61)	2005	9	88.8	NA	NA
Rossman (62)	2006	13	61.5	46.7	NA
Case series					
Aguiar (63)	2009	10	50.0	47.7	NA
Crouser (64)	2010	5	20.0	56.2	NA
Doty (65)	2005	10	90.0	37.2	110.4
Hostettler (66)	2011	16	50.0	51.00	144.0
Jounieaux (67)	2010	31	58.0	44.0	108.0
Keijsers (68)	2008	12	50.0	43.6	48.0
Moravan (69)	2009	7	85.7	46.8	50.2
Panselinas (70)	2009	14	71.4	43.2	56.7
Pritchard (71)	2004	5	60.0	43.0	NA
Saleh (72)	2006	12	75.0	56.0	103.0
Santos (73)	2010	4	25.0	35.7	NA
Utz (74)	2003	17	58.8	49.3	NA
BIOBADASER	2011	8	75.0	42.7	98.4

N, number of patients treated with TNF antagonists; NA, not available; ST: steroids; Mtx, methotrexate; A, azathioprine; C, cyclosporine; Cy, cyclophosphamide; Ant, antimalarial; M, mycophenolate; P, pentoxifylline; Th, thalidomide.

Systematic Literature Research

Medline, Embase, and the Cochrane Library were searched for articles published between 1998 and July 2011. The search strategy focused on synonyms for sarcoidosis and for TNF antagonists and was limited to articles on humans published in English, Spanish, French, Italian, or Portuguese. We also included the congress abstracts online from the European League Against Rheumatism and the American College of Rheumatology (from 2001 to 2010/2011).

Selection of Articles

The selection criteria for the articles and abstracts were as follows: (1) patients with diagnostic of sarcoidosis established by histology; (2) treatment with TNF antagonists; (3) publications that evaluated any aspect of efficacy and/or safety; and (4) clinical trials (RCT) preferably, but also including observational studies, CS, and case reports. Two reviewers (JRM and ES) screened the titles and abstracts for selection criteria independently, using a third reviewer (LC) for consensus. Once the articles unrelated to the research topic were excluded, the full report of all remaining studies was reviewed. Subsequently, articles that did not fulfill all the selection criteria were excluded and a table with the reasons for exclusion was produced. In addition, a hand search was made through the reference lists of the included articles. When the full report was not available, the author was contacted. Information from the author was obtained in 3 of 8 publications.

Data Extraction and Analysis

Publication details, characteristics of the patients and the treatments, outcome, and adverse events were extracted. Efficacy was recorded according to clinical, radiological, respiratory function parameters, analytical, or histological parameters; safety was recorded as the number of serious adverse events in total and by type.

Study quality was evaluated by a modification of the Oxford Levels of Evidence (LE) table. A qualitative analysis of the data was performed and supported by evidence tables. Detailed assessment of the heterogeneity in studies was also performed and meta-analysis was proposed only if the heterogeneity allowed it.

Table 3 Continued

Prior Treatments to the TNF Antagonists			Concomitant Treatments with the TNF Antagonists			
%ST	% DMARD	DMARD/%	%ST	Mean Doses ST (mg/d)	% DMARD	DMARD/%
NA	NA	NA	91.4	11.9	52.7	NA
NA	NA	NA	55.5	15	100.0	Mtx 100.0
NA	NA	Mtx 61.5; A 15.3; Ant 23.0; P 7.6	69.2	23.8	NA	NA
90.0	80.00	Mtx 40.0; A 40.0; Ant 30.0	90.0	NA	50.0	Mtx 30.0; A 10.0; Ant 10.0
100.0	NA	NA	NA	NA	NA	NA
60.0	50.0	Mtx 10.0; A 10.0; Ant 30.0; Th 10.0	50.0	19.0	40.0	Mtx 30.0; Ant 20.0; P 10.0
100.0	NA	NA	81.2	NA	43.7	NA
98.7	NA	NA	97.0	19.4	48.0	Mtx 45.1; A 3.2; Cy 3.2; Ant 9.6; M 6.4
100.0	91.7	Mtx 83.3; Ant 8.3	75.0	NA	91.7	Mtx 83.3; Ant 8.3
100.0	42.8	A 28.5; Cy 14.2; Ant 14.2	0.0	0.0	85.7	M 85.7
NA	NA	NA	78.5	26.5	57.1	Mtx 28.5; A 7.1; Ant 7.1; Cy 14.2
100.0	100.0	Mtx 100.0; A 20.0; C 40.0; Ant 60.0	40.0	25.0	80.0	Mtx 60.0; C 20.0; Ant 20.0
75.0	100.0	Mtx 83.3; A 25.0; Ant 83.3; P 8.3; Th 16.6	NA	NA	NA	NA
100.0	100.0	MTX 75.0;A 100.0;Cy 25.0; Ant 25.0	NA	NA	NA	NA
NA	NA	NA	0.0	0.0	0.0	0.0
62.5	75.5	Mtx 50.0; A 25.0	62.5	NA	75.5	Mtx 50.0; A 25.0

RESULTS

Descriptive Study

Eight patients with sarcoidosis receiving treatments with TNF antagonists have been registered in BIOBADASER 00 (Table 1, details are available in a table as supplementary material, available at http://www.semarthritisrheumatism.com). All fulfilled the selection criteria. Six patients were women, and they had a mean age of 43 years at treatment (range 21-59 years). The median time from diagnosis to treatment was 6 years (2 months to 15 years). Four (50%) presented uveitis; 2 (25%) were ANA positive, and 2 (25%) had a positive skin test for tuberculosis. Seven patients were treated with infliximab (IFX) and 1 with etanercept (ETN), which was switched to IFX for inefficacy. Mean treatment duration was 23 months (1-55 months). The reasons for discontinuation of treatment were serious AEs in 2 cases (22%), inefficacy in 2 (22%), and complete clinical response in 2 (22%). In 3 patients, treatment is still ongoing (33%).

