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SYSTEMATIC REVIEW AND META-ANALYSIS

Corticosteroid and Immunosuppressant Therapy for Cardiac Sarcoidosis: A Systematic Review

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BACKGROUND: Corticosteroid therapy for the treatment of clinically manifest cardiac sarcoidosis is generally recommended. Our group previously systematically reviewed the data in 2013; since then, there has been increasing quality and quantity of data and also interest in nonsteroid agents.

METHODS AND RESULTS: Studies were identified from MEDLINE, EMBASE, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, and the National Institutes of Health ClinicalTrials.gov database. The quality of included articles was rated using Scottish Intercollegiate Guidelines Network 50. Outcomes examined were atrioventricular conduction, left ventricular function, ventricular arrhythmias, and mortality. A total of 3527 references were retrieved, and 34 publications met the inclusion criteria. There were no randomized trials, and only 2 studies were rated good quality. In the 34 reports (total of 1297 patients), 1125 patients received corticosteroids, 235 received additional or other immunosuppressant therapy, and 97 patients received no therapy. There were 178 patients treated for atrioventricular conduction disease, with 76/178 (42.7%) improving. In contrast, 21 patients were not treated with corticosteroids and/or immunosuppressant therapy, and none of them improved. Therapy was associated with the prevention of deterioration in left ventricular function. A total of 8 publications reported on ventricular arrhythmia burden, and 19 reported on mortality; the data quality was too limited to draw conclusions for the latter 2 outcomes.

CONCLUSIONS: The best quality data relate to atrioventricular nodal conduction and left ventricular function recovery. In both situations, therapy with corticosteroids and/or immunosuppressant therapy were sometimes associated with positive outcomes. The data quality is too limited to draw conclusions for ventricular arrhythmias and mortality.

Key Words: cardiac sarcoidosis ■ corticosteroids ■ immunosuppression

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. Pulmonary and lymph node involvement are most common, but heart, liver, spleen, skin, eyes, phalangeal bones, parotid gland, or other organs can be affected. Approximately 5% of patients with sarcoidosis have clinically manifest cardiac involvement, and another 20% to 25% of patients have asymptomatic (ie, clinically silent) cardiac involvement (based on autopsy studies and recent data using late gadolinium-enhanced cardiac magnetic resonance technology).[1] Studies suggest an increasing prevalence of cardiac sarcoidosis (CS); however, this is most likely the result of enhanced imaging technology and/or more in-depth investigation.[2,3]

Corticosteroids for the treatment of clinically manifest CS is advocated by experts and guidelines based on very modest quality data.[4,5] Our group previously systematically reviewed the data in 2013[6]; since then,

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CLINICAL PERSPECTIVE

What Is New?

- A total of 34 publications met the inclusion criteria of the study, 1125 patients received corticosteroids, 235 received additional or other immunosuppressant therapy, and 97 patients received no therapy.

What Are the Clinical Implications?

- There were 178 patients with conduction disease treated with corticosteroid and/or immunosuppression therapy, with 76/178 (42.7%) improving. In contrast 21 patients were not treated with such therapy and none of them improved.
- Therapy was associated with the prevention of deterioration in left ventricle function; the data quality was too limited to draw conclusions regarding the other 2 outcomes: ventricular arrythmia burden and mortality.

Nonstandard Abbreviations and Acronyms

CS	cardiac sarcoidosis
FDG	F-18 fluorodeoxyglucose
IST	immunosuppressant therapy

there has been an increasing quality and quantity of data and increasing interest in other nonsteroid agents. Hence the objectives of this study were to systematically review the published data from studies on the outcomes after corticosteroid and other immunosuppressant therapies (ISTs) in patients diagnosed with CS. Specifically, we focused on atrioventricular conduction recovery, left ventricular (LV) function, ventricular arrhythmia, and mortality.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files). A literature search of electronic databases was performed by a medical librarian. The initial search was created in Medline (Ovid MEDLINE ALL from 1946 to September 11, 2018) using a combination of subject headings and keywords (Table S1). The search strategy was peer reviewed by another medical librarian using the Peer Review of Electronic Search Strategies Checklist guidelines[7] and then translated to the following databases: Embase Classic+Embase 1947 to September 11, 2018 (Ovid); Cochrane Central Register of Controlled Trials August 2018 (Ovid). The search strategy is shown in Table S1. The initial searches were run on September 12, 2018. To ensure retrieval of the most up-to-date studies before submission of the article, a second search using the same databases and search strategies was performed on October 13, 2020. A gray literature search was performed by 1 investigator (S.F.) using the search terms specified in the Table S1 and through the following databases: clinicaltrials.gov, National Institute for Health and Care Excellent, Canadian Agency for Drugs and Technologies in Health, and OpenGrey.

Inclusion criteria were (1) publications in English or translations, (2) studies reporting original outcomes in patients with CS diagnosed based on either (A) Heart Rhythm Society Expert Consensus Recommendations on Criteria for Diagnosis of CS[8] or (B) Japanese Ministry of Health and Welfare Criteria,[9] (3) patients receiving corticosteroids and/or ISTs for the treatment of CS. Exclusion criteria were studies including data from <5 patients and with <3 months of follow-up.

A total of 2 investigators (S.F., M.S.) independently reviewed all publications with regard to the inclusion and exclusion criteria. Full text of articles potentially meeting these criteria were retrieved and reviewed in detail by 2 investigators independently (S.F., M.S.), and a third investigator (D.B.) settled disagreements. The following data were retrieved from included studies: baseline patient characteristics, sample size, study design, choice of immunosuppressive agent used, and outcomes of interest. Outcomes of interest included atrioventricular conduction, LV systolic function, ventricular arrhythmia, and mortality.

Quality Rating

The Scottish Intercollegiate Guidelines Network 50[10] was used to assess the quality of each article regarding design quality and bias. Each study was assigned an overall assessment score (good, fair, poor) and given a numerical score (of 14) based on the Scottish Intercollegiate Guidelines Network 50 questionnaire.

RESULTS

Systematic Review

A total of 3527 references were retrieved (Figure); 34 published studies fulfilled the criteria for this review. There were no randomized controlled trials. Study design and inclusion and exclusion criteria are summarized in Table 1.[11–43]

Quality Rating

Quality rating using the Scottish Intercollegiate Guidelines Network 50 checklist for cohort studies is summarized in Table 1. Only 2 studies were deemed

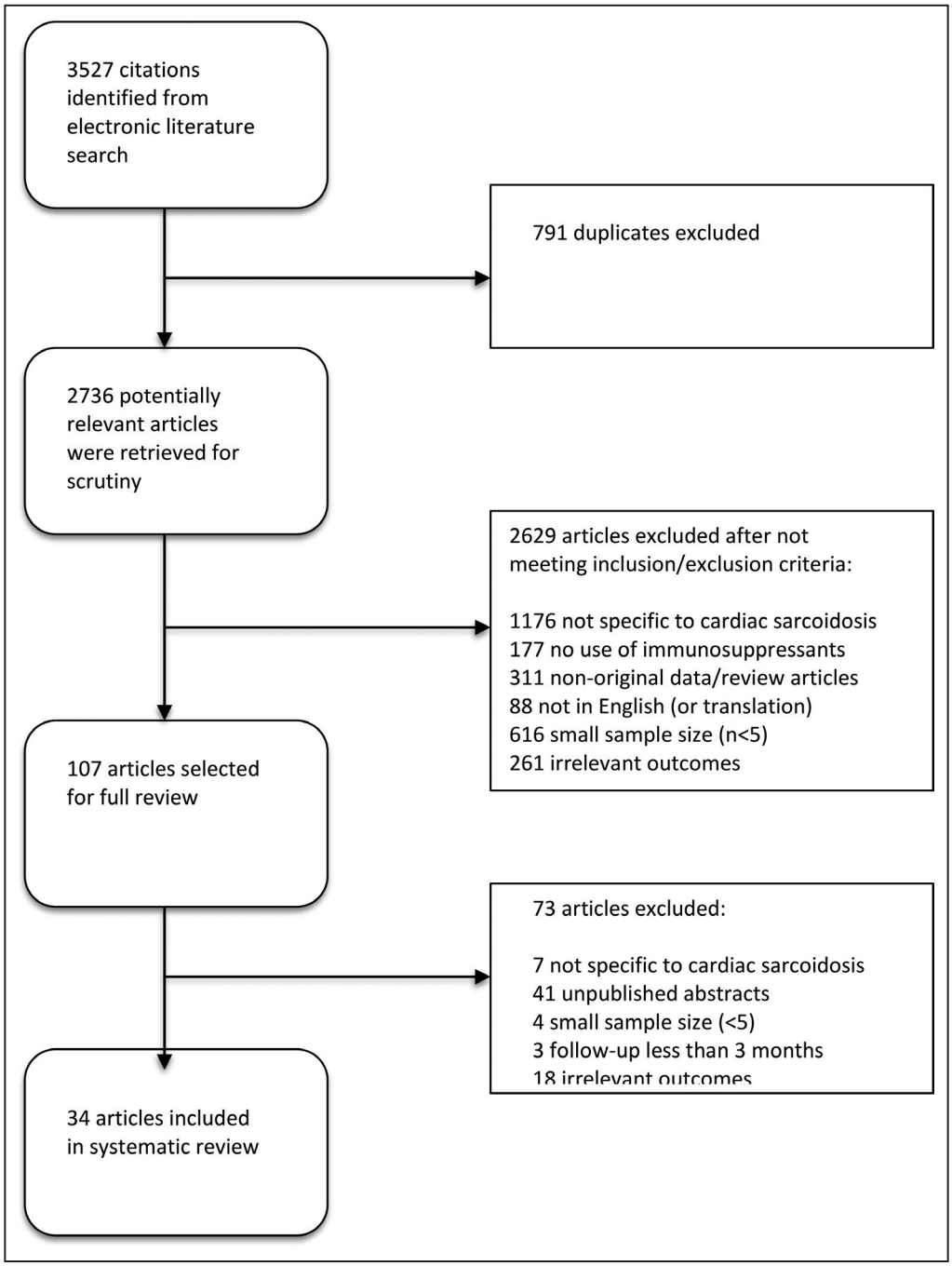

Figure. **Literature search strategy.**

to be good in quality, with 29 studies rated as fair and 3 rated as poor. The average rating was 7.0, and the highest score was 11.

