Infliximab for Refractory Cardiac Sarcoidosis

Logan J. Harper, MD[a,*], Meghann McCarthy, DO[b], Manuel L. Ribeiro Neto, MD[a], Rory Hachamovitch, MD[c], Karla Pearson, PA-C[a], Barbara Bonanno, RN[a], Josephine Shaia, RN[a], Richard Brunken, MD[d], Emer Joyce, MD, PhD[e], and Daniel A. Culver, DO[a]

Cardiac sarcoidosis (CS) is frequently difficult to treat. Infliximab (IFX) is useful for extracardiac sarcoidosis, but its use in CS has been limited due to concerns about cardiotoxicity and an FDA blackbox warning about use in heart failure. We reviewed 36 consecutive patients treated with infliximab for CS refractory to standard therapies. IFX was initiated for patients with refractory dysrhythmias, moderate to severe cardiomyopathy, and evidence of persistent F-18 fluorodeoxyglucose uptake on positron emission tomography scan, despite standard therapies. We compared the prednisone dose, ejection fraction (EF), and dysrhythmias before and after IFX therapy. The prednisone-equivalent steroid dose decreased from a median of 20 mg at initiation of infliximab to 7.5 at 6 months and 5 mg at 12 months postinitiation of infliximab ($p < 0.001$). In the 25 patients with serial EF measurements, no statistically significant difference was detected in EF (41% at baseline, 42% at 6 months). Of the 16 patients with serial dysrhythmia data, there was a trend toward reduction of percent of patients with ventricular tachycardia (VT), from 32% at baseline, to 22% at 6 months and 19% at 12 months ($p = 0.07$). Adverse events were common, occurring in 6 of 36 patients, with 3 of 36 patients stopping infliximab for a prolonged period. In responder analysis, 24 patients improved in at least 1 of 3 outcome categories. In conclusion, infliximab may be useful for refractory cardiac sarcoidosis. **(Am J Cardiol 2019;124:1630−1635)**

Treatment of cardiac sarcoidosis is difficult, in part due to the rarity of the disease and the lack of controlled trials. All current guidelines for cardiac sarcoidosis, including the Heart Rhythm Society (HRS) 2014 expert consensus,[1] the 1999 The American Thoracic Society (ATS), the European Respiratory Society (ERS) and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) statement,[2] and the British Thoracic Society (BTS) 2008 guidelines[3] recommend corticosteroids as first-line agents whereas admitting the paucity of data for preventing disease progression. Second-line therapy has less data, with methotrexate being the most common recommendation.[3] Despite some encouraging early reports, use of infliximab in cardiac sarcoidosis is complicated by evidence of TNF inhibitors worsening heart failure.[4] This resulted in a 2001 FDA safety alert for infliximab, warning of heightened incidence of mortality and hospitalization for patients with moderate to severe heart failure. Given the promising effects of infliximab for extrapulmonary sarcoidosis,[5−7] we hypothesized that infliximab would benefit patients with cardiac sarcoidosis, given that infliximab has been shown to improve the underlying pathological insult causing heart failure in this population. This study sought to evaluate the safety and efficacy of infliximab in cardiac sarcoidosis patients.

Methods

We reviewed all patients who had ICD-10 coding for "cardiac myocarditis" (D86.85) and had an order placed at any point for infliximab. We excluded patients if they had been started on infliximab <6 months before analysis, or if infliximab was initiated for noncardiac manifestations of sarcoidosis. For this study, cardiac sarcoidosis was defined according to WASOG criteria.[8]

At our institution we initiate infliximab for patients with refractory cardiac sarcoidosis, defined as progression of cardiac symptoms or cardiac involvement and failure of management with steroids and steroid sparing agents. Cardiac medications were managed by a cotreating cardiologist and dosed per current heart failure guidelines. Progression of cardiac disease requiring initiation of infliximab was defined clinically by the treating physician but typically was related to refractory dysrhythmias nonresponsive to standard antiarrhythmic therapy, heart block attributed to sarcoidosis, new or increasing ventricular tachycardia (VT) or nonsustained ventricular tachycardia (NSVT), dysrhythmias requiring ICD (implantable cardioverter-defibrillator)/pacemaker therapy, worsening cardiomyopathy, progressive symptoms of heart failure (as assessed by a multidisciplinary team including pulmonologist and cardiologists), or evidence of persistent

[a]Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio; [b]Department of Vascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; [c]Cardiovascular Imaging Section, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; [d]Department of Nuclear Medicine, Imaging Institute, Cleveland Clinic, Cleveland, Ohio; and [e]Department of Cardiovascular Medicine, Mater Misericordiae University Hospital, Dublin, Ireland. Manuscript received April 29, 2019; revised manuscript received and accepted July 31, 2019.