A total of 18 AEs occurred in 6 patients; 8 infections (5 respiratory infections, 1 herpes zoster, 2 gastrointestinal infections), 6 ocular manifestations (2 uveitis, 1 keratitis, 1 conjunctival hemorrhage, 1 retinal detachment, and 1 glaucoma), 1 acute respiratory insufficiency in a patient with interstitial lung disease, 1 relapse of disease, and 2 disease progression (1 with a grade IV sarcoidosis who died because of the progression). Eight of the 18 AEs were considered serious.

Systematic Review

The search captured 2261 references and 28 meeting abstracts. After title/abstract screening, 110 articles were retrieved for full text review and 69 fulfilled the inclusion criteria (Fig. 1). One meeting abstract was also included. A total of 41 articles were excluded after detailed review (Table 2 lists reasons for exclusion) (17-57). A hand search did not yield additional hits.

Three RCT reported in 5 articles (58-62)and 12 CS were finally included in the review (Table 1) (63-74). In 2 studies patients were treated with ETN, and in the others all patients were treated with IFX. Fifty-three case reports were also identified: 41 with IFX, 7 with ETN, and 8 with ADA. There were no reports with golimumab or certolizumab.

In the RCT and CS, 232 patients (89.9%) were treated with IFX and 26 (10.0%) with ETN. One hundred forty-

Table 4 Efficacy of TNF Antagonists in Sarcoidosis by Organ Involvement and Agent

Organ Involvement	Drug	Study (*n*)	Results (Treatment Group vs Placebo)
Systemic *n* = 95	Infliximab	Baughman[a] (*n* = 89) (58)	• ePOST (w24): 2.09 vs 3.70 (*P* = 0.019)[b] (59)
		Aguiar (*n* = 2) (63)	• Clinical improvement 2/2 (Phy)
		Panselinas (*n* = 1) (70)	• Clinical improvement 2/2 (Phy) • Deterioration after discontinuation 1/1 in 0.5 mo
		Pritchard (*n* = 1) (71)	• Clinical improvement 1/1 (Phy)
		Saleh (*n* = 2) (72)	• Clinical improvement 2/2 (Phy)
Lung *n* = 170	Infliximab	Baughman[a] (*n* = 93) (58)	• % improvement in CVF (w24): 2.5% vs 0.0% (*P* = 0.038) • SGRG total score: −3.7 vs −4.5 (w24) and −3.1 vs −2.4 (w52)[c] • Borg's CR10 dyspnea score: −0.1 vs 0.2 (w24) and 0.3 vs 0.7 (w52)[c] • 6-MWD: 7.6 vs −19.9 (w52) (*P* = 0.019) • Chest radiograph R-score: −0.87 vs 0.17 (w6) (*P* < 0.01) and −0.94 vs 019 (w24) (*P* = 0.01)
		Rossman[a] (*n* = 13) (62)	• ΔVC (w6): 15.22 vs 8.39[c] • 15% improvement in VC (w6): 2 vs 0[c] • Transitional Dyspnea Index (w6): 2.17 vs 2.08 (*P* NA) • Improvement in chest X-ray(w6): 23.00% vs 0.0% (*P* NA) • SF-36 (w6): 27.11 vs 26.4[c] • ΔVC of treated group(baseline to w6) combined with the increase in CV of placebo group (w6 to 12): improvement in VC (*P* < 0.02)
		Aguiar (*n* = 4) (63)	• Clinical improvement 4/4 (Phy) • Improvement in thoracic TC scan (*n* = 3) 3/3 • Improvement in VC (*n* = 3) 3/3
		Crouser (*n* = 5) (64)	• ΔVC > 10%: 3/5
		Hostettler (*n* = 5) (66)	• ΔVC > 10%: 1/5 • Mean improvement in FVC, %P: 6%
		Jounieaux (*n* = 17) (67)	• Improvement 11/17
		Keijsers (*n* = 12) (68)	• Clinical improvement 10/12 (Phy) • Improvement in chest X-ray 6/12 • Improvement in FVC in 10/12 (mean = +5.4%) • PET: normalized 4/12, improvement 4/12, not change 4/12
		Panselinas (*n* = 1) (70)	• Clinical improvement 0/1 (Phy) • Deterioration after discontinuation 0/1
		Pritchard (*n* = 1) (71)	• Clinical improvement 1/1 (Phy) • Improvement in thoracic TC scan 1/1
		Saleh (*n* = 2) (72)	• Clinical improvement (*n* = 2) 2/2 (Phy) • Improvement in CVF (*n* = 1) 1/1
	Etanercept	Utz (*n* = 17) (74)	• Primary endpoint 5/17 • 11 failure (5 at 3 mo, 1 at 6 mo, 1 at 9 mo and 4 at 12 mo) • Improvement in physical (*P* = 0.17) or mental (*P* = 0.15) composite scores (SF-36)[c]
Eyes *n* = 17	Infliximab	Crouser (*n* = 1) (64)	• Clinical improvement 1/1 (Phy)
		Doty (*n* = 1) (65)	• Improvement in ophthalmologic evaluation 1/1
		Jounieaux (*n* = 3) (67)	• Improvement in ophthalmologic evaluation 2/3
		Pritchard (*n* = 2) (71)	• Clinical improvement 2/2 (Phy)
		Saleh (*n* = 1) (72)	• Improvement in VA 1/1

