Prednisone vs methotrexate in treatment naïve cardiac sarcoidosis

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Background. **Side effects limit the long-term use of glucocorticoids in cardiac sarcoidosis (CS), and methotrexate has gained attention as steroid sparing agent although the supporting evidence is poor. This study compared prednisone monotherapy, methotrexate monotherapy or a combination of both, in the reduction of myocardial Fluorine-18 fluorodeoxyglucose (FDG) uptake and clinical stabilization of CS patients.**

Methods and results. **In this retrospective cohort study, 61 newly diagnosed and treatment naïve CS patients commenced treatment with prednisone (N = 21), methotrexate (N = 30) or prednisone and methotrexate (N = 10) between January 2010 and December 2017. Primary outcome was metabolic response on FDG PET/CT and secondary outcomes were treatment patterns, major adverse cardiovascular events, left ventricular ejection fraction, biomarkers and side effects. At a median treatment duration of 6.2 [5.7-7.2] months, 71.4% of patients were FDG PET/CT responders, and the overall myocardial maximum standardized uptake value decreased from 6.9 [5.0-10.1] to 3.4 [2.1-4.7] ($P < 0.001$), with no significant differences between treatment groups. During 24 months of follow-up, 7 patients (33.3%; prednisone), 6 patients (20.0%; methotrexate) and 1 patient (10.0%; combination group) experienced at least one major adverse cardiovascular event ($P = 0.292$). Left ventricular ejection fraction was preserved in all treatment groups.**

Roeland Vis and Harold Mathijssen have contributed equally to this work and are co-first authors.

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Conclusions. **Significant suppression of cardiac FDG uptake occurred in CS patients after 6 months of prednisone, methotrexate or combination therapy. There were no significant differences in clinical outcomes during follow-up. These results warrant further investigation of methotrexate treatment in CS patients. (J Nucl Cardiol 2023;30:1543–53.)**

Key Words: Cardiac sarcoidosis • prednisone • methotrexate • FDG PET/CT • immunosuppressants

Abbreviations

EANM	European Association of Nuclear Medicine
AVB	Atrioventricular block
BMI	Body mass index
CMR	Cardiac magnetic resonance imaging
CS	Cardiac sarcoidosis
CT	Computed tomography
FDG	Fluorine-18 fluorodeoxyglucose
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
MACE	Major adverse cardiovascular events
MTX	Methotrexate
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
OSA	Obstructive sleep apnea
PET	Positron emission tomography
PRED	Prednisone
RV	Right ventricular
sIL-2R	Serum soluble interleukin-2 receptor
SUVmax	Maximum standardized uptake value
VA	Ventricular arrhythmias

See related editorial, pp. 1554–1557

INTRODUCTION

Clinically manifest cardiac involvement occurs in approximately 5% of sarcoidosis patients and involves conduction abnormalities, ventricular arrhythmias (VA) and heart failure.[1] Cardiac sarcoidosis (CS) is often subclinical and under-recognized,[2] with autopsy and cardiac magnetic resonance imaging (CMR) studies reporting cardiac involvement in 25% to 30% of cases.[3] A clinical diagnosis of CS can be made based on a combination of extra-cardiac histology, clinical findings and results from advanced cardiac imaging such as CMR and Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT).[1,4] FDG PET/CT detects active inflammation in the myocardium,[5] and visual- and quantitative analysis has prognostic value.[6–8] FDG PET/CT is used in the monitoring of immunosuppressive treatment and several studies have reported an association between cardiac PET/CT improvement and favorable clinical outcomes.[9–13]

Treatment of CS with immunosuppressive therapies is recommended in patients with conduction abnormalities or VA, as well as heart failure.[1,3,4] These recommendations are based on a limited number of observational studies, in absence of randomized controlled trials in CS.[14,15] Furthermore, less is known about the treatment of CS patients without rhythm or conduction disorders and with a preserved left ventricular ejection fraction (LVEF), but with myocardial FDG uptake.[3] It has been proposed that myocardial FDG uptake should be considered an indication for treatment,[2] although this has not yet been validated in clinical studies. The management of CS is therefore highly empiric and heterogeneous, although glucocorticoids and methotrexate are generally considered as the first and second-line therapy of choice.[2,15] Multiple side effects such as hypertension, diabetes, weight gain and osteoporosis limit the long-term use of glucocorticoids,[16] and methotrexate has gained attention as steroid sparing agent with a potentially more favorable safety profile.[3,16] The objective of this study was to compare the effects of prednisone monotherapy, methotrexate monotherapy or a combination of low-dose prednisone and methotrexate on myocardial FDG uptake and clinical outcomes in treatment naïve CS patients.

METHODS

Study design

A retrospective, single center cohort study was performed in the St. Antonius Hospital, the Netherlands, a tertiary referral center for sarcoidosis including CS. All patients who were newly diagnosed with CS and subsequently treated with prednisone and/or methotrexate between January 2010 and December 2017 were included.