Patient Demographics

The number of patients (treated and not treated), follow-up, average age, sex, and presentation are summarized in Table 2. In total, the studies included 1297 patients (1125 treated with corticosteroids, 235 treated with other ISTs, and 97 patients not treated with either). Pulmonary involvement was present in 57.9% of patients.

Corticosteroid and Other Immunosuppression Therapies

The number of patients receiving steroids, other ISTs, and no therapy is summarized in Table 2. The therapy

Table 1. Study Characteristics and Inclusion Criteria

First Author	Year	Number of Centers	Sample Size	Study Design	Inclusion Criteria	Criteria for Diagnosis of CS	Exclusion Criteria	SIGN 50 Score (of 14)	SIGN 50 Overall Assessment
Okamoto[11]	1999	Single center	5	Retrospective	Cutaneous sarcoidosis patients who developed cardiac manifestations	JMHW	None	3	–
Yazaki[12]	2001	Multicenter	95	Retrospective	CS diagnosis	JMHW	None	5	+
Kato[13]	2003	Single center	20	Retrospective	Patients with CS presenting with AVB	JMHW	LVEF <50%	6	+
Chapelon-Abric[14]	2004	Multicenter	41	Retrospective	CS diagnosis	JMHW	None	6	+
Chiu[15]	2005	Single center	43	Retrospective	CS diagnosis and treatment with steroids	JMHW	CAD, no regular follow-up	8	+
Futamatsu[16]	2006	Multicenter	21	Retrospective	CS diagnosis and treatment with steroids	JMHW	None	8	+
Banba[17]	2007	Single center	15	Retrospective	CS diagnosis and presenting with PVCs	JMHW	None	5	+
Kudoh[18]	2010	Single center	10	Prospective	CS diagnosis	JMHW	Patients already treated with steroids	3	–
Yodogawa[19]	2011	Single center	31	Retrospective	CS diagnosis and presenting with PVCs	JMHW	CAD, other cardiac disease	5	+
Kandolin[20]	2011	Single center	18	Retrospective	Age 18–55 y, presenting with AVB and diagnosed with CS or GCM	JMHW	None	7	+
Yodogawa[21]	2013	Multicenter	15	Retrospective	Patients with CS presenting with AVB	JMHW	CAD, other cardiac disease	8	+
Nagai[22]	2014	Single center	17	Prospective	Patients with CS treated with immunosuppressants	JMHW	None	11	++
Ise[23]	2014	Single center	43	Retrospective	Patients with CS who had undergone CMR	JMHW	CAD	10	+
Takaya[24]	2014	Single center	30	Retrospective	Patients with CS with positive myocardial uptake of 67 Ga on 18F-FDG-PET	JMHW	None	6	+
Takaya[25]	2015	Single center	53	Retrospective	Patients with CS with initial presentation with either AVB, CHF, or VT	JMHW	None	10	+
Kandolin[3]	2015	Multicenter	110	Retrospective	CS diagnosis	JMHW	None	6	+
Nagai[26]	2015	Single center	83	Retrospective	CS diagnosis	JMHW	CAD	6	+
Orii[27]	2015	Single center	32	Retrospective	CS diagnosis	JMHW	CAD, other cardiac disease	6	+
Nagai[28]	2016	Single center	61	Retrospective	CS diagnosis and treatment with steroids	JMHW	CAD, failure to follow-up >5 y	7	+
Segawa[29]	2016	Single center	68	Retrospective	CS diagnosis	JMHW	None	4	–
Padala[30]	2017	Single center	30	Retrospective	CS diagnosis	HRS	None	5	+

(*Continued*)

Table 1. Continued

First Author	Year	Number of Centers	Sample Size	Study Design	Inclusion Criteria	Criteria for Diagnosis of CS	Exclusion Criteria	SIGN 50 Score (of 14)	SIGN 50 Overall Assessment
Ahmadian[31]	2017	Single center	17	Retrospective	Patients with CS who had undergone serial FDG-PET	JMHW	None	5	+
Yalagudri[32]	2017	Single center	18	Retrospective	Patients with CS presenting with VT	HRS	None	8	+
Kaida[33]	2018	Single center	15	Retrospective	Patients with CS presenting with AVB	JMHW	None	7	+
Muser[34]	2018	Single center	20	Retrospective	Patients with CS presenting with refractory VT referred for catheter ablation	HRS	No FDG-PET	8	+
Fussner[35]	2018	Two centers	91	Retrospective	CS diagnosis	JMHW	None	8	+
Ballul[36]	2019	Single center	36	Retrospective	Histologically proven CS	HRS	Asymptomatic patients	10	+
Chiba[37]	2020	Single center	91	Retrospective	CS diagnosis	JMHW	None	9	+
Harper[38]	2019	Single center	36	Retrospective	CS diagnosis and infliximab initiation	JMHW	Prior infliximab	9	+
Rosenthal[39]	2019	Single center	28	Retrospective	CS diagnosis and immunosuppression, at least 2 PET studies	JMHW	<6 mo follow-up, prior immunosuppression	5	+
Koyanagawa[40]	2019	Single center	38	Retrospective	Patients with CS with PET CT and SPECT studies	JMHW	Prior corticosteroid use	7	+
Orii[41]	2020	Single center	8	Retrospective	Patients with CS presenting with AVB	HRS	No CMR on file	8	+
Medor[42]	2020	Single center	20	Prospective	Patients with CS undergoing ICD implantation	HRS	Normal FDG-PET	11	++
Gilotra[43]	2020	Single center	38	Retrospective	Patients with CS treated with TNF-α inhibitor	HRS		9	+
Total			1297						

SIGN 50 overall assessment: "++"=good, "+"=fair, "–"=poor. 18F-FDG indicates 18fluourine-flourodeoxyglucose; AVB, atrioventricular block; CAD, coronary artery disease; CHF, congestive heart failure; CMR, cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; CT, computed tomography; FDG, F18-fluorodeoxyglugose; GCM, giant cell myocarditis; HRS, Heart Rhythm Society Expert Consensus Recommendations on Criteria for Diagnosis of CS; ICD, implantable cardioverter defibrillator; JMHW, Japanese Ministry of Health and Welfare Criteria; LVEF, left ventricular ejection fraction; PET, positron emission tomography; PVC, premature ventricular contraction; SIGN, Scottish Intercollegiate Guidelines Network; SPECT, single-photon emission computed tomography; TNF, tumor necrosis factor; and VT, ventricular tachycardia.