Table 4 Continued

Organ Involvement	Drug	Study (*n*)	Results (Treatment Group vs Placebo)
	Etanercept	Baughman[a] (*n* = 9) (61)	• Number of patients with oral steroids 3 vs 2, topics 7 vs 7, and periocular 3 vs 2[c] • Ophthalmology global assessment 2 vs 3[c] • Median poststudy VA 20/25 vs 20/25[c]
Skin *n* = 51	Infliximab	Baughman[a] (*n* = 19) (58)	• LuPGA (w24): 4/13 vs 1/5[c] (60)
		Aguiar (*n* = 5) (63)	• Clinical improvement 5/5 (Phy)
		Crouser (*n* = 1) (64)	• Clinical improvement 1/1 (Phy)
		Doty (*n* = 6) (65)	• Clinical improvement 6/6 (Phy)
		Hostettler (*n* = 4) (66)	• Clinical improvement 4/4 (Phy)
		Jounieaux (*n* = 9) (67)	• Improvement in >50% of skin lesion: 6/9
		Panselinas (*n* = 4) (70)	• Clinical improvement 3/4 (Phy) • Deterioration after discontinuation 3/4 in 3 moths[d]
		Saleh (*n* = 3) (72)	• Clinical improvement 1/1 (Phy)
Heart *n* = 8	Infliximab	Crouser (*n* = 3) (64)	• ΔVEF ≥ 10%: 3/3
		Hostettler (*n* = 1) (66)	• Clinical improvement 1/1 (Phy)
		Jounieaux (*n* = 4) (67)	• Improvement in cardiac MRI: 3/4
Bone *N* = 6	Infliximab	Doty (*n* = 1) (65)	• Clinical improvement 0/1 (Phy) • Improvement in spine MRI 1/1
		Jounieaux (*n* = 3) (67)	• Clinical improvement 2/4 (Phy)
		Panselinas (*n* = 1) (70)	• Clinical improvement 1/1 (Phy) • Deterioration after discontinuation 1/1 in 2 mo
		Saleh (*n* = 1) (72)	• Clinical improvement 1/1 (Phy) • Improvement in bone TC scan 1/1
Liver *N* = 8	Infliximab	Aguiar (*n* = 2) (63)	• Improvement in liver enzymes 0/2
		Doty (*n* = 1) (65)	• Improvement in liver enzymes 1/1
		Jounieaux (*n* = 4) (67)	• Improvement in liver enzymes 2/4
		Saleh (*n* = 1) (72)	• Improvement in liver enzymes 1/1
Muscle *n* = 3	Infliximab	Doty (*n* = 1) (65)	• Clinical improvement 1/1 (Phy) • Improvement in lower extremity MRI 0/1
		Jounieaux (*n* = 1) (67)	• Clinical improvement 0/1 (Phy)
		Panselinas (*n* = 1) (70)	• Clinical improvement 1/1 (Phy) • Improvement in muscle MRI 1/1 • Deterioration after discontinuation 1/1 in 13 mo
Brain *n* = 38	Infliximab	Aguiar (*n* = 3) (63)	• Clinical improvement 2/3 (Phy) • Improvement in brain MRI 2/2 (1 patient NR)
		Doty (*n* = 1) (65)	• Clinical improvement 1/1 (Phy) • Improvement in brain MRI 1/1
		Hostettler (*n* = 6) (66)	• Clinical improvement 6/6 (Phy)
		Jounieaux (*n* = 8) (67)	• Improvement in clinical and/or brain MRI 4/8
		Moravan (*n* = 7) (69)	• Clinical improvement 7/7 (Phy) • Improvement in brain MRI 7/7
		Panselinas (*n* = 6) (70)	• Clinical improvement (*n* = 4): 3/4 (Phy) • Improvement in brain MRI (*n* = 3): 3/3 • Deterioration after discontinuation 6/6 in 6.8 mo[d]

Table 4 Continued

Organ Involvement	Drug	Study (*n*)	Results (Treatment Group vs Placebo)
		Pritchard (*n* = 1) (71)	• Clinical improvement 1/1 (Phy) • Improvement in spinal MRI 1/1
		Saleh (*n* = 2) (72)	• Clinical improvement 2/2 (Phy) • Improvement in brain MRI or TC scan 2/2
		Santos (*n* = 4) (73)	• Clinical improvement 4/4 (Phy) • Improvement in brain MRI (*n* = 1) 1/1

Phy, evaluated by a physician; w, weeks; MRI, magnetic resonance imaging; CT, computed tomography; *n,* number of treated patients; NA, not available; ΔVC, increase improvement in vital capacity; ΔVEF, increase improvement in ventricular injection fraction.
[a]Clinical trial.
[b]Data published in other report (Judson et al).
[c]Not significant.
[d]Mean deterioration time.

two (55%) were women with a mean age at the start of treatment of 42 years (range, 35-56). The average disease duration was 7 years (range, 4 - 12), and the mean follow-up of the treatment was 15 months (range, 2-36). Table 3 shows the characteristics of patients and treatments.

