Use of third-line therapies in advanced sarcoidosis

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Abstract

Objective

Patients with advanced sarcoidosis often require third-line therapies including infliximab, adalimumab, rituximab, and repository corticotropin injection (RCI). Over time, some patients discontinue therapy.

Methods

In a retrospective review of patients at the University of Cincinnati Sarcoidosis Clinic, we identified patients who received one or more third-line treatments. Age, race, gender, organ involvement, and initial date of therapy were collected. For patients in whom a drug was discontinued, the last date of treatment, reason for drug discontinuation, and outcome of drug withdrawal were noted.

Results

Of the 2109 patients identified, 317 (15%) had received one or more third-line therapies (infliximab: 258 patients; adalimumab: 52 patients; rituximab: 34 patients; RCI: 101 patients). Patients with neurologic, cutaneous, or ocular sarcoidosis involvement were more likely to have received third-line therapy. Overall, 225 (50.6%) of treatment regimens were discontinued. Rate of discontinuation was higher for infliximab (55%), adalimumab (58%), or RCI (43%) than for rituximab (29%, Chi square=11.959, p=0.0075). Compared to RCI, the hazard ratio (HR) for discontinuing therapy due to infection was increased for infliximab (HR=12.14, p=0.0134) and adalimumab (HR=9.71, p=0.0356). The hazard ratio was higher for drug discontinuation due to allergic reactions to infliximab (HR=9.40, p=0.0017) or adalimumab (HR=5.83, p=0.0273). For patients receiving at least two years of therapy, drug survival was significantly shorter for infliximab compared to other therapies (Chi square=5.4054, p=0.0201).

Conclusion

While third-line therapies are often initially effective, a significant number of patients discontinued individual treatments and initiated an alternative third-line therapy.

Key words

sarcoidosis, infliximab, adalimumab, rituximab, drug survival

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Introduction

Most symptomatic sarcoidosis patients can be successfully treated with prednisone and/or immunosuppressive therapies such as methotrexate or azathioprine. However, a small but significant proportion of sarcoidosis patients require third-line therapy. These regimens include infliximab, adalimumab, rituximab, and repository corticotrophin injection (RCI) (1, 2). While these drugs can be efficacious, patients often have to switch from one treatment to another over time due to reactions to medication, adverse events, lack of efficacy, or development of contraindications to the treatment (3, 4).

The term "drug survival" has been used to describe the time until discontinuation of an agent. In rheumatoid arthritis, the reported overall drug survival of infliximab and other anti-TNF monoclonal antibodies was fifty percent after two to three years (5-8). A similar rate has been observed in other inflammatory diseases for which biologic agents have been used (9, 10). However, the duration of response has not been previously reported in sarcoidosis. We present the drug survival of four third-line agents used in advanced sarcoidosis patients from a single centre, where we have been utilising these agents for more than fifteen years.

Materials and methods

This was a retrospective chart review of sarcoidosis patients treated at the University of Cincinnati Sarcoidosis Clinic. Patients were first identified from a database capturing all sarcoidosis patients seen at University of Cincinnati Sarcoidosis Clinic. Sarcoidosis patients who received one or more third-line therapies (infliximab, adalimumab, rituximab, or RCI) were identified. Data collected included patient's age, race, sex, and organ involvement using WASOG organ assessment instrument (11). Using the patient's specific first and last known drug administration date, the duration of therapy was calculated. For patients with intermittent therapy due to insurance issues or toxicity, we used the last date of drug administration. The study was approved by the University of Cincinnati Institutional Review Board (study no. 2013-3320) and registered on ClinicalTrials.gov (NCT02356445).

Treatment regimens followed protocols previously reported by us. Infliximab was usually initiated at 5 mg/kg intravenously at initially, two weeks later, than once a month (12). After a year, tapering of therapy to every six or more weeks was attempted. Patients who experienced worsening sarcoidosis symptoms prior to the next scheduled dose returned to the more frequent dosing schedule (13). Adalimumab was administered at a dose of 40 mg subcutaneously every two weeks, and increased to every week if a patient failed to respond (14). Rituximab was administered intravenously at 1000 mg initially and two weeks later. Patients were then placed on maintenance therapy every three to eight weeks (15, 16). Repository corticotropin injection (RCI) was initially administered at 40 to 80 units subcutaneously twice a week. Patients who were benefiting from drug and tolerating dose were tapered to maintenance doses between 20 to 40 units once a week or as tolerated (4, 17).

