Treatment outcomes in 63 cases of juvenile dermatomyositis-associated calcinosis

B.Y. Yi[1], D.M. Wahezi[2], L. Covert[3], K. Ardalan[3], J. Hui-Yuen[4], N. Vasquez-Canizares[2], D.M. Mosa[5], M. Jones[6], C. Correll[7], A. Begezda[8], S. Shenoi[9], E.Y. Wu[10], L.K. Kovalick[10], W.B. Lapin[11], S.E. Tarvin[12], M.S. Oliver[12], M.M. Rodriguez[12], I. Marmor[13], K.W. Baszis[14], A.J. Taxter[15], A.C. Hanson[16], C.S. Crowson[16], A.B. Orandi[17]
for the CARRA Juvenile Dermatomyositis, Calcinosis Subcommittee

[1]Department of Paediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Paediatric Rheumatology, The Children's Hospital at Montefiore, Bronx, New York, USA; [3]Paediatric Rheumatology, Duke Health, Durham, NC, USA; [4]Paediatric Rheumatology, Cohen Children's Medical Center, New Hyde Park, New York, USA; [5]Rheumatology and Rehabilitation, Mansoura University Hospital, Mansoura City, Egypt; [6]Department of Dermatology, Keck School of Medicine at USC, Los Angeles, CA, USA; [7]Division of Paediatric Rheumatology, University of Minnesota Medical School, Minneapolis, MN, USA; [8]Paediatric Rheumatology, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA; [9]Rheumatology, Seattle Children's Hospital, Seattle, WA, USA; [10]Paediatric Rheumatology, UNC School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [11]Rheumatology, Connecticut Children's, Hartford, CT, USA; [12]Paediatric Rheumatology, Riley Children's Health, Indianapolis, IN, USA; [13]Department of Paediatrics, Dana-Dwek Children's Hospital, Tel Aviv, Israel; [14]Paediatric Rheumatology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA; [15]Rheumatology, Nationwide Children's Hospital, Columbus, OH, USA; [16]Division of Clinical Trials and Biostatistics, [17]Division of Paediatric Rheumatology, Mayo Clinic, Rochester, MN, USA.

Abstract

Objective

We performed a multi-institutional retrospective review of patients treated for juvenile dermatomyositis (JDM)-associated calcinosis to analyse the association between treatment outcomes and patient, disease, and treatment characteristics.

Methods

Childhood Arthritis and Rheumatology Research Alliance investigators searched their electronic health records for patients with JDM and calcinosis treated between 2003 and 2019 and analysed data at JDM diagnosis, calcinosis diagnosis, and calcinosis treatment. Statistical methods included univariable and multivariable analyses, Kaplan-Meier estimates, and multivariable Cox models.

Results

Data were collected for 63 patients from 11 institutions. Median (IQR) age was 7.8 (4.1–11.1) years at JDM diagnosis and 9.4 (5.7–13.3) years at calcinosis diagnosis. Calcinosis was present at JDM diagnosis in 32% of patients (n=20). JDM was active in 76% of patients (47/62) at calcinosis diagnosis. Anti-nuclear matrix protein 2 (anti-NXP2) antibody was the most commonly detected myositis autoantibody (38%, 12/32). The presence of anti-NXP2 or anti-melanoma differentiation-associated gene 5 autoantibody did not significantly affect the probability of any calcinosis improvement (p=0.30). Patients received 103 unique treatment regimens of immunomodulatory agents with or without calcium-modifying agents, but those who received both had the greatest probability of improvement. Intravenous immunoglobulin (IVIG) was associated with a significantly higher probability of calcinosis improvement (p=0.02) than treatments without IVIG. Overall, 79% of patients (n=50) showed improved calcinosis.

Conclusion

Despite wide variations in treatment, many patients showed calcinosis improvement over time, especially those treated with IVIG. Studies using validated outcomes assessments may be needed to develop effective treatment plans for JDM-associated calcinosis.

