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Concise report

Risk factors associated with *Pneumocystis jirovecii* pneumonia in juvenile myositis in North America

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Abstract

Objectives. *Pneumocystis jirovecii* pneumonia (PJP) is associated with significant morbidity and mortality in adult myositis patients; however, there are few studies examining PJP in juvenile myositis [juvenile idiopathic inflammatory myopathy (JIIM)]. The purpose of this study was to determine the risk factors and clinical phenotypes associated with PJP in JIIM.

Methods. An research electronic data capture (REDCap) questionnaire regarding myositis features, disease course, medications and PJP infection characteristics was completed by treating physicians for 13 JIIM patients who developed PJP (PJP+) from the USA and Canada. Myositis features and medications were compared with 147 JIIM patients without PJP (PJP–) from similar geographic regions who enrolled in National Institutes of Health natural history studies.

Results. PJP+ patients were more often of Asian ancestry than PJP– patients [odds ratio (OR) 8.7; 95% CI 1.3, 57.9]. Anti- melanoma differentiation associated protein 5 (MDA5) autoantibodies (OR 12.5; 95% CI 3.0, 52.4), digital infarcts (OR 43.8; 95% CI 4.2, 460.2), skin ulcerations (OR 12.0; 95% CI 3.5, 41.2) and interstitial lung disease (OR 10.6; 95% CI 2.1, 53.9) were more frequent in PJP+ patients. Before PJP diagnosis, patients more frequently received pulse steroids, rituximab and more immunosuppressive therapy compared with PJP– patients. Seven PJP+ patients were admitted to the intensive care unit and four patients died due to PJP or its complications.

Conclusions. PJP is a severe infection in JIIM that can be associated with mortality. Having PJP was associated with more immunosuppressive therapy, anti-MDA5 autoantibodies, Asian race and certain clinical features, including

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digital infarcts, cutaneous ulcerations and interstitial lung disease. Prophylaxis for PJP should be considered in juvenile myositis patients with these features.

Key words: myositis, juvenile idiopathic inflammatory myopathies, *Pneumocystis jirovecii* pneumonia, opportunistic infections, anti-MDA5 autoantibodies, interstitial lung disease

Rheumatology key messages

- *Pneumocystis jirovecii* pneumonia is a severe infection that affects juvenile idiopathic inflammatory myopathy patients soon after diagnosis.
- Immunosuppressive therapy, anti-melanoma differentiation associated protein 5 autoantibodies, interstitial lung disease and cutaneous ulcerations/infarcts are risk factors for *Pneumocystis jirovecii* pneumonia in juvenile idiopathic inflammatory myopathy.
- *Pneumocystis jirovecii* pneumonia prophylaxis should be considered in juvenile idiopathic inflammatory myopathy patients with these features.

Introduction

Adult and juvenile idiopathic inflammatory myopathies (IIM, JIIM) are heterogeneous groups of systemic autoimmune diseases characterized by muscle inflammation and characteristic rashes [1]. Numerous extramuscular manifestations occur in IIM/JIIM, which can include the gastrointestinal tract, joints and lungs [1].

Pneumocystis jirovecii pneumonia (PJP) is a rare opportunistic infection that disproportionally affects adult IIM patients compared with other CTDs [2] with a high mortality rate, ranging from 33 to 60% [3, 4]. Risk factors associated with PJP in IIM include lymphopenia, immunosuppressive therapy, and the dose and duration of CS treatment [5, 6]. In some juvenile CTD, such as JIA, PJP is rare [7]. However, in JIIM, the prevalence and associated risk factors with PJP are less known, and there are no standard recommendations for prophylaxis. Understanding the risk factors associated with PJP can help in determining which JIIM patients may benefit from prophylaxis. In this study, we report 13 JIIM patients who developed PJP and describe their demographic, clinical and treatment-related factors relative to a large North American JIIM cohort without PJP infection.