The major causes for discontinuation were determined. Adverse events leading to drug discontinuation were classified as serious infection(s), allergic reaction either locally or systemically, and other toxicities. Other toxicities included uncontrolled hyperglycaemia, oedema, drug induced arthritis, skin rashes, or others. Other reasons for discontinuations were classified as insurance incompatibility, drug ineffectiveness, remission, or lost to follow-up (two cases).

Statistics

Differences between groups were calculated using Chi square analysis and Kruskal-Wallis and drug survival was compared using Kaplan-Meier analysis. To determine if any univariate factors with p-values <0.10 were independent predictors of drug survival, a Cox proportional hazard model was created.

Results

Of the 2109 patients included in the sarcoidosis patient database, 317 (15%) were identified as receiving one or more

Table I. Demographic features of sarcoidosis patients treated with third-line therapy.

	Infliximab	Adalimumab	Rituximab	RCI	Total	Chi Square	*p*-value
Features							
Number	258	52	34	101	317[§]		
Age, years	55 (21-79)	55 (21-78)	56 (31-69)	56 (24-72)			0.385[¶]
Black/White/Other	118/138/2 (45.6%: 53.7%; 0.1%)[†]	8/35/0 1 (34.6%: 67.3%)	16/18/0 (47.1%:52.9%)	41/59/1 (40.6%:58.4%:1.0%)	137/178/2 (43.2%:56.2%:0.6%)	3.885	0.6922
Female	172/86 (66.5%)	42 (80.8%)	29 (85.3%)	71 (70.4%)	213 (67.2%)	4.301	0.2308
Drugs at time of institution of third-line therapy							
Methotrexate	90 (34.9%)	13 (25.0%)	9 (26.5%)	26 (25.7%)	108	4.325	0.2285
Prednisone	135 (52.3%)	23 (44.2%)	22 (64.7%)	60 (59.4%)	173	5.044	0.1686
Mycopheno-late	20 (7.8%)	7 (13.5%	3 (8.8%)	6 (5.9%)	23	2.710	0.4386
Azathioprine	29 (11.2%)	11 (21.2%)	6 (17.6%)	19 (18.8%)	34	5.815	0.1210
Leflunomide	17 (6.6%)	8 (15.4%)	3 (8.8%)	3 (3.0%)	21	8.412	0.0382
Hydroxychloroquine	20 (7.8%)	1 (1.9%)	2 (5.9%)	6 (5.9%)	24	2.525	0.4708

*Median (range). [†]Number (percent of total treated with specific regimen). [§]Patients may have received more than one therapy. [¶]Kruskal-Wallis.

third-line agents. Of these 317 patients, 258 received infliximab (two were not analysed), 52 received adalimumab, 34 received rituximab, and 101 received RCI. Patients could receive one or more treatments, and a total of 445 treatment regimens were analysed.

Table I summarises the demographic features of the four treatment groups. No significant differences were identified among the treatment groups in terms of age at diagnosis, race, or gender. In addition, no significant differences were seen between these patients receiving third-line therapies and the remaining 1792 sarcoidosis patients not treated with third-line therapy (Controls age median 55 (range 18 to 92) years, 67.2% female, 43.2% black, 56.2% white, and 0.6% other). Table I also lists first- and second-line treatments used concurrently with the third-line therapies. Fifteen percent of the patients receiving adalimumab were receiving leflunomide, which was slightly higher than other treatments (15.4% *vs.* 3–8.8% for other treatments, p=0.0382). There were no significant differences in rates for other first- or second-line treatments between the four agents.

Table II lists the four major organs affected by patients receiving individual third-line therapies. There were no differences in the rates for the four treatment groups. However, significant differences existed for all four organs compared to the control group. Those patients receiving third-line therapy were significantly less likely to have lung involvement, but more likely to have eye, skin, or central nervous system (CNS) involvement (p<0.0001 for all four organs). All other organ involvement including liver, spleen, extra thoracic lymph node, cardiac, bone, and upper respiratory tract was less than 15% in both groups and there was no significant differences in frequency between those treated or not treated with third-line therapy (data not shown).

Table II. Organ involvement third-line therapy *versus* controls.

	3rd line	Controls	Chi
Number of patients	317	1792	
Lungs	260 (82.1%	1616 (90.2%)	17.428*
Eyes	142 (44.8%)	404 (22.6%)	68.347*
CNS	118 (37.2%)	235 (13.1%)	193.370*
Skin	109 (34.1%)	409 (22.8%)	18.512*

*Significant difference between those treated with third therapy and those not, p<0.0001 for all four organ manifestations.