Local institutional review board (Medical Research Ethics Committees United, Nieuwegein, The Netherlands) approval was obtained with registration number R&D/Z19.004, with a waiver of informed consent. This study was designed and reported in agreement with the criteria as defined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, Table S1).[17]

Study population and treatment protocol

Eligible patients were ≥ 18 years of age and diagnosed with CS by clinical consensus in a multidisciplinary team. Diagnosis was based on clinical findings, CMR and FDG PET/CT findings and extracardiac sarcoidosis diagnosis.[18] All patients fulfilled either the 2014 Hearth Rhythm Society or the 2016 Japanese Circulatory Society diagnostic criteria for CS.[1,2]

Additional inclusion criteria were (1) baseline myocardial FDG uptake, (2) a minimum of 6 months follow-up, and (3) immunosuppressive therapy with oral prednisone and/or methotrexate had to be initiated within 3 months after CS diagnosis. Patients treated with immunosuppressive therapies in the past 3 months before baseline were excluded.

Prednisone monotherapy typically consisted of a starting dose of 40 mg daily for 1 month, followed by taper to 20 mg daily at 3 months and 10 mg daily at 6 months. Methotrexate monotherapy and combination therapy started with 10 mg weekly, and was increased to 15 mg weekly over a 4-week period. All patients on methotrexate therapy received folic acid at a dosage of 5 mg weekly or biweekly. Patients with combination therapy typically received prednisone 20 mg daily for 1 month followed by prednisone taper to approximately 10 mg daily at 3 months. For all immunosuppressive regimens, doses were subsequently adjusted based on findings from clinical follow-up, FDG PET/CT and side effects.

Clinical characteristics and outcome parameters

Data on baseline demographics, medical history, severity of disease, immunosuppressive treatment, side effects and serum biomarkers was collected by review of the electronic medical records. Baseline FDG PET/CT was performed prior to CS diagnosis and before the initiation of immunosuppressive therapy. FDG PET/CT was performed with a Philips Gemini Time of Flight PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands). Serial FDG PET/CT scans were performed at approximately six to twelve month intervals. Baseline PET scanning was performed prior to CS diagnosis and before the initiation of immunosuppressive therapy. Subsequent follow-up FDG PET/CT scans were obtained while patients were on immunosuppressive therapy. All FDG PET/CT scans were performed in accordance with the European Association of Nuclear Medicine (EANM) guidelines and the department of nuclear medicine is EARL accredited by the EANM. Patients were instructed to have a carbohydrate-restricted diet for 24 h followed by a fast of at least 6 h prior to FDG injection. From October 2013 onwards, all patients received 50 IU/kg unfractionated heparin intravenously 15 min prior to FDG injection to suppress physiologic myocardial uptake. Blood glucose level was measured in all patients prior to injecting FDG. FDG was administered when the plasma glucose level was < 10 mmol·L^{-1}. Visual interpretation of cardiac FDG uptake was assessed as no uptake, diffuse uptake, focal uptake or focal on diffuse uptake.[1,19] Myocardial FDG uptake was defined as either diffuse, focal or focal on diffuse uptake. Right ventricular (RV) FDG uptake was scored as yes or no. Quantitative assessment of FDG uptake was performed using the maximum standardized uptake value (SUVmax). Regions of interest (ROI) were drawn over the visually affected part of the heart to measure the myocardial SUVmax. ROI was drawn at the same lesion/area at baseline and follow-up scan. Furthermore, a ''normalized SUVmax'' was determined by calculating the ratio between the myocardial SUVmax and the SUVmean of the blood pool, measured in the descending thoracic aorta.[20,21] All FDG PET/CT images were scored by a single experienced nuclear medicine physician (R.G.M.K.) blinded for treatment regimens and clinical outcomes. Serial FDG PET/CT scans were performed at approximately 6 to 12 month intervals. Patients generally received CMR at baseline and CMR images were scored on both the presence of late gadolinium enhancement (LGE) and LVEF. Serum biomarkers included serum soluble interleukin-2 receptor (sIL-2R) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP).

The primary outcome parameter was the metabolic response based on visual interpretation and quantitative analysis of cardiac FDG PET/CT within 12 months from initiation of treatment. FDG PET/CT response was defined as a reduction in myocardial SUVmax ≥ 30.0%. Secondary outcomes included treatment patterns, major adverse cardiovascular events (MACE), change in LVEF, biomarkers and side effects during 24 months after treatment start. MACE was defined as cardiac death, heart transplantation, VA, new Mobitz type II second or third degree atrioventricular block (AVB), appropriate implantable cardioverter defibrillator (ICD) therapy and hospitalization due to heart failure. In patients with and without MACE, RV FDG uptake and SUVmax values were compared. LVEF during follow-up was determined by transthoracic echocardiography using the biplane Simpson's method. Only side effects requiring dose reduction or permanent discontinuation of immunosuppressive therapy and side effects requiring medical treatment or hospitalization were taken into account. Body weight was documented at baseline and at follow-up PET/CT.