Methods

Patients

An electronic research electronic data capture (REDCap) questionnaire of 215 questions regarding JIIM disease course, medication usage and PJP infection was distributed to members of the Pediatric Rheumatology Bulletin Board (an electronic list-serve) and members of the Childhood Arthritis and Rheumatology Research Alliance to obtain case record information about JIIM patients from the USA and Canada diagnosed between 2003 and 2019, who developed PJP (PJP+) during their disease course [8]. Deidentified data were entered following retrospective medical record review. Institutional review board exemption was granted by the University of California, San Francisco.

Demographics, laboratory and clinical features at myositis diagnosis, and medications received by PJP+ patients were compared with 147 JIIM patients previously enrolled in National Institutes of Health myositis natural history studies between 2003 and 2019 from the USA and Canada with no documented PJP infection (PJP–). A standardized physician questionnaire captured illness features of PJP– patients [9]. All PJP+ and PJP– patients met probable or definite JIIM by Bohan and Peter criteria [10], with a classification of JDM or juvenile polymyositis. Interstitial lung disease (ILD) was diagnosed by CT and/or chest radiograph with pulmonary function testing. Autoantibody testing was performed at various commercial labs in PJP+ patients (Table 1) and at Oklahoma Medical Research Facility in PJP– patients.

The median time from myositis diagnosis to PJP infection was 2.3 months. Therefore, CS, including prednisone and i.v. methylprednisolone (IVMP), received by PJP+ patients the month prior to infection were compared with those received by PJP– patients 1.3–2.3 months after myositis diagnosis. Other medications, including IVIG, MTX, HCQ, MMF, ciclosporin, CYC and rituximab, were received by PJP+ patients 0–6 months prior to PJP infection and compared with those received by PJP– patients 0–6 months after myositis diagnosis.

Statistical analysis

Analyses were performed using Stata/MP V.14.2 (College Station, TX, USA). Dichotomous variables were expressed as absolute frequencies and percentages

Table 1 Features of juvenile myositis patients with PJP infection

Pt	Sex	Race	Age at JM dx (years)	MSA[a]	Clinical features[b]	JM dx to PJP dx (months)	Prednisone mg; mg/kg[c]	IVMP (pulses)[c]	IVIG[d]	MTX[d]	HCQ[d]	MMF or CSA[d]	CYC (weeks)[d]	RIT (weeks)[d]	ALC $\times 10^9$/l	Age of death (years)	ICU (days)
1	F	Asian	16.0	MDA5	ILD, U, DI	27.9	60; 1.1	X (1)	X	X	X		X (4)	X (4)	**0.59**		4
2	M	Nat Am	1.6	MDA5	ILD, U, DI	1.8	12.5; 1.0	X (na)	X						2.20		
3	F	AA	2.0	MDA5	ILD	0.3	20; 2.0	X (>4)						X (0)	2.10	2.1	16
4	F	His	2.4	MDA5	U	1.8	24; 1.8		X	X					6.85	2.9	150
5	F	Asian	17.2	MDA5	U	1.6	60; 1.0	X (2)		X			X (0)		**0.76**		
6	F	C	14.6	None[e]	U	5.1	40; 1.1	X (3)	X	X	X			X (20)	1.57		1
7	M	C	2.9	None[f]	U	2.0	30; 1.7		X	X	X				1.87		
8	M	C	9.2	None[f]	U, DI	13.2	30; 0.8			X	X	X		X (20)	**0.72**		
9[g]	M	AA, C	9.5	None[e]	None	2.3	30; 0.9			X					2.10	9.8	111
10	F	AA	6.2	None[e]	None	50.8	30; 0.8	X (4)	X			X			2.27		
11	F	C	5.5	NT	None	6.6	20; 0.7	X (>4)	X	X		X			1.73		
12	M	C	2.3	NT	None	1.0	30; 2.0	X (>4)	X	X					6.41	2.5	52
13	M	C	3.1	p155/140 (TIF1)	None	7.0	12.5; 0.8			X	X				**0.11**		28