In general, the studies presented low LE (table 1) and high heterogeneity in the design and outcomes across studies. Few studies were controlled. Three studies were randomized, double-blind controlled clinical trials with LE of 2. All others but 1 open-label, uncontrolled prospective trial graded as LE 3-4 (74) were descriptive studies with LE of 4.

One RCT on pulmonary (58) and systemic (59) sarcoidosis with IFX for 52 weeks reported a modest but significant improvement in vital pulmonary vital capacity (VC) at 24 weeks. However, in another RCT with 2 infusions of IFX in pulmonary sarcoidosis no significant improvement was found at 6 weeks (62). In the open-label phase of this study, patients were treated with IFX for 14 weeks, and improvement of vital capacity was demonstrated at 14 weeks. One open-label, uncontrolled prospective trial with ETN in pulmonary sarcoidosis showed no improvement, with more than 60% of patients failing to treatment (74). Clinical improvement in patients with pulmonary sarcoidosis was reported in CS but results of improvement in VC were variable.

One RCT in ocular sarcoidosis treated with ETN did not report significant improvement (Table 4) (61).

All patients with treated systemic sarcoidosis improved. In cutaneous sarcoidosis more than 80% of patients presented improvement in CS but no significant improvement was reported in 1 RCT (60). All patients with neurosarcoidosis (94.7%) except 2 presented clinical or brain MRI improvement. In ocular sarcoidosis 85.7% presented improvement in some outcome. Other organ involvements were less frequent: in muscle sarcoidosis, 100.0% improved; in cardiac sarcoidosis, 87.5% improved; in bone sarcoidosis, 66.7% improved; and in hepatic sarcoidosis, only 50.0% improved.

Among the articles that fulfilled the selection criteria, a total of 53 corresponded to case reports. A total of 62 patients received 67 treatments with TNF antagonists. Five patients had received more than 1 TNF antagonists. The 67 treatments were reported in systemic (16), cutaneous (11), pulmonary (3), bone (7), cardiac (5), ocular (4), renal (3), sinus (3), and neurologic sarcoidosis (15). Fifty-seven (83.2%) treatments were reported as successful. The reasons for discontinuation in 29 treatments were inefficacy in 5 (7.5%), AE in 6 (9.0%), remission in 12 (18.1%), and other reasons in 6 (9.0%) (details published online in supplementary data found at http://www.semarthritisrheumatism.com).

In RCT and CS, 134 AEs were reported, 54 being serious AEs. The mean weighted rate (MWR) of AEs was 39.9 per 100 patients-years. Seventy-six infections were reported, with a MWR of 22.1 per 100 patients-years, and with 24 serious infections with a MWR of 5.9 per 100 patients-years. Six malignancies with a MWR of 1.0 per 100 patient-years, 2 disease progressions, and 2 deaths (1 "abdominal bleed" and 1 pulmonary infection) were also described (Table 5).

DISCUSSION

In the present work, we have evaluated the safety, efficacy, and effectiveness of TNF antagonists in patients with sarcoidosis. We have found that there is insufficient evidence to ensure the efficacy of TNF antagonists in sarcoidosis, yet IFX may be moderately effective in selected manifestations of the disease.

Our study has several limitations. First, there was high heterogeneity in the reviewed studies. This heterogeneity of RCTs and CS was in both the design and the outcomes leading to difficulties in the synthesis of evidence and interpretation of results. Second, sarcoidosis presents a large number of organ involvements. The number of patients included in RCT and CS was low and this also limited the evaluation of the efficacy of the therapy in these patients. Finally, pathogenesis and the degree of involvement in the different organs are variable and could affect the impact of treatment. No clear definition of these variables was included or stratified in the reviewed articles.

Table 5 Safety of TNF Antagonists in Patients with Sarcoidosis Treated with TNF Antagonists

Drug	Study (yr)	Total AR	Serious AR *n* (%)	Total Infections *n* (%)	Serious Infections *n* (%)
Infliximab	Clinical trial	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)
	Baughman (2006) (58)	80 (0.79)[a]	21 (0.20)[a]	54 (0.53)	10 (0.09)
	Rossman (2006) (62)	12 (1.17)[a]	4 (0.39)[b]	9 (0.88)	4 (0.39)
	Case series	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)
	Aguiar (2009) (63)	11 (0.68)	5 (0.31)	3 (0.18)	2 (0.12)
	Crouser (2010) (64)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Doty (2005) (65)	3 (0.27)	2 (0.18)	1 (0.09)	0 (0.0)
	Hostettler (2011) (66)	3 (0.07)	2 (0.05)	0 (0.0)	0 (0.0)
	Jounieaux (2010) (67)	13 (0.20)	7 (0.10)	6 (0.09)	5 (0.07)
	Moravan (2009) (69)	2 (0.10)	0 (0.0)	1 (0.05)	0 (0.0)
	Pritchard (2004) (71)	1 (NA)	0 (0.0)	0 (0.0)	0 (0.0)
	Saleh (2006) (72)	5 (0.13)	3 (0.08)	0 (0.0)	0 (0.0)
	Santos (2010) (73)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	BIOBADASER	18 (0.40)	8 (0.18)	8 (0.18)	3 (0.06)
Etanercept	Clinical trial	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)
	Baughman (2005) (61)	2 (0.44)	0 (0.0)	2 (0.44)	0 (0.0)
	Case series	*n* (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)
	Utz (2003) (74)	2 (0.09)	2 (0.09)	0 (0.0)	0 (0.0)

AR, adverse reaction; *N*, number of treated patients; t, time of follow-up (yr); IR, infusion reactions; NA, not available.
[a]No significance difference with control group.
[b]Significant difference with control group.