Financial disclosure: None of the authors have any financial interests to disclose.

See page 1634 for disclosure information.

*Corresponding author: Tel: (216) 444-4707

E-mail address: Harperl3@ccf.org (L.J. Harper).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.07.067

fluorodeoxyglucose uptake along with symptomatic cardiac manifestations despite standard therapies. Sarcoidosis therapies were titrated as previously described.[9]

We compared the prednisone dose, ejection fraction (EF), and dysrhythmias before and after infliximab therapy. We compared steroid dose across 3 time frames (baseline, 6 months, 12 months) with Friedman's two-way analysis of variance by ranks. Ejection fraction was compared using related samples Wilcoxon signed rank test across 2 time frames (baseline and 6 months). Dysrhythmia data were obtained by ICD interrogation (23/25) or Holter monitor (2/25). We assessed 5 categories of dysrhythmia: shocks or antitachycardia pacing from ICD, high-grade AV block, VT/ventricular fibrillation (VF), nonsustained ventricular tachycardia (NSVT), and premature ventricular contractions (PVC). Occurrence of various dysrhythmias (presence or absence) was compared using related samples Cochran's Q test across 3 time frames (baseline, 6 months, 12 months). PET data were not suitable for analysis due to a change in dietary preparation protocol midway through our study period which made direct comparison of PET studies impossible. For analysis of steroid dose, ejection fraction and dysrhythmias, only complete cases were used. We excluded patients who were on infliximab for <6 months from this analysis.

We classified patients as "responders", "stable" or "nonresponders" as part of a responder analysis. Patients were defined as a "responder" if they had either a decrease in daily steroid dose of ≥10 mg, improvement in dysrhythmia control or improvement of left ventricular ejection fraction (LVEF) by >5% without worsening in any of these 3 categories. Given that reduction of dysrhythmia burden rather than elimination is often the goal of therapy, dysrhythmias were defined as "improved" or "worsened" based on a >50% change in frequency of ventricular dysrhythmias.[10] Patients were defined as "stable" if they had no significant change in all 3 categories. Patients were defined as having "non-responder" if they had deterioration in 1 or more of the 3 categories regardless of improvement in any of the other categories. Patients who discontinued infliximab in <6 months were included in the responder analysis.

This study was approved by the Cleveland Clinic Institutional Review Board (IRB 15-1209).

Results

In total, 36 patients met inclusion criteria for the study (Table 1). Demographic data are provided in Table 1. Patients were generally in their 5th and 6th decade of life, had been diagnosed with sarcoidosis several years earlier and had multiple organs involved with sarcoidosis. There was significant cardiac morbidity among those in the cohort (Table 1). Of the patients who started therapy, 2 stopped infliximab before completing 6 months of therapy.

Data regarding therapy for sarcoidosis are presented in Table 1. Patients had failed multiple steroid sparing agents and were on moderate doses of daily prednisone. At infliximab initiation, all patients were treated with at least one other steroid sparing agent. Patents were started at 5 mg/kg of infliximab every 4 to 6 weeks with titration up to 10 mg/kg for lack of response, and lengthening of dosing interval to every 8 weeks if the patient exhibited stability. Most patients received several years of infliximab treatment.

Thirty-five patients completed at least 6 months and 29 patients completed at least 1 year of infliximab therapy.