Statistical analysis

Study data were collected and managed using the REDCap electronic data capture tool. Statistical analysis was performed with IBM SPSS 26.0 Statistics software (IBM, Armonk, New York, USA). Categorical variables are expressed as absolute numbers and percentages, continuous variables as means ± SD in case of normal distribution or as medians [25th-75th percentile]. The normality of continuous variables was assessed visually by means of the frequency histogram and Q–Q plot and was tested using the Shapiro–Wilk test. The likelihood-ratio chi-square test or Fisher's Exact test was used to compare categorical variables. The independent-samples T-test or Mann–Whitney U test was used to compare mean or median values of two continuous variables. The one-way ANOVA or Kruskal Wallis test was applied to the comparison of the means or medians of three continuous variables. The McNemar test was used to compare categorical variables of two related samples. The paired-samples T-test or Wilcoxon signed rank test was used to compare mean or median values of two related samples. Kaplan–Meier analysis was used for observed MACE free survival during follow-up with the Log-Rank test for comparison between curves. A two-tailed P value of < 0.05 was considered significant.

RESULTS

Study population

Overall, 61 patients were included in this study (Fig. 1). One patient died from esophageal cancer 7 months after treatment initiation. A methotrexate treated patient was lost to follow-up after heart transplantation 12 months after treatment initiation, after being hospitalized due to heart failure after 7 months of

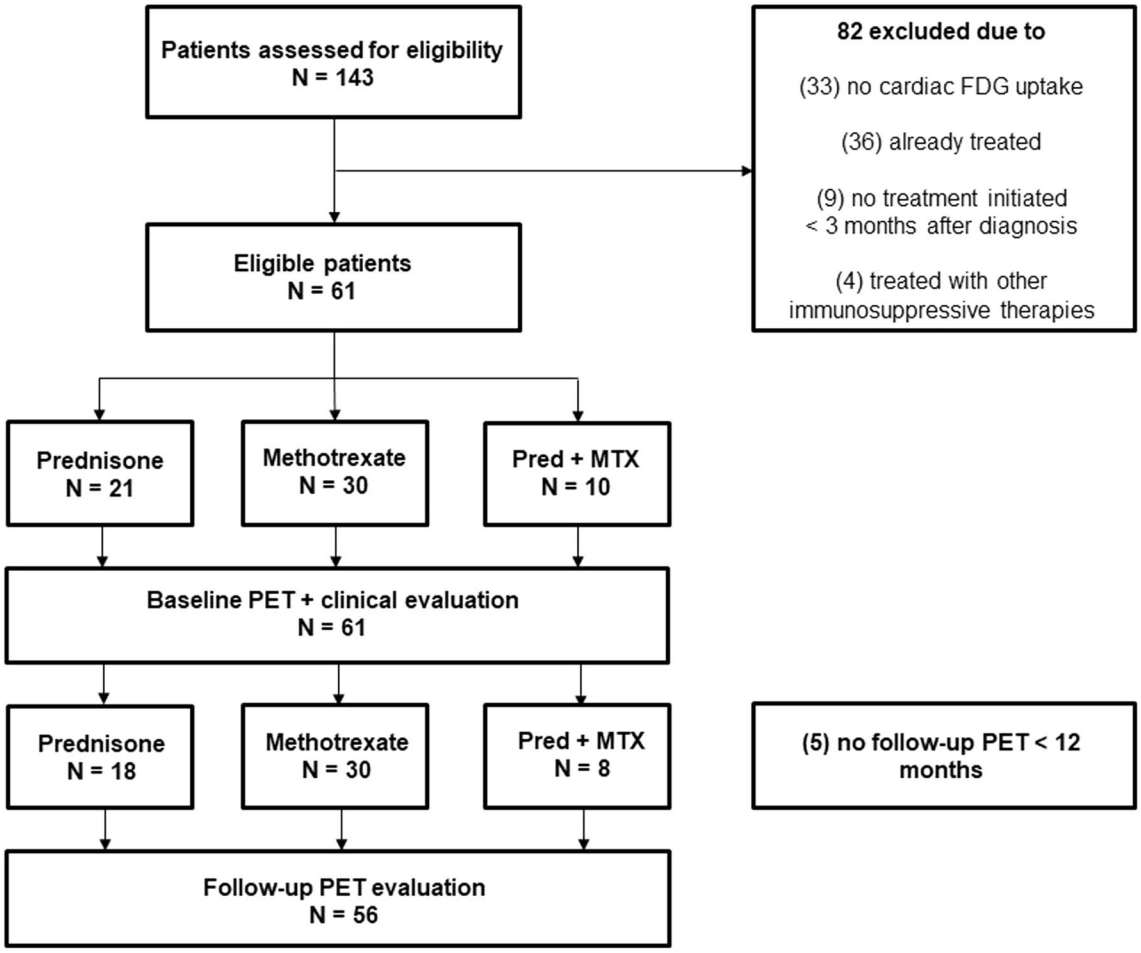

Figure 1. Patient disposition. *MTX*, methotrexate; *pred*, prednisone.

treatment. This patient was included in the analysis of follow-up PET/CT and MACE.