Table 2. Patient Demographics From Selected Studies

First Author	Number of Patients	Steroids and/or Other ISTs			Men: Women	Pulmonary Involvement, N (%)	Race/Ethnicity	Mean Follow-Up, mo*	Average Age, y*	HF, N (%)	AVB, N (%)	Ventricular Arrhythmia, N (%)
		Corticosteroids	Other ISTs	None								
Okamoto[11]	5	5	0	0	1:4	3 (60)	Japanese	>24	62.2±9.3	1 (20)	3 (60)	0
Yazaki[12]	95	75	0	20	34:61	56 (75)	Japanese	68±42	51±13, 57±15	43 (47.8)	28 (37.3)	17 (18.9)
Kato[13]	20	7	0	13	1:19	19 (95)	Japanese	79.4±39.9	67.2±8.2	0	20 (100)	0
Chapelon-Abric[14]	41	39	0	2	23:18	37 (90)	73% White, 27% non-specified	58 (7–312)	38 (18–66)	17 (41.5)	9 (22.0)	1 (2.4)
Chiu[15]	43	43	0	0	16:27	11 (26)	Japanese	88±48	48±14	N/A	N/A	N/A
Futamatsu[16]	21	21	0	0	6:15	11 (52)	Japanese	48.8±38.7	56.0±11.7	N/A	N/A	14 (66.7)
Banba[17]	15	9	0	6	8:7	9 (60)	Japanese	6	53±13	N/A	10 (66.7)	7 (56.7)
Kudoh[18]	10	10	0	0	2:8	5 (50)	Japanese	6	62.8±0.5	N/A	4 (40)	3 (30)
Yodogawa[19]	31	31	0	0	6:25	21 (68)	Japanese	7.3±5.9	60±9	N/A	12 (38.7)	14 (45.3)
Kandolin[20]	18	17	0	1	2:16	6 (33)	White	38±32	48 (36–55)	N/A	18 (100)	N/A
Yodogawa[21]	15	15	0	0	2:13	12 (80)	Japanese	85.2±63.6	59.9±9.7	5 (33.3)	15 (100)	1 (6.67)
Nagai[22]	17	7	10	0	3:14	17 (100)	Japanese	87.4±73.1	70.1±5.9	4 (24)	13 (76)	N/A
Ise[23]	43	43	0	0	15:28	9 (21)	Japanese	39±19	59±10	N/A	N/A	N/A
Takaya[24]	30	30	0	0	1:20	18 (60)	Japanese	12	61±12	N/A	13 (43)	12 (40)
Takaya[25]	53	42	0	11	20:33	34 (64)	Japanese	34 (1–149)	60±13	31 (58.5)	22 (41.5)	31 (58.5)
Kandolin[3]	110	110	62	0	33:77	11 (10)	White	79 (12–303)	51±9	65 (59)	48 (45)	36 (33)
Nagai[26]	83	67	2	16	24:59	50 (60.2)	Japanese	91.2±52.8	60±12	11 (13.2)	33 (39.8)	24 (29)
Orii[27]	32	6	0	0	8:24	19 (59.4)	Japanese	26±6	64±9	N/A	15 (46.9)	8 (25)
Nagai[28]	61	61	1	0	17:44	35 (57)	Japanese	118.8 (94.8–156)	59 (52–67)	9 (15)	18 (30)	22 (36)
Segawa[29]	69	69	0	0	18:50	52 (75.4)	Japanese	66	57±11.2	N/A	29 (42)	17 (66.7)
Padala[30]	30	27	0	3	16:14	30 (100)	…	19 (7–66)	58±10	14 (47)	5 (17)	14 (47)
Ahmadian[31]	17	17	0	0	8:9	15 (88)	70% White, 30% Black	22	58.2±12	N/A	7 (41)	N/A
Yalagudri[32]	18	14	14	4	12:6	…	…	38 (10–75)	38±14	4 (22)	0	18 (100)
Kaida[33]	15	15	0	0	4:11	6 (40)	Japanese	N/A	61.3±11	2 (13)	15 (100)	3 (20)
Muser[34]	20	20	6	0	14:6	…	…	35 (20–66)	51±9	…	…	20 (100)
Fussner[35]	91	41	29	21	65:26	38 (92.7)	74% White	44 (20–77)	51 (44–61)	47 (51.6)	31 (34.1)	22 (24.2)
Ballul[36]	36	36	12	0	20:16	36 (100)	72% Black	43 (12–182)	48.5 (22–76)	13 (38.9)	12 (33.3)	9 (25)
Chiba[37]	91	91	0	0	25:66	62 (68.1)	Japanese	84	57±11	35 (38.5)	31 (34.1)	33 (36.2)

(*Continued*)

Table 2. Continued

First Author	Number of Patients	Steroids and/or Other ISTs			Men: Women	Pulmonary Involvement, N (%)	Race/Ethnicity	Mean Follow-Up, mo*	Average Age, y*	HF, N (%)	AVB, N (%)	Ventricular Arrhythmia, N (%)
		Corticosteroids	Other ISTs	None								
Harper[38]	36	32	36	0	26:10	26 (72)	78% White, 22% Black	12	46±11	6 (16.6)	7 (19.4)	8 (22.2)
Rosenthal[39]	28	27	25	0	16:12	21 (72.4)	82% White, 11% Black	149.2±18	52.2	11 (39.3)	11 (39.3)	18 (64.3)
Koyanagawa[40]	38	38	0	0	10:28	…	Japanese	34.5 (5–51.8)	63 (51–68)	N/A	N/A	N/A
Orii[41]	8	8	0	0	0:8	…	Japanese	28±6	65±5	N/A	8 (100)	N/A
Medor[42]	20	20	0	0	8:12	9 (45)	95% White	13.8±11	59.7±7.7	12 (60)	14 (70)	2 (10)
Gilotra[43]	38	33	38	0	22:16	29 (62)	43% Black, 38% White	40.4	49.9±5.9	13 (27.7)	5 (10.6)	13 (27.7)
Totals	1297	1125	235	97								

AVB indicates atrioventricular block; HF, heart failure; IST, immunosuppressant therapy; and N/A, not available.
* Data are presented as mean±SD or median (interquartile range)

protocols, doses, duration, and so on are shown in Table S2.

Outcomes: Atrioventricular Conduction Recovery

A total of 13 studies reported outcomes with respect to recovery of high-grade atrioventricular block (Table 3). In these studies, 178 patients received corticosteroids and/or other ISTs, whereas 21 did not. Of 178 patients receiving immunosuppression, 76 had atrioventricular conduction recovery (42.6%). Of the 21 patients who were not treated with immunosuppressants, none of them had atrioventricular conduction recovery (0%).

Outcomes: LV Function

The effect of corticosteroids and/or ISTs on LV function was reported in 18 studies, and the data are summarized in Table 4. Table 4 shows the results for patients with normal LV function. There was a total of 194 treated patients in 9 studies treated with immunosuppression, and in all studies, there was no significant change in LV ejection fraction (LVEF). In contrast, in the 1 study with a nontreatment group, the LVEF fell from 60.5±6.4% to 37.6±17.3% in 13 patients (mean±SD).

Table 5 shows the results for patients with mild-moderate dysfunction. There was a total of 324 treated patients in 11 studies, and in 4 studies the mean LVEF improved with treatment and in 5 studies it did not, and on 1 study there was a slight deterioration (45.2±13.6 to 40.0±12.0%; P=0.038).[42] The other article presented results stratified by the extent of baseline late gadolinium enhancement and found that patients with extensive late gadolinium enhancement did not improve and vice versa.[23] In the 1 study with a nontreatment group, LVEF decreased from 32.5% to 18.5%; there was no P value quoted.

Table 6 shows the results for patients with severe dysfunction. There was a total of 54 treated patients in 4 studies; in 2 articles, there was no change in LVEF, and in 2 articles there was a significant improvement in mean LVEF. There were data on untreated patients in 2/4 articles. In 16 patients, the mean LVEF declined from 35.2% to 18.5%.[26] In the other report, there were 2 patients who did not receive steroids. Their data is grouped with 3 other patients who received late steroids, and in the 5 patients the mean LVEF declined from 41% to 27%.[30]

Outcomes: Ventricular Tachyarrhythmia

The effect of corticosteroids and/or ISTs on ventricular arrhythmia recurrence was examined in 8 articles (5 articles reported on sustained arrhythmia, and 3 articles reported on premature ventricular contraction [PVC] burden and nonsustained ventricular tachyarrhythmia (VT), as outlined in Tables 7 and 8, respectively[17,32]). The data quality is too limited to draw conclusions.

Table 3. Studies Investigating the Effect of Immunosuppression on Atrioventricular Recovery in Patients With CS Presenting With AVB

First Author	Number of Patients on Steroids and/or Other ISTs	Atrioventricular Recovery, N (%)	Number of Patients on No Immunosuppressants	Atrioventricular Recovery, N (%)
Okamoto[11]	3	3 (100)	0	…
Kato[13]	7	4 (57.1)	13	0 (0)
Chapelon-Abric[14]	9	7 (77.7)	0	…
Banba[17]	9	5 (55.6)	2	0 (0)
Yodogawa[19]	12	4 (33.3)	0	…
Kandolin[20]	17	4 (23.5)	1	0 (0)
Yodogawa[21]	15	7 (46.7)		
Takaya[25]	17	7 (41.1)		
Kandolin[3]	35	7 (20)		
Orii[27]	10	6 (60)	5	0/5 (0)
Padala[30]	5	2 (40)		
Chiba[37]	31	12 (38.7)	0	
Orii[41]	8	5 (62.5)	0	
Total	178	76 (42.6)	21	0 (0)

AVB indicates atrioventricular block; and CS, cardiac sarcoidosis.

Outcomes: Mortality

The mortality data are summarized in Table 9. A total of 19 studies had data on mortality (713 patients treated with corticosteroids and/or ISTs, and 61 patients did not receive treatment). The data quality is too limited to draw conclusions.

DISCUSSION

This review synthesizes data from 1297 patients from 34 articles and extends the findings of our previous work published in 2013, which included 303 patients from 10 articles.[6] Our main observations are that the best-quality data relates to atrioventricular nodal conduction and LV function recovery. In both situations, therapy with corticosteroids and/or ISTs were sometimes associated with positive outcomes. The data quality is too limited to draw conclusions for ventricular arrhythmias and mortality.