Table 1
Demographics

Age at diagnosis of cardiac sarcoidosis (years)	46 ± 11
Age at initiation of infliximab (years)	50 ± 11
Men	26 (72%)
Race	
White	28 (78%)
Black	8 (22%)
Tobacco use	
Never	27 (75%)
Former	9 (25%)
Pack years of former smokers (years)	17 ± 22
Organ systems involved	
Heart	36 (100%)
Lung	26 (72%)
Neurologic	12 (33%)
Skin	7 (19%)
Bone	3 (8%)
Ocular	2 (6%)
Liver	2 (6%)
Kidney	1 (3%)
Gastrointestinal	1 (3%)
Spleen	1 (3%)
Baseline	
Ejection fraction <30%	6 (17%)
Ventricular tachycardia	8 (22%)
High-grade heart block	7 (19%)
Biventricular pacing	4 (11%)

Table 2
Treatment characteristics

Prior therapies	
Methotrexate	34 (94%)
Leflunomide	20 (56%)
Azathioprine	8 (22%)
Hydroxychloroquine	6 (17%)
IVIG	6 (17%)
Mycophenolate	3 (8%)
Adalimumab	1 (3%)
Taking steroids at Infliximab initiation	32 (89%)
Steroid sparing agents at Infliximab initiation	
Methotrexate	25 (69%)
Leflunomide	9 (25%)
Azathioprine	1 (3%)
Hydroxychloroquine	2 (3%)
Maximum Infliximab dose patient received	
5 mg/kg	27 (75%)
7.5 mg/kg	4 (11%)
10 mg/kg	5 (14%)
Average Infliximab dose	560 ± 260
Median Infliximab dose	500 mg
Maximum Infliximab dose in cohort	1250 mg
Initial Infliximab dosing interval	
Every 4 weeks	28 (78%)
Every 6 weeks	3 (8%)
Every 8 weeks	4 (11%)
Patients with infliximab dosing interval reduced	6 (17%)
Time to dosing interval reduction (months)	24 ± 30

The median prednisone dose decreased at 6 and 12 months ($p < 0.01$) compared with the dose at initiation of infliximab (Table 3). Of the 25 patients with follow-up ejection fraction data available, there was no significant change in ejection fraction at 6 months (Table 3). In patients with dysrhythmia data, there was a significant reduction in presence of PVCs ($p = 0.05$) and a trend toward elimination of VT ($p = 0.07$).

Of the 36 patients, 24 were categorized as "responders" due to an improvement in at least 1 of the 3 outcome categories (steroid dose, ejection fraction, dysrhythmia burden), without deterioration in any of the other outcome measures (Figure 1). Among "responders", improvement in steroid dose was most common ($n = 20$). Dysrhythmia control (>50% reduction in dysrhythmia occurrence on ICD/Holter monitor) improved in 12 of 24 responders whereas EF improved in 8 of 20 responders. Among the 9 of 36 patients who were categorized as "non-responders", 5 of 9 had improvement in at least 1 domain (Figure 1). Two patients in this cohort eventually required a heart transplant. Patients who discontinued infliximab in <6 months are included in analysis. One was a "responder" based on improved dysrhythmia control at 6 months (discontinued due to noncompliance with all medical therapy including dialysis).

Adverse reactions potentially attributable to infliximab occurred in 6of 36 (17%) of the group (Table 4). The most frequently encountered adverse event was infection (5 of 6). In 2 of the patients, the infection was sufficiently severe that infliximab was held for >1 year; the other 3 required either no interruption or temporary delay of the dose. Two patients required heart transplant. The first patient received 2 doses of infliximab as part of heroic therapy following acute decompensation of cardiac function, in conjunction with evaluation for heart transplant. The patient's dysrhythmias improved following infliximab allowing discharge, but infliximab was held as an outpatient due to concern of patient's low ejection fraction. This patient received a transplant at 96 days following infliximab therapy. The second patient received a heart transplant 392 days following infliximab initiation. This patient had >50% of the heart involved on cardiac PET and an EF of 27% when infliximab was initiated. With infliximab therapy the PET involvement decreased to 37%. Despite this, the patient's LVEF dropped from 27% to 18% and a heart transplant was required. Whereas the need for heart transplant was likely due to the severity of the underlying sarcoidosis, we cannot rule out the possibility that infliximab contributed.