Key words
connective tissue diseases, intravenous immunoglobulins, myositis

Belina Y. Yi, DO
Dawn M. Wahezi, MD, MS
Lauren Covert, MD
Kaveh Ardalan, MD, MS
Joyce Hui-Yuen, MD, MS
Natalia Vasquez-Canizares, MD, MS
Doaa Mosad Mosa, MD
Madison Jones, MD
Colleen Correll, MD, MPH
Alexis Begezda, MD
Susan Shenoi, MBBS, MS, RhMSUS
Eveline Y. Wu, MD, MSCR
Leonard K. Kovalick, CPNP
W. Blaine Lapin, MD
Stacey E. Tarvin, MD, MS
Melissa S. Oliver, MD
Martha M. Rodriguez, MD
Itay Marmor, MD
Kevin W. Baszis, MD
Alysha J. Taxter, MD, MSCE
Andrew C. Hanson, MS
Cynthia S. Crowson, PhD
Amir B. Orandi, MD

Please address correspondence to:
Amir B. Orandi
Division of Pediatric Rheumatology,
Mayo Clinic,
200 First St. SW,
Rochester, MN 55905, USA.
E-mail: orandi.amir@mayo.edu

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Competing interests: see page 396.

Introduction

Juvenile dermatomyositis (JDM) is an autoimmune disease of unknown aetiology characterised by chronic inflammation of striated muscle and skin (1). JDM is the most common juvenile idiopathic inflammatory myopathy. The diagnosis of JDM is based on the Bohan and Peter criteria (2), which consist of symmetric proximal muscle weakness, elevated muscle enzyme levels, muscle inflammation on biopsy, distinctive electromyographic findings, and characteristic skin manifestations (*e.g.* Gottron papules and heliotrope rash). The European Alliance of Associations for Rheumatology/American College of Rheumatology developed classification criteria for adult and juvenile idiopathic inflammatory myopathies with a scoring system that can be calculated with or without biopsy results (3).

A common complication of JDM is calcinosis, which has a prevalence of approximately 20% to 40% in different populations (1, 4-6). Calcinosis is the dystrophic formation of calcium carbonate apatite in the skin or subcutaneous tissue, which can lead to muscle atrophy, skin ulcers, and joint contractures, resulting in pain, infection, and disability (1, 7). Consequent changes in physical appearance can also be stressful. Calcinosis is often localised to areas with increased pressure (*e.g.* hamstrings), repetitive use (*e.g.* joints such as elbows and knees), and trauma. Although the pathogenesis of calcinosis is not well understood, suggested mechanisms include inflammation driven by macrophages, proinflammatory cytokines (*e.g.* interleukin 6, 1, and 18; tumour necrosis factor [TNF]-α; and interferons), calcium metabolism-related proteins, and mitochondrial markers associated with muscle damage (1, 8). Autoantibodies associated with calcinosis include myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs). In addition, anti-nuclear matrix protein 2 (anti-NXP2) autoantibody has been associated with an increased risk of calcinosis (1, 6, 9). Other factors associated with an increased risk of calcinosis in patients with JDM are prolonged duration of untreated disease, poor control of disease, younger age at disease onset, abnormal results of nailfold capillaroscopy, and race classification of Black (10-13).

Historically, no definitive treatment approach exists for JDM-associated calcinosis, and most clinical practice is guided by the results of small observational studies, case series, and case reports (7, 14, 15). Various therapies have been used to treat calcinosis, including glucocorticoids, non-biologic disease-modifying anti-rheumatic drugs (DMARDs), intravenous immunoglobulin (IVIG), biologic DMARDs (*e.g.* TNF inhibitors, abatacept, and rituximab), and calcium-modifying agents (*e.g.* bisphosphonates, calcium channel blockers, and sodium thiosulfate) (7, 14-19). Positive outcomes in reducing the frequency of calcinosis have been observed after early and intensive treatment with glucocorticoids and/or other immunosuppressive therapy (16, 17). A recent study showed that systemic glucocorticoids administered at lower doses (median dose, 0.85 mg/kg/d) than those typically used combined with other glucocorticoid-sparing agents could be as effective as using higher, prolonged doses of glucocorticoids in controlling underlying moderate to severe JDM and calcinosis (20). However, no single agent or therapeutic class of treatment is universally effective.

In this multi-institutional retrospective study of patients diagnosed with JDM-associated calcinosis, we analysed calcinosis treatment outcomes and their association with patient, disease, and treatment characteristics.