There were 178 patients with treated atrioventricular conduction disease, with 76 (42.6%) recovering from atrioventricular conduction; in contrast, 21 patients were not treated, and none improved. However, atrioventricular nodal recovery is unpredictable and can be transient and hence our findings support the recommendations in the 2014 Heart Rhythm Society document on the management of arrhythmias associated with CS.[8] Specifically, all patients with CS and advanced conduction system disease should have a pacemaker implanted. Other accumulating data have shown that these patients, even with normal left ventricular function at presentation, have a significant risk of sudden cardiac death in follow-up, and hence guidelines and expert opinion recommend implantable cardioverter defibrillator implantation.[25,44,45]

The data on LV function suggest therapy with steroids and/or ISTs is associated with preservation of LV function in patients with normal or near normal function at presentation. This is based on data from 194 patients; however, there were only 13 untreated patients, all from the same study. In these patients, the mean LVEF declined without treatment, from 60.5±6.4% to 37.6±17.3%.[13] The data on LV function recovery in patients with initial dysfunction are not conclusive. There was a total of 324 treated patients in 11 studies, and in 4 patients the mean LVEF improved with treatment, in 5 patients it did not, and in 1 patient there was a slight deterioration (45.2±13.6% to 40.0±12.0%; P=0.038).[42] In the final article, the data showed that patients with less late gadolinium enhancement did improve.[23] In the subgroup of patients with severe baseline LV dysfunction, in 2 articles there was no change in LVEF and in 2 articles there was significant improvement in mean LVEF. It should also be noted that there were data on untreated patients in only 2 articles. In 16 patients, the mean LVEF declined from 35.2±15.8% to 18.5%.[26] In the other report, there were 2 patients who did not receive steroids. Their data is grouped with 3 other patients who received late steroids, and in the 5 patients the mean LVEF declined from 41% to 27%.[30]

The interpretation of these observations on LV function is complicated as most patients were simultaneously treated with standard heart failure medications and with cardiac resynchronization therapy in some patients. Also, in many articles the findings were not interpreted in the context of extent of active inflammation and scarring, and the timing of reevaluation

Table 4. Studies Investigating the Effect of Immunosuppression on LV Function in Patients With CS With Initially Normal LV Function

First Author	Steroids and/or Other ISTs			No Immunosuppressants			Comments
	Number of Patients	LVEF Before Treatment	LVEF After Treatment	Number of Patients	LVEF Before Treatment	LVEF After Treatment	
Kato[13]	7	66.7±6.5%	62.1±4.4%	13	60.5±6.4%	37.6±17.3%	
Chiu[15]	22	69±7%	69±5%	0	…	…	No difference (P=0.277)
Yodogawa[19]	17	52.4±13.2%	55.1±12.2%	0	…	…	Trend to improvement (P=0.06)
Nagai[22]	7	52.3±6.07%	45.7±15.5%	0	…	…	P=ns
Kandolin[3]	44	56.8±5.6	54.9±7.6	0	…	…	No difference (P=0.145)
Padala[30]	14	56%	54%	0			No difference (P=0.26)
Ahmadian[31]	17	53.18±20	54.6±14	0			No difference (P=0.682)
Rosenthal[39]	28	53.4±12.3%	48.7±11.4%	0			No difference (P=0.14)
Koyanagawa[40]	38	64.7 (58.4–72.1) %	67.0 (58.2–71.1%)	0			No difference (P=0.65)
Total	194			13			

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; IST, immunosuppressant therapy; LV, left ventricular; LVEF, left ventricular ejection fraction; and ns, nonsignificant.

of ventricular function was rarely guided by imaging, demonstrating suppression of inflammation. The sum of the data suggest that therapy is associated with prevention of deterioration of LV function. There are insufficient data to answer the additional clinical question of whether immunosuppression improves ventricular function. Both are important goals; however, a better understanding would help inform clinician and patient shared decision making and expectations, and higher quality data are required to investigate this question.

The data related to ventricular arrhythmia are too limited to conclude whether steroids and ISTs are helpful in the management of ventricular arrhythmia. We found the following 2 main issues with the current literature: (1) most patients were treated simultaneously with a combination of corticosteroids and/or ISTs and antiarrhythmic drugs and sometimes ablation and (2) few studies examined outcomes related to the disease activity with gallium or F-18 fluorodeoxyglucose (FDG) positron emission tomography scanning. It is likely that macro reentry phenomena around areas of fibrosis is the most frequent mechanism of ventricular arrhythmia in CS.[46,47] It is also possible that inflammation may play a role in initiating reentry with ventricular ectopy in patients with CS or by slowing conduction in diseased tissue.

Several studies have reported on the recurrence of sustained VT after therapy. Futamatsu et al reported on 7 patients with VT (6 sustained and 1 nonsustained).[16] Following corticosteroid therapy, 6 patients had no recurrence of VT; however, 5 of the 7 patients were also started on amiodarone therapy. Padala et al[30] investigated 14 patients with VT; early initiation of corticosteroid therapy was associated with no VT recurrence in 8/11 patients, and in contrast 3 patients with VT who did not receive early corticosteroid therapy all had recurrent arrhythmia.[30] Segawa et al examined 17 patients, and 12 of 17 patients experienced recurrent VT after initiation of corticosteroid therapy.[29] Finally, Muser et al[34] published findings on 20 patients who underwent ablation for VT after immunosuppression. There was a higher recurrence rate post-VT ablation in patients who did not have a reduction in FDG uptake on serial positron emission tomography scans.

There are 3 publications that looked at PVC burden before and after steroids. Banba et al studied 9 patients with CS and positive gallium scans and all patients had 24-hour Holter monitors done before and after treatment.[17] The average PVC burden increased from 3582±5456/day to 4673±6167/day (no P value stated).[9] Also, PVC Lown grade was unchanged in 5 patients but worsened in 4 patients (from grade 0 to grade 1 in 2 patients and from grade 1 to grade 2 in 2 patients).

[9] Yodogawa et al reported on a cohort of 31 patients who also had 24-hour Holter monitoring before

Table 5. Studies Investigating the Effect of Immunosuppression on LV Function in Patients With CS With Initially Mild-Moderate LV Dysfunction

First Author	Steroids and/or Other ISTs			No Immunosuppressants			Comments
	Number of Patients	LVEF Before Treatment	LVEF After Treatment	Number of Patients	LVEF Before Treatment	LVEF After Treatment	
Padala[30]	9	25%	46%	2 (3)*	41%	37%	*P*<0.001 for steroids
Chiu[15]	10	40±10%	51±12%	0	…	…	Increase in EF (*P*=0.008)
Kudoh[18]	10	34.6±12%	48.8±18.6%	0	…	…	Increase in EF (*P*<0.001)
Nagai[22]	10	49.7±6.9%	53.6±13.3%	0	…	…	*P*=ns
Ise,[23] small-extent LGE	21	45±11%	50±10%	0	…	…	Increase in EF (*P*<0.001)
Ise,[23] large-extent LGE	22	36±6%	35±8%	0	…	…	No difference (*P*=0.213)
Takaya[24]	30	43±15%	47±16%	0	…	…	No difference (*P*=0.367)
Kandolin[3]	36	40.9±4.1	40.8±7.6	0	…	…	No difference (*P*=0.979)
Nagai[26]	67	35.9±14.4	43.8%*	16	35.2±15.8%	18.5%*	*P*=0.03 for difference between groups
Kaida[33]	15	46.3±14.3	47.9±10.6	0			No difference
Harper[38]	36	41% (32–55)	41% (32–54)	0			No difference (*P*=0.43)
Medor[42]	20	45.2±13.6%	40.0±12.0%	0			Decrease in EF (*P*=0.038)
Gilotra[43]	38	45.0±16.5%	47.0±15.0%	0			No difference (*P*=0.10)
Total	324			18			

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; EF, ejection fraction; IST, immunosuppressant therapy; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; and ns, nonsignificant.

* A total of 2 patients did not receive steroids, and 3 patients had delayed steroids.

† Extracted from data provided in the article.

and after therapy and found no change in PVC (from 3098±5902 to 3024±8081; *P*=0.89) or nonsustained VT burden.[19] The third article used implantable cardioverter defibrillator diagnostics to assess the relationship between nonsustained VT and premature ventricular complex PVC burden in patients with newly diagnosed clinically manifest CS.[42] All 20 patients were corticosteroid responders based on serial FDG uptake. Patients with untreated CS had an average of 496.4±879.1 PVCs per day. After treatment with corticosteroids, the average PVC count increased to 1590.1±2362.2 per day (*P*=0.008). There was also a statistically significant increase in episodes of nonsustained VT before and after treatment with corticosteroids (*P*=0.017). Overall, 18 of 20 patients (90%) had an increase in PVC burden after corticosteroid initiation.

The Heart Rhythm Society consensus document recommended a stepwise approach to ventricular arrhythmia management.[8] The first suggested step is treatment with immunosuppression if there is evidence of active inflammation. Antiarrhythmic medications are often started at the same time, with catheter ablation considered if VT cannot be controlled. Yalagudri et al examined this approach and found that patients with VT in the scar phase (ie, with no inflammation) responded well to antiarrhythmic drugs and ablation.[32] A total of 14 patients had abnormal cardiac FDG uptake

Table 6. Studies Investigating the Effect of Immunosuppression on LV Function in Patients With CS With Initially Severe LV Dysfunction

First Author	Steroids and/or Other ISTs			No Immunosuppressants			Comments
Chiu[15] EF <30%	11	22±7%	19±5%	0	…	…	No difference (*P*=0.082)
Yodogawa[19] EF <30%	14	26.2±5.5%	26.5±7.5%	0	…	…	No difference (*P*=0.77)
Kandolin[3] EF <35%	22	27.9±4.1	34.1±8.3	0	…	…	Increase in EF (*P*=0.005)
Kaida[33] EF <30%	7	20%	43%	0	…	…	Increase in EF (*P*<0.001)
Total	54			0			

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; EF, ejection fraction; IST, immunosuppressant therapy; and LV, left ventricular.