Discussion

In this cohort, we observed a significant reduction in daily prednisone requirements following initiation of infliximab. This result is particularly significant given that the patients in this cohort had exceedingly refractory inflammation, having failed multiple steroid sparing agents. In addition, there was a strong trend toward reduction of ventricular tachycardia at 6 months, without worsening of other arrhythmia control measures. Finally, despite a reduction in steroid dose, no worsening of cardiac function was identified. In summary, infliximab allowed for reduction in steroid dose without worsening of cardiac function and a trend toward improvement in arrhythmia control in a cohort of cardiac sarcoidosis patients refractory to other treatment regimens.

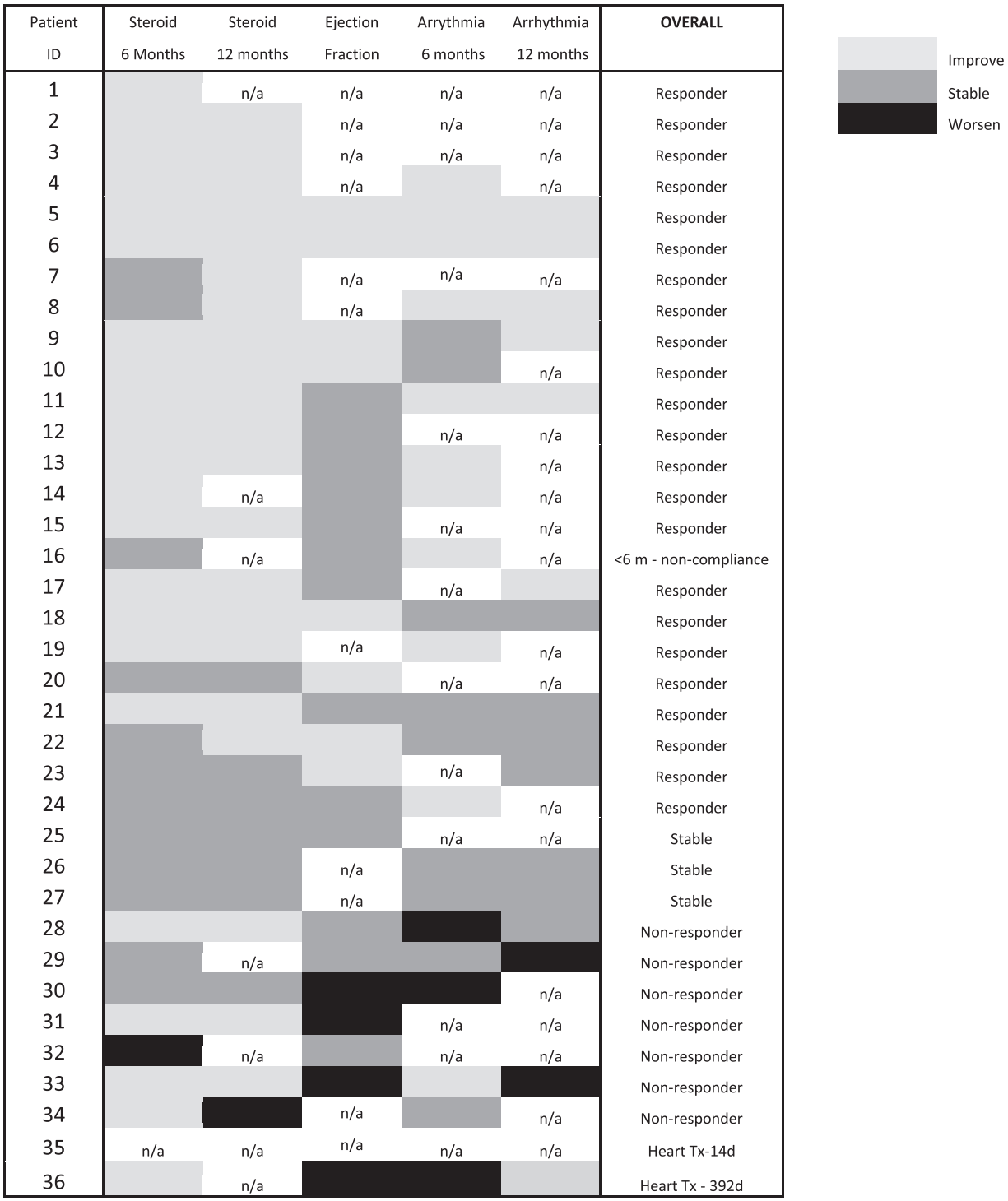
Due to the elevation of TNF in patients with heart failure, TNF inhibitors have been studied as a potential treatment for heart failure. The RENAISSANCE and RECOVER trials, analyzed together as RENEWAL, showed no difference in death or CHF hospitalization in New York Heart Association class II to IV chronic heart failure patients treated with etanercept.[4] The ATTACH trial, utilizing infliximab in patients with NYHA class II to IV heart failure showed an increase in a composite outcome of death or hospitalization for patients treated with high dose infliximab (10 mg/kg).[11] Data such as these resulted in a 2001 FDA safety alert for infliximab, warning of heightened incidence of mortality and hospitalization for patients with moderate to severe heart failure. Both of these trials, however, included patients with ischemic and nonischemic heart failure, including many patients with noninflammatory mediated heart failure. As a result, the safety of TNF antagonists for cardiac sarcoidosis is unclear.