Methods

Study design

Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a collaborative research network for paediatric rheumatologists in North America. CARRA investigators from 11 institutions used billing codes or clinical terms to retrospectively search their electronic health records for patients diagnosed with JDM and calcinosis. We included paediatric patients with both JDM and calcinosis, defined as those younger than 18 years at the time of JDM diagnosis per probable or

definite Bohan and Peter criteria. Patients were included only if they were treated between January 1, 2003, and December 31, 2019, which is the contemporary treatment era when biologic DMARDs became more prevalent and available to treat JDM (20-24). Patients were excluded who had another primary autoimmune disease or overlap syndrome. This study received exemption from the Mayo Clinic Institutional Review Board.

Data collection

Study data were collected and managed by using REDCap (Research Electronic Data Capture) hosted at Mayo Clinic (25, 26). REDCap is a secure, web-based software platform designed to support data capture for research studies. For the collection of retrospective data, CARRA investigators completed multiple data collection forms pertaining to patient, disease, and treatment characteristics at different time points of disease and/or treatment (See online Supplementary material). These time points were at JDM diagnosis, calcinosis diagnosis, and calcinosis treatment response (*i.e.* when maximal treatment response was achieved and/or when the treatment regimen was altered or discontinued).

Patient characteristics abstracted included self-reported sex assigned at birth and race and ethnicity (Asian; Black, African American, African, or Afro Caribbean; Hispanic, Latino, or Spanish origin; Middle Eastern or North African; White; or unknown). JDM disease characteristics abstracted included details of JDM disease course such as age at JDM diagnosis and follow-up visits, MSAs or MAAs present, and type of disease course (*i.e.* monocyclic, polycyclic, chronic continuous, or not applicable for disease duration <2 years). Other disease characteristics abstracted included the age at initial JDM diagnosis, approximate duration of JDM symptoms before JDM diagnosis, and types of treatment provided for JDM. Types of immunomodulatory treatments were divided into categories of glucocorticoids, immunosuppressants, non-biologic DMARDs, IVIG, and biologic DMARDs. Immunosuppressants included methotrexate, leflunomide, azathioprine, mycophenolate mofetil, mycophenolic acid, sirolimus, tacrolimus, thalidomide, lenalidomide, cyclosporine, hydroxychloroquine, sulfasalazine, cyclophosphamide, and colchicine. Non-biologic DMARDs included tofacitinib, baricitinib, and ruxolitinib. Biologic DMARDs included rituximab, etanercept, infliximab, adalimumab, certolizumab, golimumab, anakinra, canakinumab, rilonacept, abatacept, and tocilizumab. At the time of calcinosis diagnosis, any additional treatments prescribed specifically for calcinosis were recorded. These included various calcium-modifying agents that affect calcium or phosphorus, including bisphosphonates, vitamin D, vitamin C, calcium-channel blockers, sodium thiosulfate, aluminium hydroxide, warfarin, minocycline, and probenecid. Calcinosis treatment outcomes were determined by the subjective review of a clinician according to abstracted parameters and were categorised as complete/total resolution (hereafter, complete resolution), moderate/significant improvement (hereafter, moderate improvement), mild/partial improvement (hereafter, mild improvement), unchanged without new lesions, or worsened calcinosis. Patients who had moderate improvement or complete resolution were designated as the 'major improvement' subgroup. Investigators reported the maximal calcinosis treatment response for each medication that was specifically prescribed to treat JDM-associated calcinosis. Overall JDM disease activity (reported as muscle strength, muscle enzyme levels, inflammatory marker levels, skin examination results, and/or damage indicators) was recorded at initial JDM diagnosis, calcinosis diagnosis, and maximal calcinosis treatment response.

Statistical analysis

Patient, disease, and treatment characteristics are summarised as median (IQR) for continuous variables and as number (percentage) for categorical variables. Univariable and multivariable Cox models were used to assess the association between patient, disease, and treatment factors and outcomes. Outcomes of interest were any improvement and major improvement of calcinosis after treatment. Because patients underwent multiple treatments over time, treatment was included as a time-dependent variable in the Cox models. Multivariable models were adjusted for age, sex, and time from initial JDM diagnosis to calcinosis diagnosis. Results from the Cox models are reported as hazard ratios (HRs) with 95% CIs. An HR greater than 1 indicates that the factor is associated with improvement. The proportion of patients with improvement was estimated both overall and according to the initial treatment regimen by using Kaplan-Meier estimates; data are presented graphically. When not all data were available for specific characteristics, complete-case analysis was used. A *p*-value less than .05 was considered statistically significant. All analyses were performed by using R (v. 4.2.2, R Foundation for Statistical Computing).