Bold text indicates ALC below normal range for age.
[a]MSA testing completed at Oklahoma Medical Research Foundation (five), RDL Laboratory (three), Advance Diagnostics Laboratory (two) and ARUP Laboratory (one).
[b]Clinical features included: ILD, skin ulcerations, digital infarcts.
[c]Medication was received within the month prior to PJP onset; pulses: number of pulses the month prior to PJP.
[d]Medication was received within the 6 months prior to PJP onset; weeks: weeks elapsed since last dose.
[e]MSA testing did not include anti-HMGCR autoantibodies.
[f]MSA testing did not include anti-MDA5, anti-p155/140 (TIF1), anti-NXP2 or anti-HMGCR autoantibodies.
[g]Juvenile polymyositis. PJP: *Pneumocystis jirovecii* pneumonia; Pt: patient; F: female; M: male; His: Hispanic; AA: African American; C: Caucasian; Nat Am: Native American; JM: juvenile myositis; dx: diagnosis; MSA: myositis-specific autoantibody; MDA5: melanoma differentiation associated protein 5; NT: not tested; TIF1: transcription intermediary factor 1; NXP2: nuclear matrix protein-2; ILD: interstitial lung disease; U: skin ulcerations; DI: digital infarcts; IVMP: intravenous methylprednisolone; na: not answered; CSA: ciclosporin; RIT: rituximab; ALC: absolute lymphocyte count; ICU: intensive care unit.

and continuous variables as medians and interquartile range (IQR). Dichotomous comparisons for categorical variables were examined using χ^2 or Fisher's exact tests. Continuous variables were compared using Wilcoxon rank-sum. Odds ratios (ORs) and 95% CIs were calculated by logistic regression for significant differences. A two-sided *P*-value of $\leq$0.05 based on χ^2, Fisher's exact or Wilcoxon rank-sum was considered significant. Adjustment for multiple comparisons was not performed in this exploratory analysis.

Results

Myositis features

We received 13 cases of PJP+ JIIM patients. Twelve patients had JDM and one had juvenile polymyositis, seven were female, and the median age of JIIM diagnosis was 5.5 years (IQR 2.5–9.5) (Tables 1 and 2). PJP+ patients had less delay to myositis diagnosis compared with PJP– patients (2.2 *vs* 5.5 months; OR 0.9; 95% CI 0.8, 1.0) (Table 2). A higher percentage of PJP+ patients were Asian compared with PJP– patients (15 *vs* 2%; OR 8.7; 95% CI 1.3, 57.9). There were no differences in gender, clinical subgroup (JDM *vs* juvenile polymyositis) or age at myositis diagnosis (Table 2).

Of the 13 PJP+ patients, 5 had anti-melanoma differentiation associated protein 5 (MDA5) and 1 had anti-p155/140 (TIF1) autoantibodies; 3 were myositis-specific autoantibody negative and testing was incomplete in 4 patients. Anti-MDA5 autoantibodies were found more often in PJP+ compared with PJP– patients (56 *vs* 9%; OR 12.5; 95% CI 3.0, 52.4) (Table 2). At myositis diagnosis PJP+ patients also more often had digital infarcts (23 *vs* 1%; OR 43.8, 95% CI 4.2, 460.2), skin ulcerations, (54 *vs* 9%; OR 12.0, 95% CI 3.5, 41.2) and ILD (23 *vs* 3%; OR 10.6, 95% CI 2.1, 53.9), and less frequently had heliotrope rash (54 *vs* 82%; OR 0.3, 95% CI 0.1, 0.8) (Table 2). Most PJP+ patients presented with moderate or severe functional limitations (11/13) with moderate muscle weakness (7/13). There were no other significant differences in clinical features at myositis diagnosis between the groups (Table 2).

Within the month prior to PJP diagnosis, 8/13 patients received between one and more then four infusions of high-dose IVMP and PJP+ patients more often received IVMP than PJP– patients (62 *vs* 30%; OR 3.8; 95% CI 1.2, 12.4) (Tables 1 and 2). Within that time, all 13 PJP+ patients also received oral CS, 12 of whom received $\geq$20 mg and/or $\geq$1 mg/kg daily. Within 6 months prior to PJP diagnosis, 8/13 patients received IVIG, 8/13 received MTX, 2/13 received ciclosporin, 2/13 received CYC and 4/13 received rituximab (Table 1). Compared with PJP– patients, PJP+ patients more often received rituximab (31 *vs* 1%; OR 52.0; 95% CI 5.2, 515.4), and received a higher total number of immunosuppressive therapies (median 3.0 *vs* 2.0; OR 2.4; 95% CI 1.3, 4.5) (Table 2).