Although not a safe treatment option in noninflammatory-mediated heart failure, infliximab has been shown to be an effective therapy for refractory sarcoidosis. In a

Table 3
Steroid dose, ejection fraction, and dysrhythmia prevalence at 6 and 12 months while on Infliximab

Variable	Baseline		6 months		12 months		p Value
	n	results	n	results	n	results	
Steroid dose (mg/day), median (25th-75th)*	35	20 (10-30)	35	7.5 (2.5-15)	29	5 (0-10)	<0.01
Ejection fraction (%), median (25th-75th)	31	41 (32-55)	28	41 (35-54)	NA	NA	0.43
Dysrhythmia, n (%)							
Implantable cardioverter defibrillator (ICD) therapy	25	4 (16%)	23	2 (8.7%)	16	2 (12.5%)	0.45
Ventricular Tachycardia	25	8 (32%)	23	5 (21.7%)	16	3 (18.8%)	0.07
2nd (Type 2)/3rd degree atrioventricular block	25	7 (28%)	23	6 (26.1%)	16	2 (12.5%)	0.37
Nonsustained ventricular tachycardia	25	7 (28%)	23	6 (26.1%)	15	6 (40%)	0.42
Premature ventricular contraction (PVC)*	25	3 (12%)	23	0 (0%)	16	0 (0%)	0.05

* Difference significant at $p < 0.05$.



Patient ID	Steroid 6 Months	Steroid 12 months	Ejection Fraction	Arrythmia 6 months	Arrhythmia 12 months	OVERALL
1		n/a	n/a	n/a	n/a	Responder
2			n/a	n/a	n/a	Responder
3			n/a	n/a	n/a	Responder
4			n/a		n/a	Responder
5						Responder
6						Responder
7			n/a	n/a	n/a	Responder
8			n/a			Responder
9						Responder
10					n/a	Responder
11						Responder
12				n/a	n/a	Responder
13					n/a	Responder
14		n/a			n/a	Responder
15				n/a	n/a	Responder
16		n/a			n/a	<6 m - non-compliance
17				n/a		Responder
18						Responder
19			n/a		n/a	Responder
20				n/a	n/a	Responder
21						Responder
22						Responder
23				n/a		Responder
24					n/a	Responder
25				n/a	n/a	Stable
26			n/a			Stable
27			n/a			Stable
28						Non-responder
29		n/a				Non-responder
30					n/a	Non-responder
31				n/a	n/a	Non-responder
32		n/a		n/a	n/a	Non-responder
33						Non-responder
34			n/a		n/a	Non-responder
35	n/a	n/a	n/a	n/a	n/a	Heart Tx-14d
36		n/a				Heart Tx - 392d

Figure 1. Responder analysis – Patients who improved in all categories across all follow up visits were categorized as "responders". Patients with any worsening across any of the outcome measures, or without improvement were categorized as "non-responders". Patients who stopped infliximab at <6 months are marked as "<6 m" and marked with the reason infliximab was held.