Results

Our study included 63 paediatric patients with JDM-associated calcinosis. Patient, disease, and treatment characteristics are shown in Table I. The median (IQR) age at JDM diagnosis was 7.8 (4.1–11.1) years, and the median symptom duration before diagnosis was 5 (2–12) months. At calcinosis diagnosis, the median age was 9.4 (5.7–13.3) years, and the median symptom duration before diagnosis was 2 (1–4) months. Calcinosis was present at JDM diagnosis in 32% of patients (n=20). MAAs and MSAs were screened in 79% of patients (n=50), and 50% of those (25/50) had positive test results for a myositis autoantibody. The most common myositis autoantibody detected was anti-NXP2 (38%, 12/32), followed by anti-melanoma differentiation-associated gene 5 (anti-MDA5) autoantibody (15%, 5/33). Overall, the most common disease course was chronic continuous (70%, n=44).

At calcinosis diagnosis, JDM was considered active in 76% of patients (47/62), with active skin involvement in 81% (n=51) and muscle involvement in 49% (n=31); 65% of patients (n=41) were taking background medication(s).

Table I. Patient, disease, and treatment characteristics.

Characteristic	Value[a] (n=63)
Age at JDM diagnosis, y	7.8 (4.1–11.1)
Duration of JDM symptoms before JDM diagnosis, mo.	5 (2–12)
Age at calcinosis diagnosis, y	9.4 (5.7–13.3)
Duration of calcinosis symptoms before calcinosis diagnosis, mo.	2 (1–4)
Sex	
Men	18 (29)
Women	45 (71)
Race and ethnicity	
Asian	1 (2)
Black, African American, African, or Afro Caribbean	12 (19)
Hispanic, Latino, or Spanish origin	17 (27)
Middle Eastern or North African	6 (10)
White	25 (40)
Unknown	2 (3)
JDM disease course	
Monocyclic	2 (3)
Polycyclic	10 (16)
Chronic continuous	44 (70)
Not applicable (if <2 years since JDM diagnosis)	7 (11)
Myositis antibody	25 (50) (n=50)
Anti-Jo-1	3 (6) (n=47)
Anti-MDA5	5 (15) (n=33)
Anti-Mi-2	3 (7) (n=42)
Anti-NXP2	12 (38) (n=32)
Anti-TIF1-γ	5 (14) (n=35)
Anti-U1RNP	1 (3) (n=36)
Clinical characteristic at JDM diagnosis	
Calcinosis present	20 (32)
Aggressive treatment of JDM[b]	38 (60)
Clinical characteristic at calcinosis diagnosis	
Active JDM	47 (76) (n=62)
Moderate to severe JDM	33 (52)
Active muscle involvement	31 (49)
Active skin involvement	51 (81)
Background medication(s)[c]	41 (65)
Treatment after calcinosis diagnosis	
None	11 (17)
Immunomodulatory agent(s)[d]	28 (44)
Immunomodulatory agent(s) + Calcium-modifying agent(s)	19 (30)
Calcium-modifying agent(s)[e]	5 (8)
Specific type of immunomodulatory agent	
Immunosuppressant(s)	30 (48)
IVIG	20 (32)
Biologic DMARDs	4 (6)
Specific type of Calcium-modifying agent	
Bisphosphonates	13 (21)
Surgical excision resulting from referral	7 (11)

Anti-MDA5: anti-melanoma differentiation-associated gene 5; anti-NXP2: anti-nuclear matrix protein 2; anti-TIF1-γ: anti-transcriptional intermediary factor 1-gamma; anti-U1RNP: anti-U1 ribonucleoprotein; DMARDs: disease-modifying anti-rheumatic drugs; IVIG: intravenous immunoglobulin; JDM: juvenile dermatomyositis.
[a]Continuous variables are summarised as median (IQR). Categorical variables are summarised as number (%).
[b]Designates receiving intravenous methylprednisolone (≥2 mg/kg/d) for more than 1 week, and/or cyclophosphamide, and/or IVIG, and/or rituximab within the first 3 months of JDM diagnosis.
[c]Includes but is not limited to glucocorticoids, immunosuppressants, IVIG, and biologic DMARDs.
[d]Includes glucocorticoids, immunosuppressants, non-biologic DMARDs, IVIG, and biologic DMARDs.
[e]Includes agents that affect calcium or phosphorus.