Immunosuppressive treatment was initiated with prednisone (N = 21), methotrexate (N = 30), or a combination (N = 10). Initial monotherapy prednisone dose was 40 mg (N = 18), 35 mg (N = 2) or 20 mg daily (N = 1), which was tapered to a median dose of 12.5 mg [10-15 mg] at 6 months. Methotrexate was dosed at 15 mg weekly for at least 6 months in all cases (both monotherapy and combination group). The initial combination therapy prednisone dose was 40 mg (N = 2), 20 mg (N = 6) or 10 mg daily (N = 2). Of the combination group, 4 patients still used prednisone after 6 months, at a dose of 7.5 to 15 mg. Baseline characteristics were generally balanced between groups (Table 1). BMI was higher and arterial hypertension was present more frequently in methotrexate treated patients. Importantly, prednisone treated patients more often had VA at baseline ($P = 0.040$). Accordingly, ICD and pacemaker implantation and antiarrhythmic treatment occurred more frequently in the prednisone group.

FDG PET evaluation

At baseline, 48 of 61 patients (78.7%) showed focal cardiac FDG uptake and 13 of 61 patients (21.3%) showed diffuse cardiac FDG uptake, while RV FDG uptake was observed in 24 (39.3%) patients. Follow-up FDG PET/CT scans were available for 56 patients. Median intervals between baseline PET/CT and first follow-up PET/CT in the prednisone, methotrexate and combination group, were, respectively, 8.5 [6.1-11] months, 9.4 [7.4-12] months and 8.7 [7.5-10] months ($P = 0.412$) and median intervals from treatment start to first follow-up PET/CT were 6.0 [4.5-6.9] months, 6.4 [5.8-7.7] months and 6.1 [6.0-7.0] months ($P = 0.306$). Uptake pattern at first follow-up PET/CT differed significantly from baseline in all groups except for the prednisone group (Table 2). At first follow-up PET/CT, 24 patients (42.9%) showed no cardiac FDG uptake. In the combination group, 7 of 8 patients (87.5%) showed no cardiac FDG uptake, more frequent than in the prednisone group ($P = 0.005$) and methotrexate group ($P = 0.042$). At first follow-up PET/CT, myocardial SUVmax values were significantly reduced compared to baseline in all treatment groups. Overall, myocardial SUVmax was reduced from 6.9 [5.0-10.1] to 3.4 [2.1-4.7] ($P < 0.001$), corresponding to a change of − 47% [− 69 to − 25] (Table 2). Reductions in normalized myocardial SUVmax were similar to the reductions in myocardial SUVmax (data not shown). Overall, 40 of 56 patients (71.4%) were FDG PET/CT responder.

Treatment patterns

Before 2016, initial treatment of 27 patients consisted of prednisone (20), methotrexate (3) or combination treatment (4). From 2016 onwards, initial therapies in 34 patients were prednisone (1), methotrexate (27) or combination treatment (6). After 24 months of follow-up, 34 patients (55.7%) remained on methotrexate monotherapy or were switched to methotrexate monotherapy (Fig. 2). Three patients were on third line immunosuppressive therapies, such as infliximab.

Major adverse cardiovascular events and safety

During follow-up, 14 patients experienced at least one MACE, involving appropriate ICD therapy (N = 10), hospitalization due to heart failure (N = 3) and new third degree AVB (N = 1). One methotrexate treated patient underwent heart transplantation, however, this patient was hospitalized due to heart failure earlier on. One methotrexate treated patient developed new third degree AVB. Overall, 7 patients (33.3%) of the prednisone group, 6 patients (20.0%) of the methotrexate group and 1 patient (10.0%) of the combination group experienced MACE ($P = 0.292$) (Fig. 3). Importantly, 6 out of 10 patients experiencing appropriate ICD therapy during follow-up, already showed VA at baseline ($P < 0.001$).

Patients with baseline RV FDG uptake experienced MACE more often during follow-up: 11 out of 24 patients (45.8%) with RV uptake vs 3 out of 37 patients (8.1%) without RV uptake ($P = 0.001$). Myocardial FDG uptake was higher in patients experiencing MACE. In patients with and without MACE, myocardial SUVmax values were 10.4 [6.9-15.3] vs 5.9 [4.7-8.3] ($P = 0.003$) at baseline and 4.7 [3.8-7.5] vs 2.8 [1.9-4.3] ($P = 0.002$) at follow-up.