Features of PJP infection

The median age at PJP diagnosis was 6.1 years (IQR 2.6–10.5). PJP occurred shortly after myositis diagnosis in the majority of patients, with a median time from JIIM diagnosis to PJP diagnosis of 2.3 months (IQR 1.7–7) (Table 1). At PJP diagnosis, overall JIIM disease severity was rated as moderate or severe in 10/13 patients. The majority of patients who developed PJP presented with new onset dyspnoea (10/13), cough (10/13), fever (9/13), hypoxia (12/13) and tachypnoea (11/13). Lymphopenia was reported in four patients at PJP diagnosis (Table 1). The most common chest radiograph findings were diffuse reticular opacities (7/13); however, lobar and multilobar consolidations (4/13), pleural effusions (3/13) and pneumothorax with pneumomediastinum (1/13) were also observed. Although prior imaging was not available for comparison, chest CT at PJP diagnosis often revealed ground-glass opacities (6/8), with multi-lobar or lobar consolidations (3/8), reticular opacities (1/8), pulmonary nodules (1/8) and pleural effusions (1/8). PJP was often diagnosed by staining and/or PCR on bronchoalveolar lavage (11/13). Two patients also had rhinovirus/enterovirus co-infection. Seven patients were admitted to the paediatric intensive care unit for management of PJP for a median of 28 days (IQR 4–111), and five patients required mechanical ventilation, two of whom required extracorporeal membrane oxygenation. Four patients died due to PJP or infection related complications: one developed ILD after PJP onset (patient 4), one had pseudomonas/trichosporon coinfection (patient 12) and three were under the age of 3 years (Table 1). Patients 4 and 9, both of whom died, had long periods of paediatric intensive care unit admission due to severe pulmonary disease as sequelae from PJP infection (Table 1). All 13 patients were treated with trimethoprim–sulfamethoxazole following PJP diagnosis; no patients were treated with prophylaxis prior to developing PJP.

Discussion

We report 13 patients with JIIM who developed PJP infection. Children who developed PJP were more often Asian and more often had anti-MDA5 autoantibodies, digital infarcts, skin ulcerations and ILD compared with PJP– patients, which highlights the distinct clinical features of JIIM patients who may be more susceptible to PJP. Patients who developed PJP often had moderate to severe disease and more often received IVMP, rituximab and a greater number of immunosuppressive therapies, suggesting that JIIM disease severity and/or immune suppression may be associated with the development of PJP. Seven patients were admitted to the paediatric intensive care unit and four patients died, indicating that significant morbidity and mortality is associated with PJP in JIIM.

We found that anti-MDA5 autoantibodies and the phenotypic features associated with this autoantibody

TABLE 2 Comparison of clinical features at diagnosis between juvenile myositis patients who developed PJP and patients without PJP