Overall, 225 (50.6%) of the 445 treatments were discontinued. The major indications for drug discontinuation were infection, allergic reactions, other toxicity, insurance, drug ineffectiveness, in remission, and two cases lost to follow-up despite apparent drug effectiveness (one each infliximab and RCI). Figure 1 shows the rate of discontinuation for each of the four treatment groups. The overall rate of discontinuation was lowest for rituximab (29%) and highest for the anti-TNF agents infliximab (55%) and adalimumab (58%). There was a significant difference in the rate of discontinuation between the four treatments (Chi square=11.959, p=0.0075). Table III details the hazard ratio (HR) of discontinuing infliximab, adalimumab, and rituximab compared to RCI. We chose to compare to RCI since there was a large number of patients treated with the drug (101) and the reported side effects of RCI are similar to corticosteroids (4). There was an increased risk for discontinuing either infliximab or adalimumab *versus* RCI because of infections or allergic reactions.

When we compared discontinuation rates for African Americans to Caucasians, a significant difference in the drug survival was noted (Fig. 2). African American patients were less likely to have drug withdrawn compared to Caucasians or other races (Chi square=8.2809, p=0.0159). Compared to Caucasians, the HR of drug discontinuation for African Americans was 0.68 (0.506–0.913). However, there

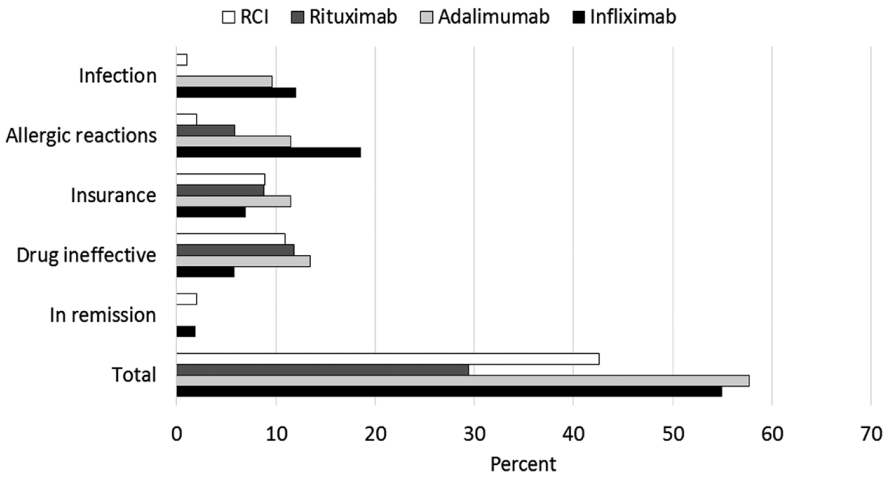

Fig. 1. Rate of discontinuation of four different treatments for advanced sarcoidosis. The overall rate and most common indications for discontinuation. There was a significant difference in rate discontinuation because of infection (Chi square=14.874, p=0.0019), allergic reaction (Chi square=20.697, p=0.0001), and total rate (Chi square=11.959, p=0.0075).

Table III. Hazard ratio for discontinuation of the therapy.

	Infliximab	Adalimumab	Rituximab
Infection	12.14*† (1.679-87.722)	9.71§ (1.165-80.977)	0.97 (0.040-23.303)
Allergic reactions	9.40¶ (2.327-37.936)	5.83** (1.218-27.868)	2.97 (0.435-20.284)
Other toxicity	0.55†† (0.310-0.984)	0.69 (0.288-1.634)	0.17 (0.242-1.264)
Insurance	0.80 (0.367-1.702)	1.31 (0.492-3.476)	1 (0.287-3.482)
Drug ineffective	0.54 (0.254-1.122)	1.24 (0.509-2.300)	1.08 (0.368-3.169)
Remission	0.98 (0.193-4.963)	0.38 (0.019-7.873)	0.58 (0.029-11.849)
Total	**1.29 §§ (1.005-1.663)**	**1.36 (0.979-1.875)**	**0.69 (0.392-1.219)**

*Hazard ratio (95% confidence interval). †Compared to RCI, p=0.0134. §Compared to RCI, p=0.0356. ¶Compared to RCI, p=0.0017. **Compared to RCI, p=0.0273. ††Compared to RCI. §§Compared to RCI, p=0.0457.