At calcinosis diagnosis, 81% of patients (51/63) were prescribed immunomodulatory agents, and 54% (34/63) were prescribed calcium-modifying agents. Overall, a total of 103 unique treatment regimens were used to treat calcinosis. Most patients received more than 1 regimen with multiple drug combinations.

Calcinosis treatment outcomes were more often determined on the basis of history and physical examination findings (96%, 122/127) than imaging (14%, 18/127) (Table II). Kaplan-Meier estimates showed that calcinosis improvement (mild improvement, moderate improvement, or complete resolution) occurred in roughly 40% of patients by 1 year and in approximately 62% of patients by 2 years (Fig. 1A). By 4 years, 80% of patients showed calcinosis improvement. Overall, 79% of patients (n=50) showed improvement: 22% (n=14) had complete resolution, 38% (n=24) had moderate improvement, and 19% (n=12) had mild improvement. When we compared the different treatment approaches, non-significant associations were observed between calcinosis improvement and treatment regimens with immunomodulatory agents, either alone or combined with calcium-modifying agents (Table III). IVIG was the only treatment regimen significantly associated with any improvement (adjusted HR, 1.95 [95% CI, 1.10–3.45]; p=0.02) (Table III). Patients who received a combination of immunomodulatory agents and calcium-modifying agents had the greatest probability of reaching improvement (Fig. 2A). Several factors were studied to determine their potential influence on the success or degree of success in treating calcinosis. Either active JDM with skin involvement at the time of calcinosis diagnosis or a positive test result for anti-NXP2 or anti-MDA5 autoantibodies showed a lower likelihood of calcinosis improvement, although these associations were not statistically significant (Table IV).

When we repeated this analysis for the major improvement subgroup, Kaplan-Meier estimates for major improvement were not substantially lower than those for any improvement over time (Fig. 1B). By 4 years, approximately 60% of patients reached major improvement, whereas 80% reached any improvement. Overall, approximately 80% of patients showed major improvement. IVIG and immunomodulatory therapies, taken with or without calcium-modifying agents, were associated with major improvement,

Table II. Parameters used to assess treatment response of calcinosis[a].

Parameter	Total no. of visits (n=127)	no. of visits with complete calcinosis resolution reported (n=14)
Change in history or physical examination findings[b]	122 (96)	13 (93)
Change in patient factors[c]	82 (65)	6 (43)
Change in other calcinosis effects[d]	44 (35)	2 (14)
Change in imaging[e]	18 (14)	2 (14)

[a]Data are presented as number (%).
[b]Size or number, warmth or redness, drainage, and/or texture.
[c]Level of pain, range of motion, mobility, cosmesis, quality of life, Childhood Health Assessment Questionnaire, and/or Depression Anxiety Stress Scale.
[d]Mass effect, contracture, infection, erosion, fistula, lipoatrophy, lipodystrophy, cutaneous atrophy, and/or sclerosis.
[e]Radiography, magnetic resonance imaging, scintigraphy, computed tomography, and/or ultrasonography.