	PJP+ (*N* = 13), % (*n*/*N*) or median (IQR)	PJP– (*N* = 147), % (*n*/*N*) or median (IQR)	*P*-value	OR (95% CI)
JDM	92 (12/13)	94 (138/147)	0.6	
JPM	8 (1/13)	6 (9/147)	0.6	
Female, %	54 (7/13)	65 (95/147)	0.5	
Age at diagnosis, years	5.5 (2.5–9.5)	7.9 (5.4–12.1)	0.1	
Delay to myositis diagnosis, months	2.2 (1.3–6.5)	5.5 (2.5–11.8)	0.02	0.9 (0.8, 1.0)
Race				
Caucasian	46 (6/13)	73 (107/147)	0.06	
African American	15 (2/13)	7 (11/147)	0.3	
Hispanic	8 (1/13)	6 (9/147)	0.6	
Asian	15 (2/13)	2 (3/147)	0.05	8.7 (1.3, 57.9)
Native American	8 (1/13)	0 (0/147)	0.08	
Mixed	8 (1/13)	12 (17/147)	1.0	
Myositis autoantibody status				
Anti-p155/140 (TIF1)	11 (1/9)[a]	37 (53/143)[b]	0.2	
Anti-NXP2	0 (0/9)[a]	28 (40/143)[b]	0.1	
Anti-MDA5	56 (5/9)[a]	9 (13/143)[b]	0.001	12.5 (3.0, 52.4)
Anti-synthetase	0 (0/11)[a]	5 (7/147)	1.0	
Anti-SRP	0 (0/11)[a]	3 (4/143)[b]	1.0	
Anti-Mi2	0 (0/11)[a]	2 (3/143)[b]	1.0	
MSA negative	33 (3/9)[a]	14 (21/147)	0.1	
Clinical features at diagnosis				
Alopecia	8 (1/12)[a]	12 (17/147)	1.0	
Malar rash	54 (7/13)	77 (112/145)[b]	0.09	
Shawl sign	15 (2/13)	28 (38/136)[b]	0.5	
Periungual capillary changes	83 (10/12)[a]	79 (104/132)[b]	1.0	
Heliotrope	54 (7/13)	82 (117/143)[b]	0.03	0.3 (0.1, 0.8)
Gottron's papules	77 (10/13)	90 (130/144)[b]	0.2	
Skin ulcerations	54 (7/13)	9 (13/147)	<0.001	12.0 (3.5, 41.2)
Digital infarcts	23 (3/13)	1 (1/147)	0.002	43.8 (4.2, 460.2)
RP	17 (2/12)[a]	6 (9/144)[b]	0.2	
Calcinosis	17 (2/12)[a]	3 (5/147)	0.09	
Interstitial lung disease	23 (3/13)	3 (4/145)[b]	0.01	10.6 (2.1, 53.9)
Dysphagia	38 (5/13)	33 (47/144)[b]	0.8	
Dysphonia	46 (6/13)	27 (38/140)[b]	0.2	
Gastrointestinal ulcerations	0 (0/13)	0 (0/147)	1.0	
Arthritis	46 (6/13)	44 (61/140)[b]	0.9	
Contractures	33 (4/12)[a]	51 (69/134)[b]	0.2	
Constitutional symptoms[c]	92 (12/13)	96 (141/147)	0.5	
Worst ACR Functional Class	4 (3–4)	4 (3–4)	0.9	
Medications received prior to PJP infection				
Oral CS[d]	100 (13/13)	96 (113/118)[b]	1.0	
Daily prednisone dose (mg/kg)	1.0 (0.8–1.7)	1.4 (0.8–2.0)	0.5	
IVMP[d]	62 (8/13)	30 (35/118)[b]	0.03	3.8 (1.2, 12.4)
MTX[e]	77 (10/13)	88 (104/118)[b]	0.4	
IVIG[e]	62 (8/13)	47 (56/118)[b]	0.3	
MMF[e]	8 (1/13)	8 (10/118)[b]	1.0	
Ciclosporin[e]	15 (2/13)	4 (5/118)[b]	0.1	
CYC[e]	15 (2/13)	5 (6/118)[b]	0.2	

(continued)

Table 2 Continued

	PJP+ (*N* = 13), % (*n*/*N*) or median (IQR)	PJP– (*N* = 147), % (*n*/*N*) or median (IQR)	*P*-value	OR (95% CI)
Rituximab[e]	31 (4/13)	1 (1/118)[b]	<0.001	52.0 (5.2, 515.4)
Total number of immunosuppressives[f]	3.0 (2.0–4.0)	2.0 (2.0–3.0)	0.02	2.4 (1.3, 4.5)

Dichotomous variables were expressed as percentage (count) and continuous variables as median (IQR). Univariate comparisons of continuous variables were made using Wilcoxon rank-sum while dichotomous variables were compared either using chi-squared test or Fisher's exact test, as appropriate.
[a]$N \neq 13$ due to missing data.
[b]$N \neq 147$ due to missing data.
[c]Fever, weight loss and/or fatigue.
[d]Received within the month prior to PJP onset or 1.3–2.3 months after myositis diagnosis in PJP– patients.
[e]Received within the 6 months prior to PJP onset or 0–6 months after myositis diagnosis in PJP– patients.
[f]Oral steroids, IVMP, MTX, MMF, CYC, ciclosporin and/or rituximab. PJP: *Pneumocystis jirovecii* pneumonia; JPM: juvenile polymyositis; TIF1: transcription intermediary factor 1; NXP2: nuclear matrix protein-2; MDA5: melanoma differentiation associated protein-5; SRP: signal recognition particle; MSA: myositis-specific autoantibody; IVMP: i.v. methylprednisolone; IQR: interquartile range; OR: odds ratio.