Table 7. Studies Evaluating the Effect of Immunosuppression on Recurrence of Sustained Ventricular Arrhythmia in Patients With CS

Year	First Author	Follow-Up, mo	End Points	Number of Patients Treated With Corticosteroids and/or Other ISTs	Arrhythmia Recurrence, N (%)	Number of Patients Not Treated With Immunosuppressants	Arrhythmia Recurrence	Comments
2006	Futamatsu[16]	48.8±38.7	Sustained VT/VF	7	1/7 (14)	0		5 of 6 patients with no recurrence were also started in amiodarone
2016	Segawa[29]	66	Sustained VT/VF	17	12/17 (71)	0		Presteroid VT was an independent predictor—7.64 (3.05–19.14)—of poststeroid VT
2017	Padala[30]	19	Sustained VT/VF	11	3/11 (33)	3	3/3	
2017	Yalagudri[32]	38	Sustained VT/VF	14†	4/14 (36)	4	0/4 (all treated with ablation)	
2018	Muser[34]	35 (20–66)	Sustained VT/VF	20†	12 (60)	0		All patients also had ablation; patients stratified to PET responders and nonresponders. Responders: 2/9 (22%) had ventricular arrhythmia recurrence. Nonresponders: 10/11 (91%) had ventricular arrhythmia recurrence.
Total				69		7		

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; IST, immunosuppressant therapy; PET, positron emission tomography; VF, ventricular fibrillation; and VT, ventricular tachycardia.

* All studies used corticosteroid monotherapy for immunosuppression except Yalagudri et al, where all 14 patients were treated with methotrexate and corticosteroid combinations.[32] In Muser et al, 14 patients were treated with corticosteroid monotherapy and 6 patients received both corticosteroids and methotrexate.[34]

Table 8. Studies Evaluating the Effect of Immunosuppression on PVC Burden and NSVT in Patients With CS

Year	First Author	Follow-Up, mo	End Points	Number of Patients Treated With Corticosteroids and/or Other ISTs	Arrhythmia Recurrence	Number of Patients Not Treated With Immunosuppressants	Arrhythmia Recurrence	Comments
2007	Banba[17]		PVC burden	9	No change in PVC burden before and after steroids	9		All patients had positive gallium scan before initiation of steroids
2011	Yodogawa[19]	7.3±5.9	NSVT or PVC burden	31	No change in PVC burden or NSVT prevalence	31		
2020	Medor[42]	13.1±11	NSVT or PVC burden	20	See comments	20	See comment	Significant increase in both end points after corticosteroids (for NSVT P=0.017, for PVC P=0.008)
Total				60		60		

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; IST, immunosuppressant therapy; NSVT, nonsustained ventricular tachycardia; and PVC, premature ventricular contraction.

on positron emission tomography and were initially treated with immunosuppression therapy. In the inflammatory group, 4 patients had a recurrence of VT during follow-up, and 3 were found to have disease reactivation. Intensified immunosuppression suppressed VT in all 3 patients, and in the other patient VT recurrence was found to be scar related and was successfully treated with ablation.[32] These data are encouraging but require validation in other centers with larger numbers of patients.

The quantity and quality of the data on mortality has improved since the last systematic review; however, it is still too limited to comment on whether therapy improves prognosis; indeed, the question is unlikely to be answered. The most important conclusion is the generally improved prognosis in more recent studies. This is based on the information from the articles in this review and others (which did not report on steroids or ISTs). For example, Yazaki et al reported that patients with depressed LVEF had a 10-year survival rate of 27%.[12] Similarly, Chiu et al found the survival rate was 91% after 1 year, 57% after 5 years, and 19% after 10 years in patients with severe dysfunction (LVEF <30%).[15] However, it should be noted that these data were published in 2001[12] and 2005.[15] In the current era of heart failure therapy, including heart transplantation and mechanical circulatory support, deaths from heart failure have become rare, and the majority of fatalities are attributed to ventricular arrhythmias. In a recent Finnish nationwide study, 10-year cardiac survival was 92.5% in 102 patients.[3] Other recent studies have also shown a much-improved prognosis in the current era.[48,49]

Our review found 97 patients treated with nonsteroid therapy (ie, other ISTs); the outcomes were generally not stratified by therapy, and hence it is not possible to draw many conclusions. Methotrexate was the most frequently used, and cyclophosphamide, cyclosporin, hydroxychloroquine, and azathioprine were also used. There has been recent interest in tumor necrosis factor inhibitors (infliximab, adalimumab) for second-line or third-line therapy for CS, and 3 publications with a total 93 treated patients met the criteria for inclusion in this systematic review.[38,39,43] The studies reported very similar findings; there were significant reductions in steroid dose and FDG uptake, but no change in other end points, including LVEF,[38,39,43] atrioventricular nodal function,[43] and VT burden.[38] A total of 2 studies found an important risk of serious infection: 14%[38] and 21%.[43] These studies highlight the need for more information specifically related to the use of the tumor necrosis factor inhibitors in the treatment of CS and in general as to the goals of care in CS therapy (eg, should we aim for clinical stability or clinical stability+complete suppression of all cardiac FDG uptake).

Table 9. Studies Investigating the Effect of Immunosuppression on Mortality in Patients With CS

Year	First Author	Follow-Up, mo	Steroids and/or Other ISTs		No Immunosuppressants	
			Number of Patients	Mortality, N (%)	Number of Patients	Mortality, N (%)
1999	Okamoto[11]	>24	5	0 (0)	0	…
2001	Yazaki[12]	68±42	75	29 (39)	20	20 (100)
2003	Kato[13]	79.4±39.9	7	0 (0)	13	2 (15.4)
2005	Chiu[15]	88±48	43	7 (16)	0	…
2006	Futamatsu[16]	48.8±38.7	21	0 (0)	0	…
2007	Banba[17]	6	9	0 (0)	6	N/A
2010	Kudoh[18]	6	10	0 (0)	0	…
2011	Kandolin[20]	48 (1–123)	17	2 (11.8)	1	0 (0)
2011	Yodogawa[19]	7.3±5.9	31	0 (0)	0	…
2013	Yodogawa[21]	85.2±63.6	15	1 (6.7)	0	…
2014	Ise[23]	39±19	43	6 (14)	0	…
2015	Kandolin[3]	79.2	102	14 (13.7)	0	
2015	Takaya[25]	34 (1–149)	42	20 (47.6)	0	
2018	Muser[34]	35 (20–66)	20	1 (5)	0	
2018	Fussner[35]	44 (20–77)	70	5 (6.8)	21	1 (4.8)
2019	Ballul[36]	43 (12–182.4)	36	3 (8.3)	0	
2020	Chiba[37]	84	91	4 (4.4)	0	
2019	Koyanagawa[40]	34.6 (5.0–51.8)	38	3 (7.9)	0	
2020	Gilotra[43]	40.4	38	0 (0)	0	
Total			713		61	

All continuous data are presented as mean±SD or median (interquartile range). CS indicates cardiac sarcoidosis; IST, immunosuppressant therapy; and N/A, not available.

Limitations

There are significant limitations to the data. There were no randomized controlled trials, and all of the studies were rated as being poor or fair quality. Most important, there were a very limited number of nontreated patients. Treatment regimens were also variable, and outcomes were not stratified by therapy subtype. Some studies had a short follow-up duration of <1 year, making it difficult to comment on the durability of corticosteroid response.

CONCLUSIONS

Our systematic review identified 34 articles reporting outcomes following steroid therapy and IST. There were no randomized trials. Treatment protocols and outcomes were not standardized, and there were a limited number of nontreated patients. The best data relate to atrioventricular conduction and LV systolic function, and therapy appears to be beneficial in some patients. In both situations, therapy with corticosteroids and/or ISTs were sometimes associated with positive outcomes. The data quality is too limited to draw conclusions for ventricular arrhythmias and mortality. However, recent data suggest that the prognosis is generally much improved compared with older studies. There is a need for large, multicenter prospective registries and trials in this patient population. Higher quality evidence is needed and should be forthcoming from ongoing studies, including the CHASM CS-RCT (Canadian/Japanese/US/European Cardiac Sarcoidosis multicenter randomized controlled trial).[50]

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2
References 3, 11–43

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SUPPLEMENTAL MATERIAL

Table S1. Details of search.

#	Searches
1	sarcoid*.mp.
2	exp Heart Diseases/
3	(cardiomyopath* or myocardiopath*).tw,kf.
4	(cardiac or cardio*).tw,kf,hw.
5	myocardial.tw,kf,hw.
6	heart.tw,kf,hw.
7	or/2-6
8	1 and 7
9	Granuloma/
10	Heart/
11	Myocardium/
12	Myocarditis/
13	or/10-12
14	9 and 13
15	(granuloma* adj3 (myocard* or cardiac or heart)).tw,kf.
16	8 or 14 or 15
17	adrenal cortex hormones/ or exp glucocorticoids/ or exp hydroxycorticosteroids/
18	(adrenal cortex hormone? or adrenal cortical hormone? or adrenocortical hormone? or adrenocorticosteroid? or cortico* or steroid*).tw,kf,rn.
19	glucocortico*.tw,kf,rn.
20	(glycocorticoid* or glycocorticosteroid*).tw,kf,rn.
21	mineralocorticoid*.tw,kf,rn.
22	(beclomet?asone or KGZ1SLC28Z).tw,kf,rn.
23	(betamethasone or 9842X06Q6M or 9IFA5XM7R2).tw,kf,rn.
24	(budesonide or Q3OKS62Q6X).tw,kf,rn.
25	(clobetasol or ADN79D536H).tw,kf,rn.
26	(desoximetasone or 4E07GXB7AU).tw,kf,rn.
27	(dexamethasone or 7S5I7G3JQL or 8LGC0BOA71).tw,kf,rn.