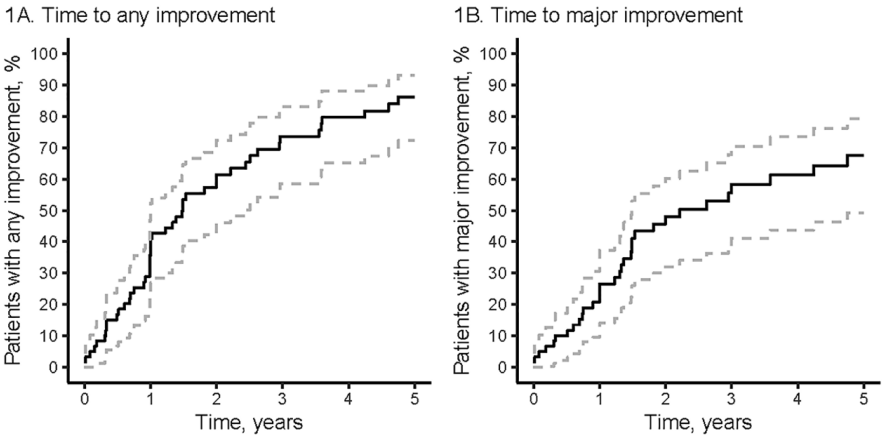

Fig. 1. Calcinosis improvement after calcinosis diagnosis. A and B, Kaplan-Meier estimates (solid lines) with 95% CIs (broken lines) show the percentage of patients with (**A**) any improvement or (**B**) major improvement. Major improvement is defined as complete resolution and/or moderate improvement.

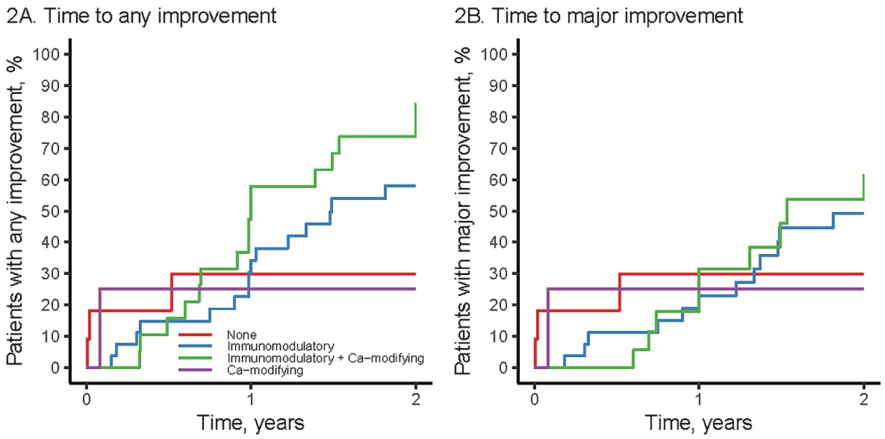

Fig. 2. Calcinosis improvement by initial treatment regimen. A and B, Kaplan-Meier estimates show the percentage of patients with (**A**) any improvement or (**B**) major improvement according to initial treatment regimen. Major improvement is defined as complete resolution and/or moderate improvement.

although these associations were not significant (Table III). Patients who received immunomodulatory therapy with concomitant calcium-modifying agent(s) were the most likely to reach major improvement (Fig. 2B). The presence of anti-NXP2 or anti-MDA5 autoantibodies was associated with a lower yet non-significant likelihood of major improvement (Table IV).

Discussion

Calcinosis is a poorly understood sequela of JDM and can lead to infection, disfigurement, pain, and limited mobility (1, 7). No standard treatment has been established for calcinosis, with possible treatment regimens ranging broadly from different immunomodulatory agents to various calcium-modifying agents (1, 7, 9, 14). In a multi-institutional survey, many paediatric rheumatologists reported limited experience with treating JDM-associated calcinosis (14). Here, we performed a collaborative, multi-institutional study to improve our understanding of factors that may affect treatment outcomes in patients with JDM-associated calcinosis. In one of the largest studies of its kind, we show that most patients treated for JDM-associated calcinosis showed partial improvement over time. In our cohort of 63 patients with JDM-associated calcinosis, 103 unique treatment regimens were used, including immunomodulatory agents and calcium-modifying agents. Although most patients showed no improvement within the first 1 to 2 years of calcinosis treatment, most patients showed some improvement by 4 years. Thus, noticeable improvement may require long-term treatment. In our sub-analysis of patients who showed major improvement, more than 50% of them reached major improvement by 3 years. However, many patients reached major improvement during follow-up years 3 through 10. Given our findings that some patients may require long-term treatment to reach major improvement, studies using validated outcomes assessments may be needed to develop effective treatment plans for JDM-associated calcinosis.

We found that treatment with IVIG was significantly associated with improved calcinosis. According to a CARRA survey (14) and CARRA Legacy Registry (27), IVIG was the immunomodulatory agent most frequently used for treating JDM-associated calcinosis. Furthermore, some published reports have shown improved refractory calcinosis after IVIG treatments (28, 29). Although the mechanism of IVIG in treating JDM-associated calcinosis is unclear, it could be related to improve-

Table III. Multivariable Cox regression analysis of the estimated association between treatment regimen and treatment responses.