randomized trial, infliximab improved pulmonary function at 24 weeks in a randomized trial.[5] A post-hoc analysis of this trial demonstrated an improvement in a composite outcome of extrapulmonary involvement for patients receiving infliximab.[6] More recently, case reports and small case series have suggested benefit with infliximab for cardiac sarcoidosis.[7,12,13]

Despite these small case series, up to now, there have been few reported cases of cardiac sarcoidosis treated with infliximab. Most reported cases are part of larger cohorts with heterogeneous organ involvement or treatment strategies.[7,12–14] This case series is the largest cohort of cardiac sarcoidosis patients treated with infliximab for the indication of cardiac involvement. In addition, all patients had the

Table 4
Adverse drug reactions while on Infliximab

Reaction	Days after IFX initiate	IFX management	Other therapy required
Pneumonia, pulmonary embolism	288	Continued	Antibiotic, Anticoagulation
C. difficile diarrhea	329	Held 1 dose	Antibiotic
Shingles	657	Held 2 dose	Antivirals
Sepsis	122	Held 2 years	Antibiotic
Disseminated cryptococcus	73	Discontinued	Antifungal therapy
Decompensation of heart failure*	392	Discontinued	Heart Transplant at 392d

* Patient's decompensation in heart failure was thought to be secondary to the severity of the patient's cardiac sarcoidosis and not due to infliximab therapy by treating physicians.

entirety of their antisarcoidosis treatment at a single institution allowing for more sensitive assessment of the safety and efficacy of the drug.

In this cohort, a high proportion of patients experienced a potential ADR from infliximab treatment. When compared with other studies utilizing infliximab, the rate of adverse events and infections was similar to those reported in patients receiving infliximab for rheumatoid arthritis[15,16] and Crohn's disease.[17] As described above, the 2 patients who required a heart transplant were not deemed likely by their treating physicians to have decompensated due to use of Infliximab.

This study has several limitations. The lack of guidelines on monitoring of patients with cardiac sarcoidosis being treated with infliximab made assessment of clinical outcomes difficult. Although almost all patients had good records of steroid use, the diagnostic modality used to follow the patient whereas on infliximab varied greatly based on provider, the overriding symptomology (e.g., heart failure vs dysrhythmias), and lack of insurance approval for serial PET scans. Further many of the patients received cardiac care elsewhere; we chose not to include echocardiographic data from other institutions. Due to this, dysrhythmia, LVEF and PET scan data was not available for all patients. Bias introduced by lack of standardized follow up would most likely serve to understate the benefits of infliximab as patients who are doing well would be less likely to get follow-up studies at our institution. It is impossible to define exactly the efficacy of Infliximab without a control group, and more careful accounting for the effects of nonimmunosuppressive therapies. However, it is unlikely that all the observed benefit was due to spontaneous remission or other treatment modalities given that all patients had prolonged courses of refractory sarcoidosis and multiple attempts by cardiology specialists to optimize cardiac morbidity before initiation of infliximab. Because of this, we feel that the benefit we saw with infliximab in this sample is most likely a true representation of the benefits of infliximab in patients with cardiac sarcoidosis. A prospective controlled study with structured monitoring of patient's response to infliximab would be necessary to comment more definitively on the effects of this drug on cardiac involvement and dysrhythmia control.

This is the largest cohort of patients with cardiac sarcoidosis patients treated with infliximab to date. There was a significant improvement in disease, as demonstrated by reduction of steroid dose and a trend toward improvement in dysrhythmia control without a worsening in systolic function. Whereas potential adverse events were common, they were generally anticipated and manageable. Taken together, these results suggest that infliximab is a promising therapy for patients with refractory cardiac sarcoidosis, but close monitoring for adverse drug events is warranted. The favorable safety profile observed in this sample likewise suggests that TNF inhibition need not be withheld from sarcoidosis patients simply due to cardiac involvement. Future studies will be needed to determine the effect of infliximab on functional outcomes and quality of life.

Disclosures

Conflict of interest: No conflicts of interest.

1. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Hear Rhythm* 2014;11:1305–1324.
2. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. *Eur Respir J* 1999;14:735–737.
3. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, Hirani N, Hubbard R, Lake F, Millar AB, Wallace WAH, Wells AU, Whyte MK, Wilsher ML. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;63(Suppl 5):v1–v58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757459.
4. Mann DL, McMurray JJV, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, Veldhuisen DJ Van, 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.
5. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, Du Bois R, Albera C, Brutsche M, Davis G, Donohue JF, Müller-Quernheim J, Schlenker-Herceg 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.
6. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, Drent M, Culver DA, Davis GS, Fogarty CM, Hunninghake GW, Teirstein AS, Mandel M, McNally D, Tanoue L, Newman L, Wasfi Y, Patrick H, Rossman MD, Raghu G, Sharma O, Wilkes D, Yeager H, Donahue JF, Kaye M, Sweiss N, Vetter N, Thomeer M, Brutsche M, Nicod L, Valeyre D, Chanez P, Albera C, Grutters J, Hoogsteden H, Muller-Quernheim J, Bonnet R, Kanniess F. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008;31:1189–1196.
7. Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Pérard L, Bouillet L, Deroux A, Abad S, Bielefeld P, Bouvry D, André M, Noel N, Bienvenu B, Proux A, Vukusic S, Bodaghi B, Sarrot-Reynauld F, Iwaz J, Amoura Z, Broussolle C, Cacoub P, Saadoun D, Valeyre D, Sève P. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: a multicenter study of 132 patients. *Semin Arthritis Rheum* 2017;47:288–294.

8. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, Shigemitsu H, Culver DA, Gelfand J, Valeyre D, Sweiss N, Crouser E, Morgenthau AS, Lower EE, Azuma A, Ishihara M, Morimoto S-I, Tetsuo Yamaguchi T, Shijubo N, Grutters JC, Rosenbach M, Li H-P, Rottoli P, Inoue Y, Prasse A, Baughman RP, Organ Assessment Instrument Investigators TWS. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. *Sarcoidosis, Vasc Diffus Lung Dis* 2014;31:19–27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24751450. Accessed January 28, 2019.
9. Ribeiro Neto ML, Culver DA. Sarcoidosis: treatments beyond prednisone and methotrexate. *Expert Rev Respir Med* 2017;11:167–170. Available at: https://www.tandfonline.com/doi/full/10.1080/17476348.2017.1289842. Accessed July 9, 2019.
10. Isiguzo M, Brunken R, Tchou P, Xu M, Culver DA. Metabolism-perfusion imaging to predict disease activity in cardiac sarcoidosis. *Sarcoidosis Vasc Diffus Lung Dis* 2011;28:50–55.
11. Chung ES, Packer M, Lo KH, Fasanmade AA. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe {. . .}. *Circulation* 2003. Available at: http://circ.ahajournals.org/content/107/25/3133.short.
12. Uthman I, Touma Z, Khoury M. Cardiac sarcoidosis responding to monotherapy with infliximab. *Clin Rheumatol* 2007;26:2001–2003.
13. Chapelon-Abric C, Saadoun D, Biard L, Sene D, Resche-Rigon M, Hervier B, Costedoat-Chalumeau N, Drier A, Leger JM, Cacoub P. Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. *Clin Exp Rheumatol* 2015;33:509–515.
14. Fussner LA, Karlstedt E, Hodge DO, Fine NM, Kalra S, Carmona EM, Utz JP, Isaac DL, Cooper LT. Management and outcomes of cardiac sarcoidosis: a 20-year experience in two tertiary care centres. *Eur J Heart Fail* 2018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30378224. Accessed November 29, 2018.
15. Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T. RISING study. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol* 2009;19:478–487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19626391. Accessed July 10, 2018.
16. Rahman MU, Strusberg I, Geusens P, Berman A, Yocum D, Baker D, Wagner C, Han J, Westhovens R. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:1233–1238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17392352. Accessed July 10, 2018.
17. Hibi T, Sakuraba A, Watanabe M, Motoya S, Ito H, Motegi K, Kinouchi Y, Takazoe M, Suzuki Y, Matsumoto T, Kawakami K, Hirata I, Tanaka S, Ashida T, Matsui T, Matsui T. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn′s disease. *Inflamm Bowel Dis* 2012;18:1480–1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21987418. Accessed July 10, 2018.