28	(diflucortolone or K253365DXI).tw,kf,rn.
29	(flumethasone or LR3CD8SX89).tw,kf,rn.
30	(fluocinolone Acetonide or 0CD5FD6S2M).tw,kf,rn.
31	(fluocinonide or 2W4A77YPAN).tw,kf,rn.
32	(Fluocortolone or 65VXC1MH0J).tw,kf,rn.
33	(Fluorometholone or SV0CSG527L).tw,kf,rn.
34	(Fluprednisolone or 9H05937G3X).tw,kf,rn.
35	(Flurandrenolone or 8EUL29XUQT).tw,kf,rn.
36	(Fluticasone adj2 salmeterol).tw,kf.
37	(Melengestrol Acetate or 4W5HDS3936).tw,kf,rn.
38	(Methylprednisolone or X4W7ZR7023 or 5GMR90S4KN).tw,kf,rn.
39	(Paramethasone or VFC6ZX3584).tw,kf,rn.
40	(Prednisolone or 9PHQ9Y1OLM).tw,kf,rn.
41	(Prednisone or VB0R961HZT).tw,kf,rn.
42	(Triamcinolone or 1ZK20VI6TY or F446C597KA).tw,kf,rn.
43	hydroxycorticoster*.tw,kf,rn.
44	(aldosterone or 4964P6T9RB).tw,kf,rn.
45	(Hydrocortisone or WI4X0X7BPJ).tw,kf,rn.
46	(Tetrahydrocortisol or 7P2O6MFN8O).tw,kf,rn.
47	(cortodoxone or WDT5SLP0HQ).tw,kf,rn.
48	(Tetrahydrocortisone or 5HF9TM2D15).tw,kf,rn.
49	(Cortisone or V27W9254FZ).tw,kf,rn.
50	(Desoxycorticosterone or 40GP35YQ49 or 6E0A168OB8).tw,kf,rn.
51	Hydroxydesoxycorticosterone.tw,kf,rn.
52	(pregnenolone or 73R90F7MQ8).tw,kf,rn.
53	(Hydroxypregnenolone or 77ME40334S).tw,kf,rn.
54	exp Immunosuppressive Agents/
55	(Immunosuppressive* or immuno suppressive* or immunosuppressant* or immuno suppressant* or immunesuppressant* or immune suppressant* or immunodepressant* or immuno depressant* or

	immunodepressive* or immuno depressive* or immunosuppressor* or immuno suppressor* or immune suppressor* or immunesuppressor*).tw,kf,rn.
56	(Abatacept or 7D0YB67S97).tw,kf,rn.
57	(Antilymphocyte Serum or D7RD81HE4W).tw,kf,rn.
58	(Azaserine or 87299V3Q9W).tw,kf,rn.
59	(Azathioprine or MRK240IY2L).tw,kf,rn.
60	(Busulfan or G1LN9045DK).tw,kf,rn.
61	(Certolizumab Pegol or UMD07X179E).tw,kf,rn.
62	(Cladribine or 47M74X9YT5).tw,kf,rn.
63	(Coformycin or E49510ZL0H).tw,kf,rn.
64	(Cyclophosphamide or 6UXW23996M).tw,kf,rn.
65	(Cyclosporine or 83HN0GTJ6D).tw,kf,rn.
66	Cyclosporins.tw,kf,rn.
67	(Cytarabine or 04079A1RDZ).tw,kf,rn.
68	(Dimethyl Fumarate or FO2303MNI2).tw,kf,rn.
69	(Ellipticines or 117VLW7484).tw,kf,rn.
70	(Etanercept or OP401G7OJC).tw,kf,rn.
71	(Everolimus or 9HW64Q8G6G).tw,kf,rn.
72	(Fingolimod Hydrochloride or G926EC510T).tw,kf,rn.
73	(Fluorouracil or U3P01618RT).tw,kf,rn.
74	(Glatiramer Acetate or 5M691HL4BO).tw,kf,rn.
75	(Gliotoxin or 5L648PH06K).tw,kf,rn.
76	(Mercaptopurine or PKK6MUZ20G).tw,kf,rn.
77	(Methotrexate or YL5FZ2Y5U1).tw,kf,rn.
78	(Muromonab-CD3 or JGA39ICE2V).tw,kf,rn.
79	(Sirolimus or W36ZG6FT64).tw,kf,rn.
80	(Tacrolimus or Y5L2157C4J).tw,kf,rn.
81	(Thalidomide or 4Z8R6ORS6L).tw,kf,rn.
82	(Thioinosine or 46S541971T).tw,kf,rn.

83	(Triamcinolone Acetonide or F446C597KA).tw,kf,rn.
84	antibodies, monoclonal/ or exp antibodies, monoclonal, humanized/ or infliximab/
85	((monoclonal or clonal or hybridoma) adj (antibody or antibodies)).tw,kf.
86	(Adalimumab or FYS6T7F842).tw,kf,rn.
87	(Alemtuzumab or 3A189DH42V).tw,kf,rn.
88	(Bevacizumab or 2S9ZZM9Q9V).tw,kf,rn.
89	(Cetuximab or PQX0D8J21J).tw,kf,rn.
90	(Denosumab or 4EQZ6YO2HI).tw,kf,rn.
91	(Ipilimumab or 6T8C155666).tw,kf,rn.
92	(Natalizumab or 3JB47N2Q2P).tw,kf,rn.
93	(Omalizumab or 2P471X1Z11).tw,kf,rn.
94	(Palivizumab or DQ448MW7KS).tw,kf,rn.
95	(Ranibizumab or ZL1R02VT79).tw,kf,rn.
96	(Trastuzumab or P188ANX8CK).tw,kf,rn.
97	(Ustekinumab or FU77B4U5Z0).tw,kf,rn.
98	(Leflunomide or G162GK9U4W).tw,kf,rn.
99	Mycophenolic Acid/
100	(Mycophenolate or HU9DX48N0T).tw,kf,rn.
101	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
102	(Anti TNF or anti tumo?r necrosis factor).tw,kf.
103	((tumo?r necrosis factor or TNF) adj2 (inhibitor? or antagonist? or antibody or antibodies)).tw,kf.
104	tumor necrosis factor antibody.rn.
105	(bleselumab or AS3AZ5R46K).tw,kf,rn.
106	(efizonerimod alfa or 1MH7C2X8KE).tw,kf,rn.
107	(pegilodecakin or 5Z9850I25F).tw,kf,rn.
108	(Selicrelumab or 0O39RGI33V).tw,kf,rn.
109	(Remtolumab or 1V8WRH3RVX).tw,kf,rn.
110	(Tavolixizumab or 4LU9B48U4D).tw,kf,rn.
111	(tibulizumab or 42HQ15W1ZF).tw,kf,rn.

112	(Myeloablative adj (agonist? or agent?)).tw,kf.
113	(Melphalan or Q41OR9510P).tw,kf,rn.
114	(Thiotepa or 905Z5W3GKH).tw,kf,rn.
115	chloroquine/ or hydroxychloroquine/
116	(chloroquine or 886U3H6UFF).tw,kf,rn.
117	(hydroxychloroquine or 4QWG6N8QKH).tw,kf,rn.
118	or/17-117
119	16 and 118
120	animals/ not humans.sh.
121	119 not 120
122	(comment or editorial or interview or news).pt.
123	121 not 122
124	123 use medall
125	sarcoid*.mp.
126	exp Heart Disease/
127	(cardiomyopath* or myocardiopath*).tw,kw.
128	(cardiac or cardio*).tw,kw,hw.
129	myocardial.tw,kw,hw.
130	heart.tw,kw,hw.
131	or/126-130
132	125 and 131
133	Granuloma/
134	Heart/
135	Cardiac Muscle/
136	Myocarditis/
137	or/134-136
138	133 and 137
139	(granuloma* adj3 (myocard* or cardiac or heart)).tw,kw.
140	132 or 138 or 139

141	exp corticosteroid/
142	(adrenal cortex hormone? or adrenal cortical hormone? or adrenocortical hormone? or adrenocorticosteroid? or cortico* or steroid*).tw,kw,rn.
143	glucocortico*.tw,kw,rn.
144	(glycocorticoid* or glycocorticosteroid*).tw,kw,rn.
145	mineralocorticoid*.tw,kw,rn.
146	(beclomet?asone or 4419-39-0).tw,kw,rn.
147	(betamethasone or 378-44-9 or 2152-44-5).tw,kw,rn.
148	(budesonide or 51333-22-3).tw,kw,rn.
149	(clobetasol or 25122-41-2).tw,kw,rn.
150	(desoximetasone or 382-67-2).tw,kw,rn.
151	(dexamethasone or 50-02-2 or 2265-64-7).tw,kw,rn.
152	(diflucortolone or 2607-06-9).tw,kw,rn.
153	(flumethasone or 2135-17-3).tw,kw,rn.
154	(fluocinolone Acetonide or 67-73-2).tw,kw,rn.
155	(fluocinonide or 356-12-7).tw,kw,rn.
156	(Fluocortolone or 152-97-6).tw,kw,rn.
157	(Fluorometholone or 426-13-1).tw,kw,rn.
158	(Fluprednisolone or 53-34-9).tw,kw,rn.
159	(Flurandrenolone or 1524-88-5).tw,kw,rn.
160	(Fluticasone adj2 salmeterol).tw,kw.
161	(Melengestrol Acetate or 2919-66-6).tw,kw,rn.
162	(Methylprednisolone or 83-43-2 or 2921-57-5).tw,kw,rn.
163	(Paramethasone or 53-33-8).tw,kw,rn.
164	(Prednisolone or 50-24-8).tw,kw,rn.
165	(Prednisone or 53-03-2).tw,kw,rn.
166	(Triamcinolone or 124-94-7 or 76-25-5).tw,kw,rn.
167	hydroxycorticoster*.tw,kw,rn.
168	(aldosterone or 52-39-1).tw,kw,rn.