For 53 patients LVEF measurements were available at a median of 16 [13–21] months since treatment start. Median follow-up LVEF measurements did not differ significantly from baseline values in all treatment groups (Table 3). For 39 patients, NT-proBNP measurements were performed at a median of 21 [16–24] months after treatment start. Only in the combination treatment group, NT-pro-BNP values were significantly decreased at follow-up (Table S2). Follow-up sIL-2R values were available for 60 patients at a median interval of 22 [20–24] months since treatment start and were significantly lower than baseline in all groups (Table S2).

Side effects occurred in 3 (prednisone), 7 (methotrexate) and 4 (combination group) patients. In prednisone treated patients, side effects were obstructive

Table 1. Baseline characteristics of all eligible patients

Characteristic	Total N = 61	Prednisone N = 21	MTX N = 30	Pred + MTX N = 10	*P* value
Demographics					
Age (years)	52.5 ± 10.5	50.8 ± 9.7	54.8 ± 11.1	49.2 ± 9.8	0.229
Male sex	46 (75.4)	17 (81.0)	21 (70.0)	8 (80.0)	0.625
Caucasian ethnicity	60 (98.4)	20 (95.2)	30 (100.0)	10 (100.0)	0.339
BMI (kg/m^2)	27.9 ± 4.2	25.4 ± 3.0	29.4 ± 4.0	28.5 ± 5.2	0.003*
Hypertension	19 (31.1)	2 (9.5)	14 (46.7)	3 (30.0)	0.012*
Diabetes mellitus	5 (8.2)	0 (0.0)	4 (13.3)	1 (10.0)	0.104
Coronary artery disease	2 (3.3)	0 (0.0)	2 (6.7)	0 (0.0)	0.234
Disease severity					
Extra-cardiac sarcoidosis					
- Pulmonary	52 (85.2)	19 (90.5)	24 (80.0)	9 (90.0)	0.519
- Neurologic	3 (4.9)	1 (4.8)	2 (6.7)	0 (0.0)	0.552
- Liver	11 (18.0)	6 (28.6)	3 (10.0)	2 (20.0)	0.231
- Ocular	5 (8.2)	1 (4.8)	3 (10.0)	1 (10.0)	0.761
Isolated cardiac sarcoidosis	2 (3.3)	1 (4.8)	1 (3.3)	0 (0.0)	0.672
Cardiac manifestations					
NYHA functional class					
I	25 (41.0)	10 (47.6)	12 (40.0)	3 (30.0)	0.670
II	25 (41.0)	9 (42.9)	11 (36.7)	5 (50.0)	
III	11 (18.0)	2 (9.5)	7 (23.3)	2 (20.0)	
Ventricular arrhythmias	9 (14.8)	6 (28.6)	3 (10.0)	0 (0.0)	0.040
Second/third degree AVB	15 (24.6)	6 (28.6)	5 (16.7)	4 (40.0)	0.297
LVEF (%)	53.5 [46.8 - 60.0] (N = 58)	52.0 [44.3 - 58.0] (N = 21)	56.0 [47.0 - 60.0] (N = 27)	56.0 [45.8 - 60.0] (N = 10)	0.407
LGE on CMR	52 (89.7) (N = 58)	19 (90.5) (N = 21)	24 (88.9) (N = 27)	9 (90.0) (N = 10)	0.983
Treatment					
ICD or pacemaker implanted	35 (57.4)	16 (76.2)	13 (43.3)	6 (60.0)	0.059*
Antiarrhythmic treatment	25 (41.0)	12 (57.1)	12 (40.0)	1 (10.0)	0.030†
Biomarkers					
sIL-2R (pg/ml) (Baseline)	4940 [2768-7325]	4152 [3301-6104]	4851 [2354-6915]	7325 [3619-10085]	0.354
NT-proBNP (pg/ml) (Baseline)	190 [71-547] (N = 45)	217 [116-1212] (N = 13)	184 [68-504] (N = 24)	141 [42-449] (N = 8)	0.489

Data are presented as No. (%) or as mean ± SD. LVEF is presented as median [25th - 75th percentile]
*P value < 0.05 (prednisone vs MTX); †P value < 0.05 (prednisone vs prednisone + MTX)
AVB, atrioventricular block; *BMI*, body mass index; *CMR*, cardiac magnetic resonance imaging; *ICD*, implantable cardioverter defibrillator; *LGE*, late gadolinium enhancement; *LVEF*, left ventricular ejection fraction; *MTX*, methotrexate; *NYHA*, New York Heart Association

sleep apnea (OSA) (N = 1), osteopenia (N = 1) and Achilles tendon rupture (N = 1). In methotrexate treated patients, abnormal liver function tests (N = 2), hospitalization for infection (N = 1), complex partial seizures (N = 1), OSA (N = 1), erectile dysfunction (N = 1) and hair loss (N = 1) occurred. Hospitalization