	Any improvement		Major improvement[a]	
Treatment regimen	HR (95% CI)[b]	*p*-value	HR (95% CI)[b]	*p*-value
None	Reference		Reference	
Immunomodulatory agent(s)	2.57 (0.74–8.96)	0.14	1.98 (0.56–7.01)	0.29
Calcium-modifying agent(s)	1.79 (0.38–8.32)	0.46	1.47 (0.31–6.88)	0.63
Immunomodulatory agent(s) + Calcium-modifying agent(s)	3.08 (0.90–10.55)	0.07	1.51 (0.42–5.42)	0.53
Type of immunomodulatory agent				
Immunosuppressant(s)	1.40 (0.78–2.49)	0.26	1.15 (0.60–2.20)	0.67
IVIG	1.95 (1.10–3.45)	0.02	1.62 (0.84–3.14)	0.15
Biologic DMARDs	1.40 (0.66–3.00)	0.38	1.71 (0.74–3.94)	0.21
Type of Calcium-modifying agent				
Bisphosphonates	1.23 (0.67–2.24)	0.51	0.92 (0.45–1.89)	0.82
Surgical excision	0.82 (0.24–2.79)	0.75	0.79 (0.23–9.80)	0.72

DMARDs: disease-modifying anti-rheumatic drugs; HR: hazard ratio; IVIG: intravenous immunoglobulin.
[a]Those who reportedly reached complete resolution and/or moderate improvement.
[b]Results are from Cox proportional hazards models adjusted for age, sex, and time.

ment of underlying inflammation from JDM (19). Thus, IVIG remains a potentially effective treatment option for calcinosis and JDM. However, statistical significance was not observed when repeat analysis was performed for the major improvement subgroup, suggesting that IVIG alone may not be sufficient to achieve complete resolution of calcinosis.

The pathophysiology of calcinosis remains unclear but most likely involves active inflammation and calcium metabolism. Studies of surgically excised calcinosis tissue samples have shown the presence of various immune reactive cells, including macrophages and monocytes, and the TNF-308A allele, suggesting the possibility that major cytokines are involved in JDM-associated calcinosis (30, 31). The use of calcium-modifying agents is based on the hypothesis that calcium from muscle and fibroblasts is involved in calcinosis formation (19). Our study suggests that the combination of immunomodulatory therapy and calcium-modifying agents has the highest probability of improving calcinosis, indicating that simultaneously targeting different mechanisms of calcinosis may represent a favourable approach for treating calcinosis.

The detection of MSAs and MAAs by validated laboratories with expertise is a recommended clinical practice for patients with newly diagnosed JDM (32). MSAs are associated with distinct clinical presentations and disease course, potentially providing prognostic information (33, 34). Anti-NXP2 has been previously associated with and is potentially a risk factor for JDM-associated calcinosis (1, 6, 9). In our cohort, anti-NXP2 was the most commonly detected MSA, followed by anti-MDA5. Anti-MDA5 is associated with interstitial lung disease and amyopathic JDM, but its association with calcinosis development remains uncertain (35, 36). Patients in our cohort with positive test results for anti-NXP2 or anti-MDA5 were shown to have a lower likelihood of a treatment response than other patients, but this was not statistically significant. Additional studies are needed to demonstrate that patients with these MSAs and calcinosis may require more aggressive or unique therapies.

Our study had several limitations. First, given that this is a retrospective study, our findings may carry an inherent risk of recall bias and are subject to the limitations associated with the documenta-

Table IV. Multivariable Cox regression analysis of the estimated association between patient or disease characteristics and treatment responses.