The strength of our study is the report of safety. In the safety analysis, we use weighted rates to facilitate comparison with safety in other clinical conditions.

Chronic pulmonary manifestations of sarcoidosis are troublesome, and on occasion, resistant to the treatment with steroids. Different results were reported in RCT with IFX in pulmonary sarcoidosis. In 1 RCT, standard administration of IFX improved pulmonary VC at 24 weeks (58). In the other RCT, VC at 6 weeks did not improve VC (62). However, in the open phase of this study improvement was seen at 14 weeks. It may be that the cause of low VC in the studies was different, or alternatively long-term treatment with IFX is required as in many other immune-mediated chronic inflammatory conditions. In support, in around 65% of CS in lung disease improvement of lung VC was reported. Nevertheless, progression of pulmonary diseases has been reported in other conditions treated with TNF antagonists (75). In other than pulmonary disease, no RCTs were reported. In lupus pernio, no significant improvement was reported in 1 RCT with IFX, yet this study was not designed to evaluate this outcome (60). A variable improvement of cutaneous, neurologic, hepatic, cardiac, bone, muscle, and ocular sarcoidosis was reported in a high percentage of reports of patients treated with IFX. This could merely reflect the bias to report positive results of new therapies.

In contrast with the result reported with IFX, no improvement was reported with ETN in RCT and CS. TNF seems to play an important role in the pathogenesis of granulomatous diseases. Interestingly, a lack of effectiveness of ETN in granulomatous diseases is common (76-78). Currently, disintegration of established granuloma by the monoclonal antibodies but not ETN is suggested. Differences in the affinity of monoclonal antibodies and ETN for soluble compared with transmembrane TNF seem to be at play. Monoclonal antibodies inhibit both TNFp55 and TNFp75, whereas ETN only partially inhibits TNFp75-mediated signaling (79,80). In a murine model of TB infected with *Mycobacterium tuberculosis*, neutralizing TNF with a monoclonal antibody results in disintegration of previously formed granulomas (81). Also, substantial protection against microbacterial infection was also reported in transgenic mice expressing only the transmembrane TNF signaling pathway (82). Overall, monoclonal anti-TNF antibodies may be effective in the therapy of this sarcoidosis but not the TNF receptor ETN.

In 2 RCT with IFX, no significance differences in AEs were reported compared with the control groups. In the other RCT a significance difference (31% vs 17%) in serious AEs were reported (62). In BIOBADASER, more AEs and specific reactions in off-label use (including sarcoidosis) than in approved indications of TNF antagonists were reported (83). Herein, MWR of AEs in sarcoidosis is similar to BIOBADASER in rheumatoid arthritis and higher than in psoriatic arthritis and ankylosing spondylitis (83). Numerically the infections and malignancies were higher than in BIOBADASER (84) and other registries (85). However, the wide confidence interval prevents a solid conclusion. In our case series, there were a high number of ocular AEs, although this was not confirmed by others. Nevertheless, the appearance of sarcoidosis following therapy of rheumatoid arthritis with

Table 5 Continued

Malignancies *n* (%)	Progression *n* (%)	Ocular *n* (%)	Deaths (%)	IR/Patient *n* (%)	IR/Infusion *n* (%)
n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (%)	n (%)
2 (0.01)	1 (0.01)	NA	0 (0.0)	8 (8.6)	12 (2.3)
0 (0.0)	0 (0.0)	1 (0.09)	1 (0.09)	0 (0.0)	0 (0.0)
n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (%)	N (%)
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 (0.09)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (1.0)
0 (0.0)	1 (0.02)	0 (0.0)	0 (0.0)	1 (6.2)	NA
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.2)	NA
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	NA
1 (0.02)	0 (0.0)	0 (0.0)	1 (0.02)	1 (20.0)	NA
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0 (0.0)	2 (0.04)	6 (0.13)	1 (0.02)	0 (0.0)	0 (0.0)
n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (%)	n (%)
0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	n (AR/N*t)	N (%)	n (%)
2 (0.09)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TNF antagonists has been reported (57). Whether these cases of eye inflammation reported here represent reactivation of the disease induced by the TNF antagonists or otherwise remains unsettled. On the whole, IFX and ETN in the treatment of sarcoidosis are accompanied by a larger number of AEs than in other approved indications.

In summary, there is insufficient evidence to ensure the efficacy of TNF antagonists in sarcoidosis. However, IFX produces a moderate improvement in selected manifestations of the disease. Therefore, before starting treatment of sarcoidosis with TNF antagonists, a careful evaluation of the benefit/risk ratio must be considered on an individual basis.