Table 2. Results from visual and quantitative PET evaluation

	Total	Prednisone	MTX	Pred + MTX	*P* value
Visual PET evaluation					
Baseline PET	*N = 61*	*N = 21*	*N = 30*	*N = 10*	
Diffuse	13 (21.3)	3 (14.3)	8 (26.7)	2 (20)	0.556
Focal/focal on diffuse	48 (78.7)	18 (85.7)	22 (73.3)	8 (80)	
Follow-up PET	*N = 56*	*N = 18*	*N = 30*	*N = 8*	
No uptake	24 (42.9)	4 (22.2)	13 (43.3)	7 (87.5)	0.019* †
Diffuse	9 (16.1)	3 (16.7)	6 (20.0)	0 (0.0)	
Focal/focal on diffuse	23 (41.1)	11 (61.1)	11 (36.7)	1 (12.5)	
	$P < 0.001$	$P = 0.125$	$P < 0.001$	$P = 0.016$	
Quantitative PET evaluation					
Baseline PET	*N = 61*	*N = 21*	*N = 30*	*N = 10*	
Myocardial SUVmax	6.9 [5.0 - 10.1]	7.3 [5.4 - 11.3]	6.5 [4.7 - 9.0]	6.3 [4.5 - 9.7]	0.465
Follow-up PET	*N = 56*	*N = 18*	*N = 30*	*N = 8*	
Myocardial SUVmax	3.4 [2.1 - 4.7]	3.7 [2.7 - 5.4]	3.4 [1.9 - 4.8]	2.2 [1.8 - 2.7]	0.093*
	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.012$	
Change SUVmax (%)	− 47 [− 69 to − 25]	− 47 [− 70 to − 26]	− 38 [− 66 to − 12]	− 67 [− 72 to − 56]	0.248
PET treatment responder	40 (71.4)	13 (72.2)	20 (66.7)	7 (87.5)	0.468

*P value < 0.05 (prednisone vs pred + MTX); †P value < 0.05 (MTX vs pred + MTX)
MTX, methotrexate; *PET*, positron emission tomography; *pred*, prednisone; *SUV*, standardized uptake value

for infection (N = 2), new onset diabetes (N = 1) and unacceptable weight gain (N = 1) were observed in the combination group. Both patients developing new onset OSA, experienced significant weight gain (> 10% from baseline) during treatment. One patient experienced tinnitus after methotrexate addition to initial prednisone treatment, one patient was hospitalized for infection during methotrexate monotherapy after initial combination therapy. Between baseline and follow-up FDG PET/CT, BMI increased significantly from 25.6 ± 3.2 to 26.3 ± 3.3 kg/m^2 in the prednisone group ($P = 0.020$). In the methotrexate (29.4 ± 4.0 to 29.9 ± 4.6 kg/m^2; $P = 0.086$) and combination group (28.2 ± 3.6 to 29.7 ± 5.0 kg/m^2; $P = 0.161$) this increase was not statistically significant.

DISCUSSION

This is the first study comparing monotherapy prednisone, methotrexate and a combination of both in CS patients. This study showed significant suppression of cardiac inflammation measured by FDG uptake after 6 months of treatment, irrespective of the regimen. During 24 months of follow-up, there were no significant differences in the occurrence of MACE or the preservation of LVEF between the three initial treatment strategies.

Comparison to prior literature

Few studies have reported on the effects of methotrexate in CS. In a prospective study by Nagai et al., treatment with glucocorticoids and a low-dose of 6 mg methotrexate weekly resulted in a higher LVEF and lower NT-pro-BNP levels at 3-year follow-up compared to glucocorticoids alone, in a population with an average baseline LVEF of 51%.[22] Fussner et al. compared prednisone monotherapy with steroid sparing agents (including methotrexate) with or without prednisone and concluded that clinical presentation of CS had a larger impact on outcomes than treatment regimen.[23] In a study of Ballul et al., patients treated with glucocorticoids and azathioprine or methotrexate showed lower cardiac relapse rates than patients treated with glucocorticoids monotherapy.[24] Event rate was high in this cohort, with cardiac relapse in 36.1% of patients and a mortality rate of 8.3% during a median follow-up of 3.6 years. A treatment regimen of prednisone and methotrexate followed by prednisone taper was studied by Rosenthal et al.[21] Despite good initial