169	(Hydrocortisone or 50-23-7).tw,kw,rn.
170	(Tetrahydrocortisol or 53-02-1).tw,kw,rn.
171	(cortodoxone or 152-58-9).tw,kw,rn.
172	(Tetrahydrocortisone or 53-05-4).tw,kw,rn.
173	(Cortisone or 53-06-5).tw,kw,rn.
174	(Desoxycorticosterone or 64-85-7 or 56-47-3).tw,kw,rn.
175	Hydroxydesoxycorticosterone.tw,kw,rn.
176	(pregnenolone or 145-13-1).tw,kw,rn.
177	(Hydroxypregnenolone or 387-79-1).tw,kw,rn.
178	exp Immunosuppressive Agent/
179	(Immunosuppressive* or immuno suppressive* or immunosuppressant* or immuno suppressant* or immune suppressant* or immune suppressant* or immunodepressant* or immuno depressant* or immunodepressive* or immuno depressive* or immunosuppressor* or immuno suppressor* or immune suppressor* or immunesuppressor*).tw,kw,rn.
180	(Abatacept or 332348-12-6).tw,kw,rn.
181	(Antilymphocyte Serum or 308067-60-9).tw,kw,rn.
182	(Azaserine or 115-02-6).tw,kw,rn.
183	(Azathioprine or 446-86-6).tw,kw,rn.
184	(Busulfan or 55-98-1).tw,kw,rn.
185	(Certolizumab Pegol or 428863-50-7).tw,kw,rn.
186	(Cladribine or 4291-63-8).tw,kw,rn.
187	(Coformycin or 11033-22-0).tw,kw,rn.
188	(Cyclophosphamide or 50-18-0).tw,kw,rn.
189	(Cyclosporine or 59865-13-3).tw,kw,rn.
190	Cyclosporins.tw,kw,rn.
191	(Cytarabine or 147-94-4).tw,kw,rn.
192	(Dimethyl Fumarate or 624-49-7).tw,kw,rn.
193	(Ellipticines or 519-23-3).tw,kw,rn.
194	(Etanercept or 185243-69-0).tw,kw,rn.
195	(Everolimus or 159351-69-6).tw,kw,rn.

196	(Fingolimod Hydrochloride or 162359-56-0).tw,kw,rn.
197	(Fluorouracil or 51-21-8).tw,kw,rn.
198	(Glatiramer Acetate or 147245-92-9).tw,kw,rn.
199	(Gliotoxin or 67-99-2).tw,kw,rn.
200	(Mercaptopurine or 50-44-2).tw,kw,rn.
201	(Methotrexate or 59-05-2).tw,kw,rn.
202	(Muromonab-CD3 or 140608-64-6).tw,kw,rn.
203	(Sirolimus or 53123-88-9).tw,kw,rn.
204	(Tacrolimus or 104987-11-3).tw,kw,rn.
205	(Thalidomide or 50-35-1).tw,kw,rn.
206	(Thioinosine or 574-25-4).tw,kw,rn.
207	(Triamcinolone Acetonide or 76-25-5).tw,kw,rn.
208	exp monoclonal antibody/
209	((monoclonal or clonal or hybridoma) adj (antibody or antibodies)).tw,kw.
210	(Adalimumab or 331731-18-1).tw,kw,rn.
211	(Alemtuzumab or 216503-57-0).tw,kw,rn.
212	(Bevacizumab or 216974-75-3).tw,kw,rn.
213	(Cetuximab or 205923-56-4).tw,kw,rn.
214	(Denosumab or 615258-40-7).tw,kw,rn.
215	(Ipilimumab or 477202-00-9).tw,kw,rn.
216	(Natalizumab or 189261-10-7).tw,kw,rn.
217	(Omalizumab or 242138-07-4).tw,kw,rn.
218	(Palivizumab or 188039-54-5).tw,kw,rn.
219	(Ranibizumab or 347396-82-1).tw,kw,rn.
220	(Trastuzumab or 180288-69-1).tw,kw,rn.
221	(Ustekinumab or 815610-63-0).tw,kw,rn.
222	(Leflunomide or 75706-12-6).tw,kw,rn.
223	(Mycophenolate or 24280-93-1).tw,kw,rn.
224	exp tumor necrosis factor inhibitor/

225	(Anti TNF or anti tumo?r necrosis factor).tw,kw.
226	((tumo?r necrosis factor or TNF) adj2 (inhibitor? or antagonist? or antibody or antibodies)).tw,kw.
227	tumor necrosis factor antibody/
228	tumor necrosis factor antibody.rn.
229	(bleselumab or 1453067-91-8).tw,kw,rn.
230	(efizonerimod alfa or 1635395-27-5).tw,kw,rn.
231	(pegilodecakin or 1966111-35-2).tw,kw,rn.
232	(Selicrelumab or 1622140-49-1).tw,kw,rn.
233	(Remtolumab or 1791410-27-9).tw,kw,rn.
234	(Tavolixizumab or 1635395-25-3).tw,kw,rn.
235	(Tibulizumab or 1849636-24-3).tw,kw,rn.
236	(Myeloablative adj (agonist? or agent?)).tw,kw.
237	(Melphalan or 148-82-3).tw,kw,rn.
238	(Thiotepa or 52-24-4).tw,kw,rn.
239	chloroquine/ or hydroxychloroquine/
240	(chloroquine or 54-05-7).tw,kw,rn.
241	(hydroxychloroquine or 118-42-3).tw,kw,rn.
242	or/141-241
243	140 and 242
244	exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
245	exp human/ or exp human experimentation/ or exp human experiment/
246	244 not 245
247	243 not 246
248	editorial.pt.
249	247 not 248
250	249 use emczd
251	sarcoid*.mp.
252	exp Heart Diseases/

253	(cardiomyopath* or myocardiopath*).tw,kw.
254	(cardiac or cardio*).tw,hw.
255	myocardial.tw,hw.
256	heart.tw,hw.
257	or/252-256
258	251 and 257
259	Granuloma/
260	Heart/
261	Myocardium/
262	Myocarditis/
263	or/260-262
264	259 and 263
265	(granuloma* adj3 (myocard* or cardiac or heart)).tw,kw.
266	258 or 264 or 265
267	adrenal cortex hormones/ or exp glucocorticoids/ or exp hydroxycorticosteroids/
268	(adrenal cortex hormone? or adrenal cortical hormone? or adrenocortical hormone? or adrenocorticosteroid? or cortico* or steroid*).tw,kw.
269	glucocortico*.tw,kw.
270	(glycocorticoid* or glycocorticosteroid*).tw,kw.
271	mineralocorticoid*.tw,kw.
272	beclomet?asone.tw,kw.
273	betamethasone.tw,kw.
274	budesonide.tw,kw.
275	clobetasol.tw,kw.
276	desoximetasone.tw,kw.
277	dexamethasone.tw,kw.
278	diflucortolone.tw,kw.
279	flumethasone.tw,kw.
280	fluocinolone acetonide.tw,kw.

281	fluocinonide.tw,kw.
282	Fluocortolone.tw,kw.
283	Fluorometholone.tw,kw.
284	Fluprednisolone.tw,kw.
285	Flurandrenolone.tw,kw.
286	(Fluticasone adj2 salmeterol).tw,kw.
287	Melengestrol Acetate.tw,kw.
288	Methylprednisolone.tw,kw.
289	Paramethasone.tw,kw.
290	Prednisolone.tw,kw.
291	Prednisone.tw,kw.
292	Triamcinolone.tw,kw.
293	hydroxycorticoster*.tw,kw.
294	aldosterone.tw,kw.
295	Hydrocortisone.tw,kw.
296	Tetrahydrocortisol.tw,kw.
297	cortodoxone.tw,kw.
298	Tetrahydrocortisone.tw,kw.
299	Cortisone.tw,kw.
300	Desoxycorticosterone.tw,kw.
301	Hydroxydesoxycorticosterone.tw,kw.
302	pregnenolone.tw,kw.
303	Hydroxypregnenolone.tw,kw.
304	exp Immunosuppressive Agents/
305	(Immunosuppressive* or immuno suppressive* or immunosuppressant* or immuno suppressant* or immunesuppressant* or immune suppressant* or immunodepressant* or immuno depressant* or immunodepressive* or immuno depressive* or immunosuppressor* or immuno suppressor* or immune suppressor* or immunesuppressor*).tw,kw.
306	Abatacept.tw,kw.
307	Antilymphocyte Serum.tw,kw.