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APPENDIX 1

The BIOBADASER 2.0 Study Group includes the following: Agustí Sellas, Basilio Rodríguez y Mireia Barceló (Ciudad Sanitaria Vall d'Hebron); Laura Cebrián, María Montoro (Hospital Gregorio Marañon); Dolores Montesinos (Hospital Universitario Virgen Macarena); Eva Pérez-Pampín (Hospital Clínico Universitario de Santiago); Ana Mª Ortiz (Hospital Universitario de La Princesa); Fred Antón, Antonio Zea (Hospital Ramón y Cajal); Francisco Javier Manero Ruiz, Chesús Beltrán, Eugenio Giménez Úbeda, Fernando Jiménez Zorzo, Jesús Marzo, Marta Medrano, Ángela Pecondón (Hospital Universitario Miguel Servet); Mª Victoria Hernández, Raimon Sanmartí, Juan D Cañete (Hospital Clinic I Provincial); Carlos Rodríguez Lozano, Antonio Naranjo, Soledad Ojeda, Félix Francisco Hernández, Celia Erausquin, Íñigo Rúa (Hospital de Gran Canaria Dr Negrin); Inmaculada Ureña, María Victoria Irigoyen, Laura Cano (Hospital General Carlos Haya); Rosa Roselló Pardo, Carlos Vázquez Galeano (Hospital General San Jorge), Alexia de Juanes, Beatriz Joven, Javier García (Hospital 12 De Octubre); Javier Calvo, Cristina Campos (Hospital General Universitario de Valencia), Juan José García Borras, Rosa Negueroles, Luisa Muñoz, J.L. Valero, D. Ybañez (Hospital La Fe).

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2011.12.006.

REFERENCES

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160(2):736-55.
2. Paramothayan S, Lasserson T, Walters EH. Immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis. Cochrane Database Syst Rev 2003(3):CD003536.
3. Kiltz U, Braun J. Use of methotrexate in patients with sarcoidosis. Clin Exp Rheumatol 2010;28(5 Suppl 61):S183-5.