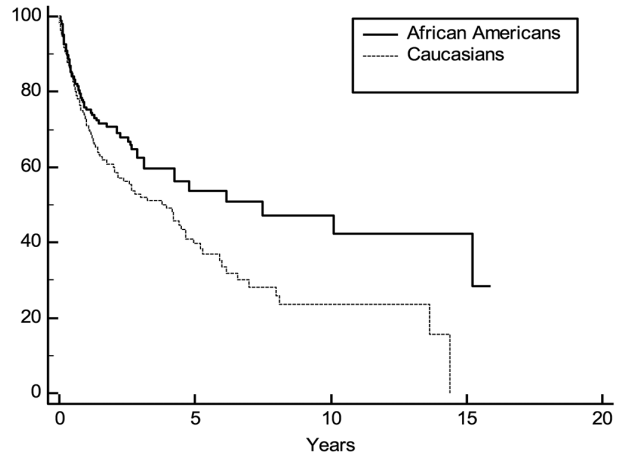

Fig. 2. Comparison of drug survival for any third-line treatment for African American *vs*. Caucasians. Significant difference using Kaplan-Meier analysis (Chi square=8.2809, p=0.0159).

was no difference in the rate of discontinuation for females *versus* males or for lung, ocular, or nervous system involvement. A borderline higher rate of drug discontinuation was seen in patients with skin involvement (Chi square=3.5206, p=0.0606).

Table IV provides information regarding outcome of drug withdrawal in those in there was adequate follow-up. Patients were characterised as clinically improved, unchanged, or worsened after treatment discontinuation. Most patients clinically worsened after drug was withdrawn. A statistically higher rate of relapse was witnessed in patients after the anti-TNF antibodies were withdrawn (Chi square=13.943, p=0.0030). Occasionally, the drug was reinstituted, with some patients responding to the re-challenge.

Drug survival was calculated using Kaplan-Meier analysis. Figure 3 depicts the rate of discontinuation for all four drugs. There was a trend for differences in drug survival (Chi square=6.3956, p=0.0939). The mean survival for infliximab was 6.13±0.530 years (mean ± SEM) and adalimumab was 6.32±1.097 years. Less than half of the patients had discontinued either rituximab or RCI.

A total of 165 patients received more than two years of treatment, including 109 patients treated with infliximab, 18 with adalimumab, 8 with rituximab, and 32 with RCI. Figure 4 compares the drug discontinuation rates for infliximab *versus* all other drugs. Drug survival was significantly shorter for infliximab by Kaplan-Meier analysis (Chi square=5.4054, p=0.0201).

The Cox proportional model examined those significant factors identified by univariate analysis: race, skin involvement, and infliximab treatment for more than two years. The model found that both Caucasian race and prolonged use of infliximab were independent factors associated with decreased drug survival (p=0.0169 and p=0.0235 respectively).

Discussion

In our clinic, fifteen percent of patients treated for sarcoidosis received one or more third-line therapies. Initial response to these third-line treatments was seen in more than eighty percent of cases. While pulmonary disease was reported in the majority of our patients, extra-pulmonary disease was a significantly more common phenotype for patients receiving third-line therapy (Table II). Ocular, neurologic, or cutaneous disease phenotypes were two to three times more likely to receive third-line treatments. After progressing with first- or second-line agents, patients with ocular disease often respond to third-line agents such as anti-TNF drugs or rituximab (15), (18-20). Neurologic disease also responds well to anti-TNF agents when other treatments have failed (21, 22). Additionally, chronic cutaneous

Table IV. Outcome of drug discontinuation*.

	Total Withdrawn	Improved/unchanged	Worse†	Better with reinstitution§
Infliximab	142	41 (28.9%)	101 (71.1%)	4 (2.8%)
Adalimumab	30	2 (6.7%)	28 (93.3%)	1 (3.3%)
RCI	43	19 (44.1%)	24 (55.8%)	1 (2.3%)
Rituximab	10	5 (50.0%)	5 (50.0%)	1 (10.0%)

*Outcome of drug discontinuation not available on all patients.
†Difference in rate of worsening between drugs (Chi square=13.943, p=0.0030).
§Outcome of patients who were worse after discontinuation and were rechallenged with agent.