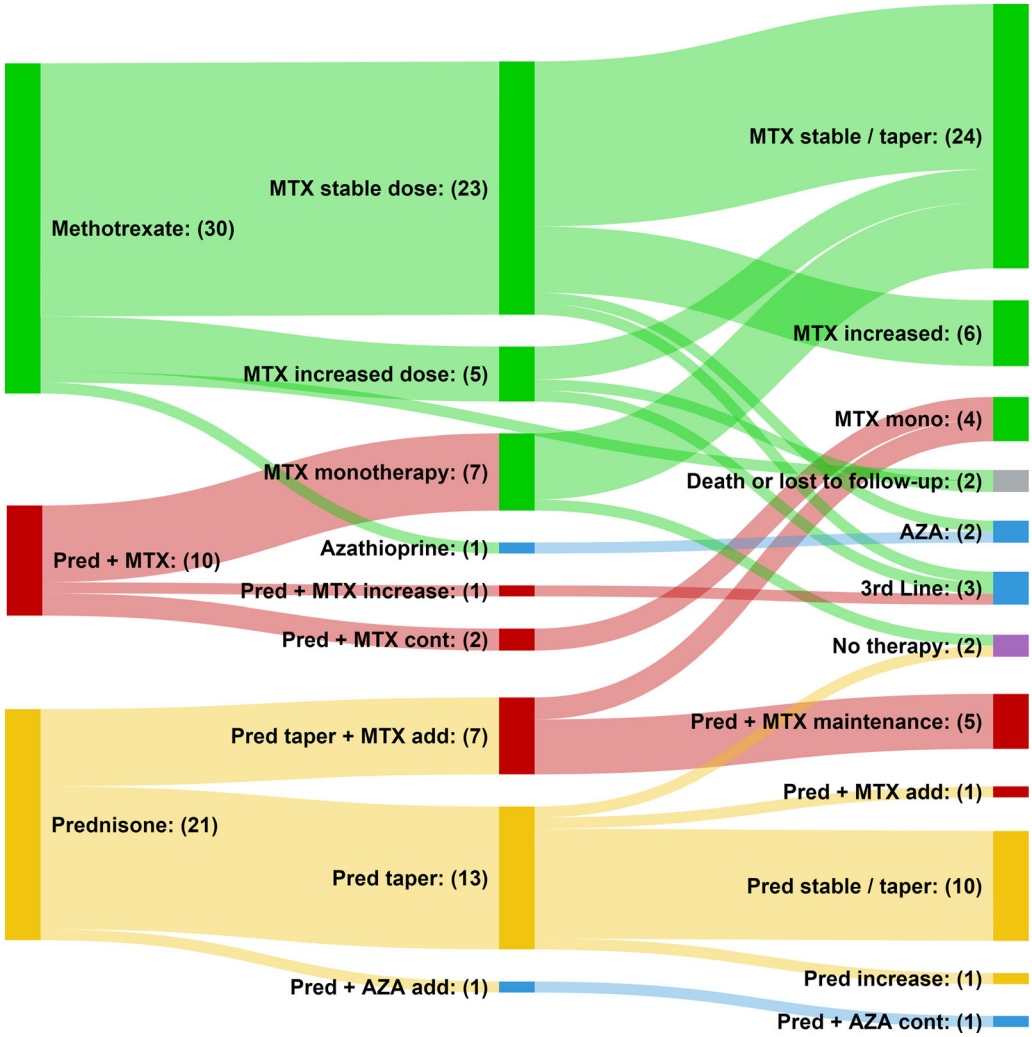

Figure 2. Treatment patterns at baseline, at 12 months and 24 months after treatment start. *Add*, addition; *AZA*, azathioprine; *cont*, continued; *MTX*, methotrexate; *pred*, prednisone.

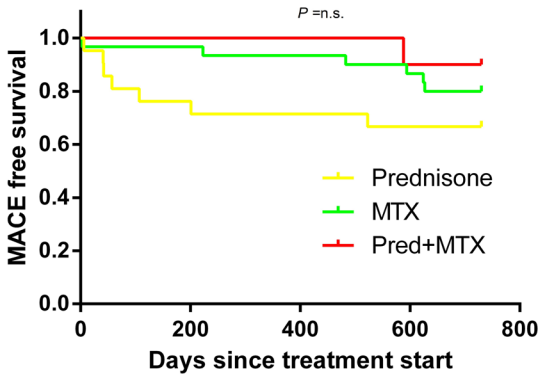

Figure 3. MACE free survival in prednisone, methotrexate and combined prednisone and methotrexate treated patients. *MACE*, major adverse cardiovascular events; *MTX*, methotrexate; *pred*, prednisone.

suppression of myocardial FDG uptake under combination treatment or methotrexate maintenance, a substantial number of patients required third line therapy due to persistent or recurrent myocardial FDG uptake. Higher quality evidence is needed to compare the safety and efficacy of prednisone and methotrexate (combination) therapy, and the results of the CHASM CS-RCT are therefore highly anticipated.[15]

Treatment patterns and safety

In our clinic, immunosuppressive treatment is initiated after a CS diagnosis with suspicious myocardial FDG uptake, whether or not conduction abnormalities, VA or cardiomyopathy are present. Besides myocardial FDG uptake, 90% of our population showed LGE on CMR, a combination that poses a higher risk of death,

Table 3. Results from LVEF analysis

	Total	Prednisone	MTX	Pred + MTX	*P* value
Baseline	*N = 58*	*N = 21*	*N = 27*	*N = 10*	
LVEF (%)	53.5 [46.8-60.0]	52.0 [44.3-58.0]	56.0 [47.0-60.0]	56.0 [45.8-60.0]	0.407
Follow-up	*N = 53*	*N = 17*	*N = 26*	*N = 10*	
LVEF (%)	55.0 [50.0-60.0]	50.0 [46.0-57.5]	57.5 [50.0-60.0]	60.0 [56.3-60.0]	0.069
	P = 0.666	*P* = 0.836	*P* = 0.810	*P* = 0.326	
LVEF difference (Follow-up vs baseline)	0.0 [− 4.5-5.5]	3.0 [− 7.0-7.5]	0.0 [− 5.0-3.5]	2.5 [− 1.0-5.3]	0.523