4. Hehlgans T, Pfeffer K. The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: players, rules and the games. Immunology 2005;115(1):1-20.
5. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol 2002;168(9):4620-7.
6. Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. Lancet Infect Dis 2008;8(10):601-11.
7. Baughman RP, Strohofer SA, Buchsbaum J, Lower EE. Release of tumor necrosis factor by alveolar macrophages of patients with sarcoidosis. J Lab Clin Med 1990;115(1):36-42.
8. Ziegenhagen MW, Benner UK, Zissel G, Zabel P, Schlaak M, Muller-Quernheim J. Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. Am J Respir Crit Care Med 1997;156(5):1586-92.
9. Baughman RP, Lower EE. The effect of corticosteroid or methotrexate therapy on lung lymphocytes and macrophages in sarcoidosis. Am Rev Respir Dis 1990;142(6 Pt. 1):1268-71.
10. Tong Z, Dai H, Chen B, Abdoh Z, Guzman J, Costabel U. Inhibition of cytokine release from alveolar macrophages in pulmonary sarcoidosis by pentoxifylline: comparison with dexamethasone. Chest 2003;124(4):1526-32.
11. Tavares JL, Wangoo A, Dilworth P, Marshall B, Kotecha S, Shaw RJ. Thalidomide reduces tumour necrosis factor-alpha production by human alveolar macrophages. Respir Med 1997;91(1):31-9.
12. Carmona L, Gomez-Reino JJ. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 2006;8(3):R72.
13. Curtis JR, Jain A, Askling J, Bridges SL Jr, Carmona L, Dixon W, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. Semin Arthritis Rheum 2010;40(1):2-14, e1.
14. Carmona L. Actualización de BIOBADASER. Reumatol Clin 2009;5(Suppl 1):66-70.
15. Descalzo MA, Carmona L, Grupo de estudio BIOBADASER. Biobadaser 2.0: análisis y tendencias en 2009. Reumatol Clin 2010;6:240-3.
16. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312(7023):71-2.
17. Baughman RP, Bradley DA, Raymond LO, Lower EE, Kerr MA, Winget DB, et al. Double blind randomized trial of a tumor necrosis factor receptor antagonist (Etanercept) for treatment of chronic ocular sarcoidosis. Am J Respir Crit Care Med [serial on the Internet]. 2002;(Suppl 8): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/275/CN-00382275/frame.html.
18. Baughman RP, Bradley DA, Lower EE. Infliximab in chronic ocular inflammation. Int J Clin Pharmacol Ther 2005;43(1):7-11.
19. Baughman RP, Judson MA, Drent M, Costabel U, du Bois R, Kavuru M, et al. Impact of withdrawal of infliximab after 6 months treatment [Abstract]. Proceedings of the American Thoracic Society [serial on the Internet]. 2006: Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/785/CN-00591785/frame.html.
20. Judson MA, Baughman RP, Kavuru M, Costabel U, Drent M, DuBois R. Improvement in 6 minute walk distance in a double-blind randomized placebo-controlled trial of infliximab for chronic pulmonary sarcoidosis [Abstract]. Proceedings of the American Thoracic Society [serial on the Internet]. 2006: Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/517/CN-00591517/frame.html.
21. Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Keenan GF, et al. A double-blind randomized placebo-controlled trial of infliximab in active pulmonary sarcoidosis [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California [serial on the Internet]. 2005: Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/642/CN-00525642/frame.html.
22. Summaries for patients. A new anti-inflammatory therapy (Infliximab) for complicated sarcoidosis. Ann Intern Med 2001;135(1):S20.
23. Wells AU. Infliximab in extrapulmonary sarcoidosis: tantalising but inconclusive. Eur Respir J 2008;31(6):1148-9.
24. Cook MC. Infliximab therapy for complicated sarcoidosis. Ann Intern Med 2002;137(4):296-7; author reply 297.
25. Corbett J. Treating CNS sarcoidosis with infliximab and mycophenolate mofetil [Short Survey]. Curr Neurol Neurosci Rep 2009;9(5):339-40.
26. Kahler CM, Heininger P, Loeffler-Ragg J, Vogelsinger H. Infliximab therapy in pulmonary sarcoidosis. Am J Respir Crit Care Med 2007;176(4):417; author reply 418.
27. Morcos Z. Refractory neurosarcoidosis responding to infliximab. Neurology 2003;60(7):1220-1; author reply 1221.
28. O'Connor TM, Shanahan F, Bredin CP. Infliximab therapy for complicated sarcoidosis. Ann Intern Med 2002;137(4):296-7; author reply 297.
29. Chintamaneni S, Patel AM, Pegram SB, Patel H, Roppelt H. Dramatic response to infliximab in refractory neurosarcoidosis. Ann Indian Acad Neurol 2010;13(3):207-10.
30. Cufi-Benet M, Sabadell C, Codina O. [Adalimumab in the treatment of parotid sarcoidosis]. Arch Bronconeumol 2010;46(1):49-50.
31. Dhingra N, Morgan J, Dick AD. Switching biologic agents for uveitis. Eye (Lond) 2009;23(9):1868-70.
32. 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(3):212-9.
33. Jonker G, van Kan G, Hoor-de Groot ET, Drent M. Improvement of the clinical response to infiximab in refractory sarcoidosis by reducing the dose interval [Abstract]. European Respiratory Journal [serial on the Internet]. 2007;(Suppl 51): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/679/CN-00642679/frame.html.
34. Lindstedt EW, Baarsma GS, Kuijpers RW, van Hagen PM. Anti-TNF-alpha therapy for sight threatening uveitis. Br J Ophthalmol 2005;89(5):533-6.
35. Malaviya AN, Sawhney S, Kapoor S, Garg S. Vertebral sarcoid mimicking ankylosing spondylitis or just a co-incidence? J Assoc Physicians India 2010;58:709-11.
36. Marnane M, Lynch T, Scott J, Stack J, Kelly PJ. Steroid-unresponsive neurosarcoidosis successfully treated with adalimumab. J Neurol 2009;256(1):139-40.
37. Menon Y, Cucurull E, Reisin E, Espinoza LR. Interferon-alpha-associated sarcoidosis responsive to infliximab therapy. Am J Med Sci 2004;328(3):173-5.
38. Migliore A, Signore A, Capuano A, Bizzi E, Massafra U, Vacca E, et al. Relevance of 99mTc-HYNIC-tir-octreotide scintigraphy in a patient affected by sarcoidosis with lung and joints involvement and secondary Sjogren's syndrome treated with infliximab: case report. Eur Rev Med Pharmacol Sci 2008;12(2):127-30.
39. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology (Oxford) 2006;45(8):982-9.
40. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. Arthritis Care Res (Hoboken) 2011;63(4):612-8.