308	Azaserine.tw,kw.
309	Azathioprine.tw,kw.
310	Busulfan.tw,kw.
311	Certolizumab Pegol.tw,kw.
312	Cladribine.tw,kw.
313	Coformycin.tw,kw.
314	Cyclophosphamide.tw,kw.
315	Cyclosporine.tw,kw.
316	Cyclosporins.tw,kw.
317	Cytarabine.tw,kw.
318	Dimethyl Fumarate.tw,kw.
319	Ellipticines.tw,kw.
320	Etanercept.tw,kw.
321	Everolimus.tw,kw.
322	Fingolimod Hydrochloride.tw,kw.
323	Fluorouracil.tw,kw.
324	Glatiramer Acetate.tw,kw.
325	Gliotoxin.tw,kw.
326	Mercaptopurine.tw,kw.
327	Methotrexate.tw,kw.
328	Muromonab-CD3.tw,kw.
329	Sirolimus.tw,kw.
330	Tacrolimus.tw,kw.
331	Thalidomide.tw,kw.
332	Thioinosine.tw,kw.
333	Triamcinolone Acetonide.tw,kw.
334	antibodies, monoclonal/ or exp antibodies, monoclonal, humanized/ or infliximab/
335	((monoclonal or clonal or hybridoma) adj (antibody or antibodies)).tw,kw.
336	Adalimumab.tw,kw.

337	Alemtuzumab.tw,kw.
338	Bevacizumab.tw,kw.
339	Cetuximab.tw,kw.
340	Denosumab.tw,kw.
341	Ipilimumab.tw,kw.
342	Natalizumab.tw,kw.
343	Omalizumab.tw,kw.
344	Palivizumab.tw,kw.
345	Ranibizumab.tw,kw.
346	Trastuzumab.tw,kw.
347	Ustekinumab.tw,kw.
348	Leflunomide.tw,kw.
349	Mycophenolic Acid/
350	Mycophenolate.tw,kw.
351	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
352	(Anti TNF or anti tumo?r necrosis factor).tw,kw.
353	((tumo?r necrosis factor or TNF) adj2 (inhibitor? or antagonist? or antibody or antibodies)).tw,kw.
354	bleselumab.tw,kw.
355	efizonerimod alfa.tw,kw.
356	pegilodecakin.tw,kw.
357	Selicrelumab.tw,kw.
358	Remtolumab.tw,kw.
359	Tavolixizumab.tw,kw.
360	tibulizumab.tw,kw.
361	(Myeloablative adj (agonist? or agent?)).tw,kw.
362	Melphalan.tw,kw.
363	Thiotepa.tw,kw.
364	chloroquine/ or hydroxychloroquine/
365	chloroquine.tw,kw.

366	hydroxychloroquine.tw,kw.
367	or/267-366
368	266 and 366
369	368 use cctr
370	124 or 250 or 369
371	remove duplicates from 370

Table S2. Corticosteroid and other IST Duration and Dosing Details.

First Author	Corticosteroid and other IST Regimens
Okamoto[11]	Prednisone 30-60 mg daily tapered over 3-6 months
Yazaki[12]	Patients were divided into two cohort: - High dose group (n=30) – received 40 mg daily or more - Low dose group (n = 45) – received 30 mg daily or less A maintenance dose of 5-10 mg daily was continued in majority (72/75) patients
Kato[13]	Prednisone 30-40 mg/day, tapered by 5 mg every 4 weeks until a dose of 4-10 mg/day was reached. Mean period of administration was 75.0±20.5 months.
Chapelon-Abricpe[14]	No uniform protocol Prednisone 0.25-1 mg/kg daily for 6-8 weeks gradually tapered to a maintenance dose of 5-10 mg daily. (8 patients received IV methylprednisolone at 10-15 mg/kg for 3 consecutive days due to severe cardiac or non-cardiac sarcoidosis.) Other Immunosuppressants (n=11): - Cyclophosphamide (8 times with a monthly bolus of 500–700 mg/m2) - Methotrexate (6 times with weekly intramuscular injections of 20–30 mg) - Cyclosporin (3 times with doses between 3-5 mg/kg daily giving a radioimmunologic dosage between 80 and 180 ng/mL)
Chiu[15]	Prednisolone 60 mg every other day for 2 months, which was tapered gradually to the final maintenance dose of 10 mg every other day
Futamatsu[16]	Prednisone of varying dose. Mean initial starting dose of 35.7±14.4 mg/day. Mean maintenance dose of 9.2±7.0 mg/day.
Banba[17]	Prednisone initial dose 20-30 mg per day or 50-60 mg every other day, tapered over a period of 6 to 12 months to a maintenance dose of 5-10 mg/day.
Kudoh[18]	Corticosteroids - Unspecified dosing
Yodogawa[19]	Prednisone 30 mg/day or its equivalent on alternate days, tapered over a period of 6 months to a maintenance dose of 10 mg/day.
Kandolin[20]	Corticosteroids – Unspecified dosing Other immunosuppressants (n=6): azathioprine
Yodogawa[21]	Prednisone 30 mg daily on alternate days, tapered over a period of 6 months to a maintenance dosage of 5-10 mg daily
Nagai[22]	Patients were divided into two cohorts: corticosteroids only or combination therapy (corticosteroids and methotrexate) Corticosteroids: 30-60 mg daily as the initial dose Methotrexate: 6 mg/week
Ise[23]	Prenisolone 60 mg daily on alternate days, dose tapered gradually over 6 months to maintenance dose of 10 mg daily on alternate days
Takaya[24]	Prednisone at an initial dose of 30-40 mg daily
Takaya[25]	Prednisone 30 to 40 mg daily tapered over 6-12 months to a dose of 5-10 mg daily
Kandolin[3]	Prednisone (or equivalent) at initial dose of 30-80 mg daily Other immunosuppressants (unspecified doses): azathioprine (n=50), methotrexate (n=6), mycophenolatemofetil (n=3), cyclosporine (n=2), infliximab (n=1)
Nagai[26]	Mean induction dose 29.5+/- 4.0 mg daily Other immunosuppressants: 2 patients were on another agent – unspecified agent and dose

Orii[27]	Prednisolone 30 mg daily for 4 weeks then over 8 weeks decreased to a maintenance dose of 10 mg daily
Nagai[28]	Patients were divided to two cohorts: Prednisolone continuation group (n=49) and prednisolone discontinuation group (n=21) In all patients prednisolone was started at 30 mg daily and was tapered to a minimum maintenance dose of 10 mg daily. In the discontinuation group, all immunosuppressants had been discontinued over a medial follow up of 9.9 years. Other immunosuppressants: 2 patients were on another agent – unspecified agent and dose
Segawa[29]	Prednisone 30 mg for 4 weeks then stepwise reduction by 5 mg q2weeks to 5-10 mg daily. (5 patients started at 40 mg daily, 1 patient at 10 mg daily)
Padala[30]	Prednisone (or equivalent) initiated at 30-40 daily for at least one month, tapering was individualized based on response to therapy (n=30) Other immunosuppressants: 10 patients were on other agents in combination with corticosteroids – methotrexate, hydroxychloroquine, azathioprine, infliximab, mycophenolate mofetil (dose unspecified)
Ahmadian[31]	No uniform protocol for immunosuppression but usual practice was prednisone 30-40 mg daily followed by taper to 5-10 mg daily after FDG-PET/CT evidence of efficacy.
Yalagudri[32]	Prednisolone 1mg/kg/day (maximum dose 60 mg daily) - or equivalent dose of methylprednisolone – for 8 weeks then tapered over a period of 3-4 months before stopping Other immunosuppressants: All patients in "inflammatory phase" based on FDG-PET were also started on methotrexate 7.5 mg weekly for 2 years (increased up to 20 mg weekly as tolerated)
Kaida[33]	No specified protocol
Muser[34]	All patients received prednisone (mean dose 40 mg +/- 13) 6 patients (30%) also received methotrexate as second-line therapy (mean dose 10 mg +/-3)
Fussner[35]	45% of patients were on corticosteroids. 31.9% of patients were on other immunosuppressive agents with or withot corticosteroids and 23.1 % were not on any immunosuppressants. Other immunosuppressants: mycophenolate, methotrexate, infliximab, hydroxychloroquine, azathioprine, cyclosporine, etanercept, leflunamide, pentoxyfylline, rituximab
Ballul[36]	All patients received corticosteroids at median dose of 60 mg daily [20-100 mg daily] 12 patients (33.3%) received another immunosuppressant with corticosteroids. Azathioprine 2 mg/kg/day Methotrexate 15-20 mg weekly Cyclophosphamide 0.7 mg/m2 every 4 weeks for 24 weeks
Chiba[37]	All patients received corticosteroid monotherapy at initial dose of 30-40 mg daily, tapered by 5 mg q2weeks until dose of 20 mg daily, then tapered to 6-12 months to 5-10 mg daily maintenance dose
Harper[38]	All patients received Infliximab at starting dose of 5mg/kg q4-6 weeks, titrated to 10 mg/kg

	Other immunosuppressants: corticosteroids (89%), methotrexate (69%), leflunamide (25%), azathioprine (3%), hydroxychloroquine (3%)
Rosenthal[39]	Patients were started on prednisone 40-60 mg daily, tapered gradually to a dose of 5 mg daily Methotrexate was started at a dose of 10-15 mg weekly, uptitrated to 20 mg weekly 19 patients (68%) were started on adalimumab if they had persistently active CS or intolerance to methotrexate (adalimumab dose 40 mg SC q2weeks)
Koyanagawa[40]	All patients received corticosteroid therapy. Majority of patients were started on prednisone 30 mg daily, tapered by 5 mg per week
Orii[41]	Prednisolone 30 mg daily for 4 weeks then over 8 weeks decreased to a maintenance dose of 10 mg daily
Medor[42]	Prednisone at 0.5 mg/kg daily to a maximum of 40 mg daily
Gilotra[43]	All 38 patients were started on a TNF alpha inhibitor (30 infliximab, 8 adalimumab) 33 patients also received corticosteroids.