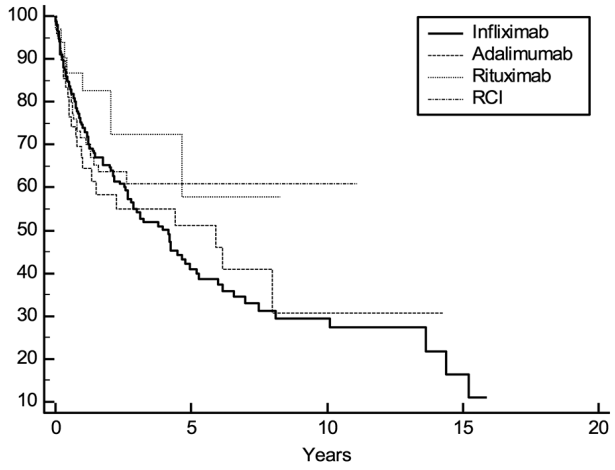

Fig. 3. The drug survival rate for the four treatment regimens using Kaplan-Meier analysis for all patients. There was a trend for longer survival for rituximab but the difference was not significant (Chi square=6.3956, p=0.0939).

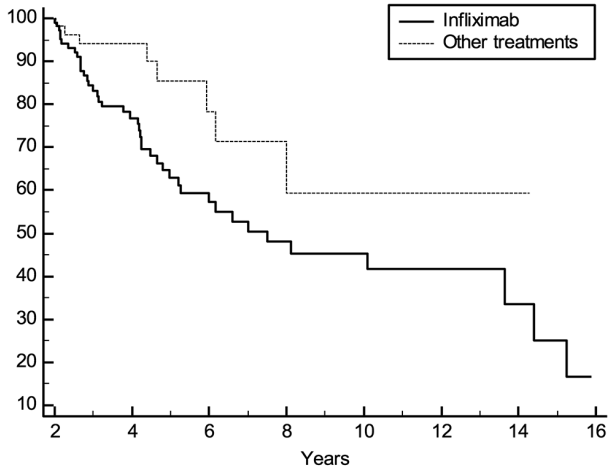

Fig. 4. Comparison of drug survival rate for infliximab *vs*. other third-line treatments for those patients treated with at least two years of individual agents. The rate of discontinuation was significantly higher for infliximab *vs*. all other drugs by Kaplan-Meier analysis (Chi square=5.4054, p=0.0201).

sarcoidosis, especially lupus pernio, responds well to anti-TNF and RCI interventions (4, 12, 23, 24).

In our study, more than half of patients receiving anti-TNF therapy eventually discontinued drug. Others have reported discontinuing anti-TNF therapy in ten to fifty percent of their sarcoidosis cases (25, 26). Lower discontinuation rates appear more likely in studies with shorter follow-up. In contrast, the rates of discontinuation approximate 50 percent in other conditions where prolonged anti-TNF therapies are prescribed (5-7, 9). In these other conditions including inflammatory bowel disease, drug discontinuation was often the result of lack of efficacy. In our study, approximately ten per cent of drug discontinuation was attributed lack of effectiveness to third-line agents. This is similar to other previously reported experiences in sarcoidosis (22, 26, 27). In this study, over half of patients were still on drug more than five years after institution of infliximab. This is longer than reported in rheumatoid arthritis, where over half of patients have stopped therapy within four years (5-8).This may be due the relatively limited number of alternatives in sarcoidosis *versus* rheumatoid arthritis.

Infliximab was the most commonly used third-line agent in our study. This may reflect the earlier recognition of the effectiveness of infliximab for chronic sarcoidosis (12) along with the positive randomised placebo controlled trials demonstrating effectiveness of the drug (28, 29). In our practice infliximab is usually prescribed as the first third-line agent with adalimumab, if available, prescribed for patients who develop infusion reactions or intolerance to infliximab. This is similar to the practice patterns in other centres reporting anti-TNF therapy prescribing (3). Although the rate of discontinuation for adalimumab was similar to that of infliximab, we were less likely to encounter adverse events as the cause for drug discontinuation. However, adalimumab was less likely to be effective and was associated with a lower remission rate when the drug was discontinued. In addition, adalimumab was not available to many of our patients because if insurance issues or contraindications to the agent.

We calculated the HR of adverse events leading to drug discontinuation for infliximab, adalimumab and rituximab compared to RCI. The HR for allergic reactions for infliximab was 9.40 and adalimumab was 5.83. Both of these were significantly higher than for RCI. Allergic reactions, including anaphylaxis (30, 31), were more severe with infliximab than the other agents. The reactions to the injectables adalimumab or RCI were usually local. In some cases, patients tolerated switching from infliximab to adalimumab (3). However, some patients chose to stop adalimumab because of repeated local reactions.