41. Thielen AM, Barde C, Saurat JH, Laffitte E. Refractory chronic cutaneous sarcoidosis responsive to dose escalation of TNF-alpha antagonists. Dermatology 2009;219(1):59-62.
42. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2001;18(1):70-4.
43. 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(1):73-7.
44. 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(5):457-61.
45. Tuchinda C, Wong HK. Etanercept for chronic progressive cutaneous sarcoidosis. J Drugs Dermatol 2006;5(6):538-40.
46. Sorrentino D, Avellini C, Zearo E. Colonic sarcoidosis, infliximab, and tuberculosis: a cautionary tale. Inflamm Bowel Dis 2004;10(4):438-40.
47. Stagaki E, Mountford WK, Lackland DT, Judson MA. The treatment of lupus pernio: results of 116 treatment courses in 54 patients. Chest 2009;135(2):468-76.
48. Baughman RP, Shipley R, Desai S, Drent M, Judson MA, Costabel U, et al. Changes in chest roentgenogram of sarcoidosis patients during a clinical trial of infliximab therapy: comparison of different methods of evaluation. Chest 2009;136(2):526-35.
49. Drent M, Costabel U, Shipley R, Desai S, Judson M, du Bois R, et al. Changes of chest roentgenogram during a double blind randomized trial of infliximab for chronic pulmonary sarcoidosis [Abstract]. European Respiratory Journal [serial on the Internet]. 2006;(Suppl 50): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/578/CN-00623578/frame.html.
50. Loza MJ, Brodmerkel C, Du Bois RM, Judson MA, Costabel U, Drent M, et al. Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis. Clin Vaccine Immunol 2011;18(6):931-9.
51. Sweiss NJ, Barnathan ES, Lo K, Judson MA, Baughman R. C-reactive protein predicts response to infliximab in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2010;27(1):49-56.
52. Evrard P, Evrard AS, Gouzou M, Brisbois D, Quatresooz P, Engelen M. [Cardiac sarcoidosis: a case report]. Rev Med Liege 2008;63(12):707-9.
53. Gallagher M, Quinones K, Cervantes-Castaneda RA, Yilmaz T, Foster CS. Biological response modifier therapy for refractory childhood uveitis. Br J Ophthalmol 2007;91(10):1341-4.
54. Mana J, Capdevila O, Solanich X, Jucgla A, Marcoval J. [Lupus pernio. A report of a series of 8 patients]. Rev Clin Esp 2010;210(11):550-5.
55. Markert JM, Powell K, Tubbs RS, Riley KO, Hadley MN, Palmer CA. Necrotizing neurosarcoid: three cases with varying presentations. Clin Neuropathol 2007;26(2):59-67.
56. Baughman RP. Clinical characteristics of patients participating in multicenter randomized double-blind placebo-controlled trial evaluating the safety and efficacy of infliximab in patients with chronic sarcoidosis with pulmonary involvement [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California [serial on the Internet]. 2005: Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/441/CN-00524441/frame.html.
57. Suzuki J, Goto H. Uveitis associated with sarcoidosis exacerbated by etanercept therapy. Jpn J Ophthalmol 2009;53(4):439-40.
58. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006;174(7):795-802.
59. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology [serial on the Internet]. 2008;(6): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/728/CN-00637728/frame.html.
60. Baughman R, Lo K, Guzzo C, Barnathan E. Efficacy of infliximab in improving lupus pernio in patients receiving treatment for chronic pulmonary sarcoidosis. [Abstract P50. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006]. Journal of the American Academy of Dermatology [serial on the Internet]. 2006;(Suppl 3): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/504/CN-00623504/frame.html.
61. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest [serial on the Internet]. 2005;(2): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/879/CN-00523879/frame.html.
62. Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller W, et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. Sarcoidosis, vasculitis, and diffuse lung diseases: official journal of WASOG/World Association of Sarcoidosis and Other Granulomatous Disorders [serial on the Internet]. 2006;(3): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/292/CN-00621292/frame.html.
63. Aguiar M, Marcal N, Mendes AC, Bugalho de Almeida A. Infliximab for treating sarcoidosis patients. Portuguese experience. Rev Port Pneumol 2011;17(2):85-93.
64. Crouser ED, Lozanski G, Fox CC, Hauswirth DW, Raveendran R, Julian MW. The CD4+ lymphopenic sarcoidosis phenotype is highly responsive to anti-tumor necrosis factor-α therapy. Chest 2010;137(6):1432-5.
65. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest 2005;127(3):1064-71.
66. Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. Respiration 2011 (in press).
67. Jounieaux F, Chapelon C, Valeyre D, Israel Biet D, Cottin V, Tazi A, et al. [Infliximab treatment for chronic sarcoidosis—a case series]. Rev Mal Respir 2010;27(7):685-92.
68. 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(2):143-9.
69. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. Neurology 2009;72(4):337-40.
70. Panselinas E, Rodgers JK, Judson MA. Clinical outcomes in sarcoidosis after cessation of infliximab treatment. Respirology 2009;14(4):522-8.
71. Pritchard C, Nadarajah K. Tumour necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. Ann Rheum Dis 2004;63(3):318-20.
72. Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med 2006;100(11):2053-9.
73. Santos E, Shaunak S, Renowden S, Scolding NJ. Treatment of refractory neurosarcoidosis with Infliximab. J Neurol Neurosurg Psychiatry 2010;81(3):241-6.
74. Utz JP, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest 2003;124(1):177-85.
75. Tournadre A, Ledoux-Eberst J, Poujol D, Dubost JJ, Ristori JM, Soubrier M. Exacerbation of interstitial lung disease during etanercept therapy: Two cases. Joint Bone Spine 2008;75(2):215-8.
76. D'Haens G, Swijsen C, Noman M, Lemmens L, Ceuppens J, Agbahiwe H, et al. Etanercept in the treatment of active refractory

Crohn's disease: a single-center pilot trial. Am J Gastroenterol 2001;96(9):2564-8.
77. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001; 121(5):1088-94.
78. Wegener's granulomatosis Etanercept trial (WGET) research group. N Engl J Med 2005;352(4):351-61.
79. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 2008;117(2):244-79.
80. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301(2):418-26.
81. Mohan VP, Scanga CA, Yu K, Scott HM, Tanaka KE, Tsang E, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun 2001;69(3):1847-55.
82. Olleros ML, Guler R, Corazza N, Vesin D, Eugster HP, Marchal G, et al. Transmembrane TNF induces an efficient cell-mediated immunity and resistance to Mycobacterium bovis bacillus Calmette-Guerin infection in the absence of secreted TNF and lymphotoxin-alpha. J Immunol 2002;168(7):3394-401.
83. Carmona L, Descalzo MA, Ruiz-Montesinos D, Manero-Ruiz FJ, Perez-Pampin E, Gomez-Reino JJ. Safety and retention rate of off-label uses of TNF antagonists in rheumatic conditions: data from the Spanish registry BIOBADASER 2.0. Rheumatology (Oxford) 2011;50(1):85-92.
84. Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis 2007; 66(7):880-5.
85. Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moens HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford) 2011;50(1):196-203.