group [9, 11, 12], including Asian race, ILD, skin ulcerations and digital infarcts, were present at higher frequencies in PJP+ patients. Our findings corroborate reports of severe PJP infections in anti-MDA5 autoantibody-positive IIM patients [13], and descriptions of coexisting pulmonary disease as a risk factor for PJP in RA [14]. Furthermore, our findings are consistent with the recent report from an American nationwide hospital study by Ren *et al.* [15], which found ILD to be a risk factor for infections, including PJP, in IIM/JIIM. PJP infections are known to disproportionally affect patients with non-rheumatic pulmonary disorders [16, 17], suggesting that underlying lung disease may serve as a permissive environment for opportunistic pathogens. It is also plausible that some JIIM patients have pre-existing PJP colonization prior to the initiation of immunosuppressive therapy [18]. Screening for PJP by bronchoalveolar lavage should be considered in JIIM patients presenting with ILD or severe respiratory symptoms, and all JIIM patients should be screened for ILD at diagnosis [19].

In studies of IIM, risk factors for PJP include more immunosuppressive therapy, oral prednisone ≥20 mg/day and lymphopenia [5]. Thus, the association of PJP infection with more immunosuppression, especially rituximab and IVMP, was not unexpected; however, we found daily oral steroid dosing was similar between groups. This may be explained by the generally accepted practice to initiate high-dose CS early in JIIM disease course [19, 20]. It is notable that PJP+ patients who developed infection further out from myositis diagnosis (13–51 months) were receiving ≥20 mg/day prednisone daily, and the only PJP+ JIIM patient receiving lower doses of daily prednisone had profound lymphopenia. In our PJP+ cohort, four patients had lymphopenia at PJP diagnosis. Thus, higher doses of oral steroids and lymphopenia may also be associated with PJP infection in JIIM, but we were unable to identify these as risk factors due to our small sample size and data limitations. Overall, our study supports the use of prophylaxis in patients on more intensive immunosuppressive regimens, including patients receiving rituximab and i.v. pulse steroids.

The median time that patients developed PJP infection was 2.3 months after myositis diagnosis, implying this infection disproportionately affects patients early in their disease, when JIIM manifestations are typically most severe and potent induction immunosuppressive therapy is being administered. Most patients with PJP also had moderate-to-severe disease at JIIM onset, suggesting that risk factors for PJP not only include more immunosuppressive therapy, but also more severe disease. Lastly, PJP+ patients had significantly less time from initial JIIM symptom onset to JIIM diagnosis, suggesting that their initial disease manifestations may have been not only severe, but also more accelerated compared with PJP– patients. The association of PJP infection early in the course of JIIM diagnosis underscores the importance of considering prophylaxis in newly diagnosed JIIM. It is also notable that three of the four patients who died were under the age of 3 years, highlighting that younger children may be affected more severely with PJP and its complications.

This study has several limitations, and follow-up confirmatory studies are needed. First, since patient data were collected retrospectively by physician chart review, patients had incomplete or unavailable data, such as cumulative medication dosage and standardized strength testing by the Childhood Myositis Assessment Scale; in addition, the diagnosis of ILD was not standardized among patients. Secondly, several PJP+ patients also had incomplete or no myositis autoantibody testing, and testing was performed at several commercial laboratories using different methods. Furthermore, the PJP–medication analysis may have resulted in comparing

different time periods in the illness course from PJP+ patients, resulting in differences in the immunosuppressive therapies. In addition, some of the identified risk factors for PJP have wide CIs due to the small sample size of PJP+ patients. Lastly, this study was susceptible to both recall and referral biases, as physicians may have submitted patients with the most severe PJP infections or referred PJP– patients with more severe disease to the National Institutes of Health studies. However, the decision to use the National Institutes of Health cohort as the PJP– comparator population was based on geographic similarity and the availability of more complete clinical and laboratory data, including myositis-specific autoantibody testing and medications received.