Data are presented as median [25th to 75th percentile]
LVEF, left ventricular ejection fraction; *MTX*, methotrexate; *pred*, prednisone

arrhythmia and decompensated heart failure.[7] We therefore aimed for early treatment, at a minimum of side effects. In 2016 and 2017, methotrexate monotherapy has been used in the majority of new CS diagnoses in our clinic. As of 2018 high risk patients are treated with methylprednisolone pulse therapy before methotrexate, with or without prednisone, is started.

Our results suggest that in the first two years after diagnosis, methotrexate monotherapy results in a substantial suppression of myocardial inflammation and clinical stabilization. While more than a third of methotrexate treated patients required a dose increase during follow-up, only 4 out of 30 patients switched to other second or third line therapies.

Glucocorticoids are considered first-line therapy, but they may lead to significant morbidity.[25] In a study by Kahn et al., the cumulative incidence of glucocorticoids associated toxicity kept increasing during the median follow-up of 101 months.[25] In a recent survey of patient reported side effects in sarcoidosis, methotrexate gave fewer and less bothersome side effects than prednisone, although median treatment duration was longer in the prednisone than methotrexate group (24 vs 12 months).[16] In our study, methotrexate was not better tolerated than prednisone during the follow-up of 24 months.

FDG PET findings and major adverse cardiovascular events

Our observation that RV FDG uptake is associated with the occurrence of MACE is in line with previous studies, reporting adverse cardiac events in 26-36% of patients with RV FDG uptake compared to 3-7% in those without.[6,7,26,27] It has been suggested that RV involvement occurs in the advanced stages of the disease, and is associated with a broader distribution of sarcoid lesions in the LV.[27] We noted higher SUVmax values in patients with MACE, an association that has been found before.[7,8,28] In our cohort, adverse events primarily involved appropriate ICD therapy in VA. Considering VA in CS can be either due to sarcoid granulomas or myocardial scarring, there is no uniform correlation between the extent of myocardial inflammation in imaging studies and VA.[29–31] In line with these findings are the results of a recent meta-analysis showing recurrence of VA in a wide range of 14-71% of CS patients treated with immunosuppressant therapy.[32] Based on the significantly higher SUVmax values, myocardial inflammation seems to be linked to VA in our population. Besides myocardial inflammation, pre-treatment VA, and the concomitant use of antiarrhythmic drugs need to be taken into account.

LIMITATIONS

Small patient numbers and imbalances in baseline characteristics warrant a cautious comparison of treatment regimens. Especially the higher occurrence of VA at baseline in the prednisone group, and some evidence of more frequent baseline AVB in the combination group seems to be relevant. Concerning clinical features could have urged the treating physicians to initiate prednisone therapy, and this could indicate that the prednisone and combination groups are at higher risk of MACE than the methotrexate group. Appropriate ICD therapy in VA was the most frequently observed event. In our cohort with generally normal or mildly reduced LVEF at baseline, LVEF was preserved in all treatment groups. This is consistent with a recent meta-analysis, in which immunosuppressive treatment was associated with preservation of LVEF in patients who presented

with normal LVEF or mild to moderate LV dysfunction.[32] However, a possible confounder in the stabilization of LVEF might be the effect of heart failure therapy.

An important limitation of this study is the lack of a control group. Therefore the observed effect on myocardial inflammation could represent the natural course of the disease. Another limitation is the modest sample size of the study population, although our population is one of the largest compared to previous published studies. Finally, in our cohort, a small proportion of patients showed diffuse FDG uptake, which is less suspicious than focal or focal on diffuse uptake and might have been caused by inadequate dietary preparation.

CONCLUSION

We described different treatment strategies in treatment naïve cardiac sarcoidosis patients, and found significant suppression of cardiac FDG uptake after 6 months of prednisone, methotrexate or combination therapy. There were no significant differences between the treatment strategies in the occurrence of MACE or the preservation of LVEF during follow-up. During 24 months of immunosuppressive therapy, we report a shift from prednisone therapy towards methotrexate monotherapy, without an increase in adverse events. These results warrant further investigation of methotrexate treatment in CS patients.

NEW KNOWLEDGE GAINED

In patients with active sarcoidosis, methotrexate monotherapy and prednisone monotherapy resulted in a significant and comparable decrease in myocardial FDG uptake, and no significant differences in the prevalence of adverse cardiac events. With long-term prednisone treatment being hampered by its side effects, methotrexate monotherapy seems to be a feasible alternative.

Disclosures

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