Compared to RCI, the risk for infection discontinuing therapy was also significantly higher for infliximab (HR=12.14) and adalimumab (HR=9.71). In this study, 10 per cent of patients discontinued anti-TNF therapy because of infection. This is similar to data in other anti-TNF treated patient populations (32). Heidelberger *et al*. reported serious infections in 30% of cutaneous sarcoido-

sis patients treated with anti-TNF agents (24) and a 20 percent overall discontinuation rate. In a report of 132 patients treated with anti-TNF agents for various forms of chronic sarcoidosis, Jammilloux *et al*. noted that that over half of patients experiencing adverse events including infections in 36% and adverse events in 8% of all patients (26).

Other adverse events occurred with all four drugs. The anti-TNF agents caused some patients to develop significant skin reactions which led to drug discontinuation (33). Also, some patients had increasing myalgias and other connective tissue disease associated symptoms which often became more severe with continued therapy. These were usually associated with high titre ANA testing and were felt to be auto-immune reactions due to the anti-TNF agents (30). For those treated with RCI, worsening hyperglycaemia, hypertension, oedema, and/or anxiety were common causes for drug discontinuation. This had been reported in prior studies (4, 17). For rituximab, leukopenia could be seen, as has been previously noted (15). We did not encounter serious infections, including no cases of progressive multifocal leukoenephalopathy. Increased rates of infections have been noted by others (34, 35).

In rheumatoid arthritis patients, rituximab has been associated with better drug survival compared to anti-TNF agents (5). This improved drug survival was also observed in our study of sarcoidosis patients. Rituximab, which has been used less frequently than anti-TNF agents for sarcoidosis, appears to have a lower response rate compared to anti-TNF therapy (16). Time to clinical improvement also appears longer with rituximab (16). However, the drug has a better toxicity profile (36) and seems unlikely to be associated with autoantibodies since it is a B cell depleting agent. It is also associated with fewer infections (37). In the current study, no patient discontinued rituximab because of infection. The use of rituximab in sarcoidosis remains limited because of difficulties in obtaining approval from insurance companies. Our experience suggests that this drug should be considered for more sarcoidosis patients.

There is limited data on the long-term outcome of sarcoidosis patients treated with RCI. Adverse events were commonly encountered and appear dose related (17). In one study, over a third of patients discontinued therapy within three months of starting treatment (4). The current study reports over forty percent of patients eventually discontinuing RCI, which is similar to the discontinuation rate for anti-TNF therapy. In the current study, RCI was used in a significant number of patients. The six-month outcome of some of these patients had been previously reported (4, 17).

Race was an independent predictor of discontinuation, with whites encountering shorter drug survival. This was not observed in drug survival studies in Crohn's disease (38). This may reflect the underlying treatment indication for third-line agents. For African Americans, the indications for treatment may be different and hence the duration of treatment may be longer. For example, lupus pernio is more common in African Americans (23, 39). Patients with lupus pernio respond better to anti-TNF therapy than other choices (23) and therefore may remain on treatment longer than for other conditions.

Disease worsening was experienced by over half of the cases after drug discontinuation. This mimics the previously 50 percent post drug discontinuation relapse rate of sarcoidosis patients treated with infliximab (27, 40). This observation has been reported in patients who appear to be in clinical remission (22). In some cases, reinstitution of therapy was associated with improvement. The differences among different agents were significant with higher relapse rates seen for the anti-TNF therapies. However, withdrawal of any of the third-line therapies could be associated with disease relapse.

For pulmonary sarcoidosis, infliximab is the only third-line agent which has been shown to be more effective than placebo (28, 29). Both infliximab and adalimumab were more effective than placebo in treating chronic cutaneous sarcoidosis (41, 42). Rituximab and RCI have been shown to be effective in open label, prospective trials (17, 43). The current study was not designed to determine effectiveness of any particular third-line regimen for treating sarcoidosis. The relatively large number of patients treated with each regimen suggests that all four agents have a role in management of advanced sarcoidosis.

While usually deemed initially effective, the four most commonly used third-line treatments for sarcoidosis had a defined drug survival time. While infliximab was associated with the shortest drug survival, each drug was discontinued in a significant proportion of patients. This highlights the need to continue to develop alternative third-line treatments for sarcoidosis patients. While only fifteen percent of patients seen in our clinic required such therapy, this group represents the more advanced patient who may experience increased morbidity and mortality. These patients may have significantly higher medical costs than the average patient with sarcoidosis. This cost includes not just medication administration but also underlying disease severity and complications of therapy (44).

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