These limitations notwithstanding, our study shows that PJP can be a serious complication in JIIM. We identified that PJP more often affects JIIM patients early in their disease course, when patients have more severe manifestations requiring more intensive therapy. Importantly, we also identified anti-MDA5 autoantibodies, digital infarcts, skin ulcerations and ILD as risk factors for developing PJP infection in JIIM. Thus, prophylaxis should be strongly considered in JIIM patients, especially those early in the disease course with these clinical features, and those who have received IVMP and multiple immunosuppressive therapies, particularly rituximab.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008;371:2201–12.

2 Marie I, Hachulla E, Cherin P *et al.* Opportunistic infections in polymyositis and dermatomyositis. Arthritis Rheum 2005;53:155–65.

3 Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol 2007;26:663–70.

4 Mecoli CA, Saylor D, Gelber AC, Christopher-Stine L. Pneumocystis jiroveci pneumonia in rheumatic disease: a 20-year single-centre experience. Clin Exp Rheumatol 2017;35:671–3.

5 Tadros S, Teichtahl AJ, Ciciriello S, Wicks IP. Pneumocystis jirovecii pneumonia in systemic autoimmune rheumatic disease: a case-control study. Semin Arthritis Rheum 2017;46:804–9.

6 Schmajuk G, Jafri K, Evans M *et al.* Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum 2019;48:1087–92.

7 Giancane G, Swart JF, Castagnola E *et al.* Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. Arthritis Res Ther 2020;22:71.

8 Harris PA, Taylor R, Thielke R *et al.* Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

9 Rider LG, Shah M, Mamyrova G *et al.* The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) 2013;92:223–43.

10 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.

11 Tansley SL, Betteridge ZE, Gunawardena H *et al.* Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. Arthritis Res Ther 2014;16:R138.

12 Kobayashi I, Okura Y, Yamada M *et al.* Anti-melanoma differentiation-associated gene 5 antibody is a diagnostic and predictive marker for interstitial lung diseases associated with juvenile dermatomyositis. J Pediatr 2011;158:675–7.

13 Aymonier M, Abed S, Boyé T *et al.* Dermatomyositis associated with anti-MDA5 antibodies and pneumocystis pneumonia: two lethal cases. Ann Dermatol Venereol 2017;144:279–83.

14 Katsuyama T, Saito K, Kubo S, Nawata M, Tanaka Y. Prophylaxis for Pneumocystis pneumonia in patients with rheumatoid arthritis treated with biologics, based on risk factors found in a retrospective study. Arthritis Res Ther 2014;16:R43.

15 Ren Z, Laumann AE, Silverberg JI. Association of dermatomyositis with systemic and opportunistic infections in the United States. Arch Dermatol Res 2019;311:377–87.

16 Khodavaisy S, Mortaz E, Mohammadi F *et al.* Pneumocystis jirovecii colonization in chronic obstructive pulmonary disease (COPD). Curr Med Mycol 2015;1:42–8.

17 Sing A, Roggenkamp A, Autenrieth IB, Heesemann J. Pneumocystis carinii carriage in immunocompetent patients with primary pulmonary disorders as detected by single or nested PCR. J Clin Microbiol 1999;37:3409–10.

18 Xue T, Ma Z, Liu F *et al.* Pneumocystis jirovecii colonization and its association with pulmonary diseases: a multicenter study based on a modified loop-mediated isothermal amplification assay. BMC Pulm Med 2020;20:70.

19 Bellutti Enders F, Bader-Meunier B, Baildam E *et al.* Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis 2017;76:329–40.

20 Huber AM, Robinson AB, Reed AM *et al.* Consensus treatments for moderate juvenile dermatomyositis: beyond the first two months. Results of the second Childhood Arthritis and Rheumatology Research Alliance consensus conference. Arthritis Care Res (Hoboken) 2012;64:546–53.