	Any improvement		Major improvement[a]	
Patient or disease characteristic	HR (95% CI)[b]	*p*-value	HR (95% CI)[b]	*p*-value
Patient age at calcinosis diagnosis, per 1-y increase in age	1.06 (0.99–1.13)	0.12	1.03 (0.95–1.11)	0.52
Female sex	1.45 (0.76–2.76)	0.26	1.42 (0.68–2.99)	0.36
Any myositis antibody	1.09 (0.58–2.06)	0.79	1.36 (0.65–2.83)	0.41
Calcinosis at initial JDM diagnosis	1.95 (0.88–4.33)	0.10	1.21 (0.51–2.91)	0.67
Active JDM at calcinosis diagnosis	1.54 (0.73–3.25)	0.26	1.42 (0.60–3.38)	0.43
Aggressive treatment of JDM at JDM diagnosis	1.39 (0.78–2.48)	0.26	1.45 (0.74–2.84)	0.28
Moderate to severe JDM at calcinosis diagnosis	1.24 (0.68–2.26)	0.49	1.07 (0.52–2.20)	0.85
Active muscle involvement at calcinosis diagnosis	1.51 (0.80–2.88)	0.21	1.21 (0.59–2.48)	0.60
Active skin involvement at calcinosis diagnosis	0.85 (0.40–1.81)	0.67	1.05 (0.43–2.58)	0.92
Anti-NXP2 or anti-MDA5	0.65 (0.29–1.46)	.30	0.67 (0.26–1.72)	0.40

Anti-MDA5: anti-melanoma differentiation-associated gene 5; anti-NXP2: anti-nuclear matrix protein 2; HR: hazard ratio; JDM: juvenile dermatomyositis.
[a] Patients who reportedly reached complete resolution and/or moderate improvement.
[b] Results are from Cox proportional hazards models adjusted for age, sex, and time.

tion of clinical data by investigators, who obtained data regarding patient treatment responses and determined whether calcinosis improved or worsened. We attempted to decrease selection bias by searching the electronic health record for patients treated during a specific period and by using billing codes and clinical diagnoses. Second, although this is one of the largest multi-institutional studies on JDM-associated calcinosis, our sample size nonetheless rendered our study underpowered to detect smaller, potentially clinically meaningful effect sizes. Similarly, because 103 unique treatment regimens were used for 63 patients, it was difficult to provide insight into which specific treatment regimens were effective in treating calcinosis. Sample sizes of treatment groups were inadequate to compare outcomes among all observed treatments, limiting our ability to detect differences in general. Third, IVIG was significantly associated with some degree of improved calcinosis but not major improvement. In this study, the degree of improvement was physician reported and largely based on subjective assessment (history and physical examination findings) rather than objective measures such as imaging. Thus, an accurate measure of a "complete" response was not possible because calcinosis may not be clinically discernible and may exist in underlying fascia and muscles. Notably, a recent study showed the feasibility of using low-dose-radiation computed tomography to assess JDM-associated calcinosis and its progression (37). Finally, Janus kinase inhibitors such as tofacitinib and baricitinib to treat JDM-associated calcinosis have shown promising results (38-40); however, no Janus kinase inhibitors were used in any of our cases, most likely due to the dates of the study period.

In summary, our study showed that multiple drug regimens, including immunomodulatory and calcium-modifying agents, were used to treat patients with JDM-associated calcinosis. In most patients, especially those treated with IVIG, calcinosis eventually improved, although major improvement sometimes required several years of treatment. Patients who received both immunomodulatory and calcium-modifying agents were more likely to improve than those who received other therapy regimens. In patients screened for MAAs and MSAs, anti-NXP2 and anti-MDA5 were most commonly detected and associated with a lower but non-significant likelihood of improvement. Although treatment with IVIG was significantly associated with improvement, its use did not always result in major improvement or resolution of calcinosis. Prospective studies and standardised assessment approaches are needed to further our understanding of the relationship between treatment choices and outcomes in patients with JDM-associated calcinosis.

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Competing interests

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K. Ardalan has served on a scientific advisory board of Cabaletta Bio, completed paid consulting for Cabaletta Bio, serves as the Vice Chair of the Juvenile Derma-tomyositis Committee for the Childhood Arthritis & Rheumatology Research Alliance (paid consultant position), received honoraria/travel reimbursement from the Rheumatology Research Foundation, honoraria from the American College of Rheumatology, honoraria (paid to institution) from SingHealth for grant pre-review program organised by Office of Duke-NUS Affairs, and receives research funding from the Rheumatology Research Foundation, Childhood Arthritis & Rheumatology Research Alliance/ Arthritis Foundation, Chan Zuckerberg Initiative, Cure JM Foundation, Patient-Centered Outcomes Research Institute, and National Institutes of Health/Technical Resources International.

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