Effectiveness of Rituximab Therapy on Severe Calcinosis in 4 Children with Juvenile Dermatomyositis

Mohammad Alhemairi¹, Mohammed Muzaffer²

¹Department of General Pediatrics, Rabigh General Hospital, Rabigh, Kingdom of Saudi Arabia
²Department of Pediatrics and Pediatric Rheumatology, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia

Email: alhemairi-m@hotmail.com, mmuzaffer@hotmail.com


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Abstract

Background: Calcinosis is an important sequela of JDM which may cause significant morbidity and mortality. There is no standard curative treatment for calcinosis but different agents were used with variable efficacy. We report the favorable outcome of rituximab on severe calcinosis in 4 JDM patients and present their clinical data. Patients and Methods: A retrospective chart review of 4 children with JDM and severe calcinosis who received rituximab for relapsing or polycyclic JDM course. Diagnosis and follow up of calcinosis was clinically and by X-ray. Review data included: age of patients at onset of JDM symptoms and diagnosis, clinical and laboratory criteria at diagnosis, disease course and duration of follow up. Data about calcinosis onset, sites, severity and its progression were also included. Further data about rituximab therapy included: dosage, side effects, other treatment used before, during or after this drug and outcome and duration of follow up of calcinosis after therapy. Results: 4 patients (2 male, 2 female), interval between onset of symptoms and diagnosis was 6 - 12 months, course of JDM was polycyclic or relapsing, duration of follow up was 5 - 7 years. Calciosis was severe causing ulceration, recurrent skin infections and joint limitation. It was not improving despite treatment with different DMARDs and/or bisphosphonates, colchicine and warfarin. Reason to start rituximab was inadequate disease control with conventional DMARDs. All patients received steroids and more than one DMARD before starting rituximab and were continued thereafter, follow up after rituximab was 3 to 5 years. All patients had improvement in disease activity and frequency of admission especially due to complications of calcinosis. One patient had complete clearance of calcinosis for the last 5 years. Others had significant improvement in calcinosis with no new lesions, decreased sites and density and decreased calcinosis related contractures. There were no serious side effects to rituximab. Conclusion: Our study showed the favorable
effect of rituximab in treatment of calcinosis in 4 patients with JDM-associated severe calcinosis when it was used with other conventional DMARDs.

Keywords
Calcinosis, Rituximab, Juvenile Dermatomyositis

1. Introduction
Juvenile dermatomyositis (JDM) is a rare disease but it is the most common inflammatory myopathy in children. It is an autoimmune vasculopathy which primarily affects skin and proximal striated muscles. Involvement of major organs like heart, lungs, and gastrointestinal tract may lead to irreversible organ damage and life threatening complications and death. Calcinosis, a dystrophic calcification of unknown cause, is a significant sequela of JDM in which there is pathological deposition of calcium in skin, subcutaneous tissue, muscle and tendons in patients who has generally normal calcium and phosphorus levels. It may lead to impaired physical function and impaired quality of life.

Unlike adults with dermatomyositis, calcinosis is more common in JDM as it occurs in up to 70% of cases [1]. Although it may precede JDM diagnosis [2], its development was related to delayed diagnosis and treatment and chronicity of JDM [3].

Currently there is no curable treatment for calcinosis but early diagnosis and aggressive treatment of JDM were led to decrease in incidence [4]. Different therapeutic agents have been used to treat myositis-associated calcinosis; however, their therapeutic effects were variable. Rituximab is a biologic agent which showed efficacy in treatment different rheumatological conditions including dermatomyositis [5] [6]. Herein, we report its favorable effect on treatment of calcinosis in 4 children with JDM with severe calcinosis and disability.

2. Methods
A retrospective chart review of 4 children with JDM and severe calcinosis who were diagnosed at King Abdul Aziz University Hospital, Jeddah, Saudi Arabia and received rituximab for relapsing or polycyclic JDM course between March 2008 and July 2014 was conducted. Diagnosis of JDM was based on the criteria proposed by Bohan and Peter [7].

Diagnosis and follow up of calcinosis was clinically and by radiologically by X-ray by a pediatric rheumatologist and radiologist.

Review data included: age of patients at onset of JDM symptoms and at diagnosis, clinical and laboratory criteria which included: Creatinine Kinase (CK), Lactate dehydrogenase (LDH), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) levels as well as MRI and muscle biopsy results at diagnosis, complications, disease course and duration of follow up.

Data about calcinosis onset, sites, severity and its progression were also in-
Treatment used for JDM as well as calcinosis management before, during or after Rituximab introduction and outcome of JDM and calcinosis were recorded. Further data about rituximab therapy included: dose, number of courses and adverse effects.

Approvals from medical research and ethical committee of King Abdul Aziz University Hospital (KAUH) as well as written informed consents from the patient’s caregivers for publication of these case reports and any accompanying clinical data or images were obtained before writing this report.

3. Results

4 patients (2 male, 2 female), interval between onset of symptoms and diagnosis was 6 - 12 months, course of JDM was polycyclic or relapsing, duration of follow up was 5 - 7 years.

Calcinosis was present in one patient at diagnosis and at 9, 13 and 16 months after diagnosis.

All patients had calcinosis affecting elbows, hands, thighs, knees, ankles and buttocks.

Calcinosis was severe causing ulceration, recurrent skin infections, joint limitation, severe disability and inability to walk. It was not improving despite improvement in muscle and skin function with different disease-modifying antirheumatic drugs (DMARDs) and/or bisphosphonates, colchicine and warfarin (Table 1 and Table 2).

Reason to start rituximab was inadequate disease control, disability and frequent relapses.

Only one patient given 2 courses of rituximab; others were given one course.

All patients received steroids and more than one DMARD before starting rituximab and were continued thereafter, follow up after rituximab was 3 to 5 years.

All patients had improvement in disease activity and frequency of admissions especially due to complications of calcinosis. One patient had complete clearance of calcinosis by 2 years, others had significant improvement in calcinosis with no new lesions, decreased sites and density and decreased calcinosis-related contractures. There were no serious side effects to rituximab.

Case 1:

7 years old who was referred to pediatric rheumatology clinic due JDM, after a history of proximal muscle weakness, myalgia and calf muscle tenderness which was associated with typical heliotrope rash and nail fold capillary changes, she was on oral steroids.

Her laboratory work up in pediatric rheumatology clinic showed: Creatinine kinase 2154 U/L, LDH: 230 U/L, AST 190 U/L ALT 217U/L, ANA 1:1280, MRI showed perimuscular edema and increased signal intensity in fat suppression on T2 weighted image.

She had calcinosis at both elbows clinically and X-ray showed further calcium...
<table>
<thead>
<tr>
<th>No.</th>
<th>Age at onset/</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>Clinical manifestations</th>
<th>Calcination</th>
<th>Laboratory investigations (at diagnosis)</th>
<th>MRI</th>
<th>Biopsy</th>
<th>Course</th>
<th>Treatment received*</th>
<th>Duration of follow up after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/F</td>
<td></td>
<td>7</td>
<td>Dysphagia, voice changes, roximal muscle weakness, myalgia, muscle tenderness, positive gower’s sign</td>
<td>Heliotrope rash, periorbital edema, telangiectasia of the eyelid capillaries, Gottron’s papules: knuckles, extensor aspects of the elbows, knees, and medial malleoli</td>
<td>Calcination, ulceration, Nailfold capillary changes including capillary dilatation, tortuosity, and dropout</td>
<td>At diagnosis</td>
<td>elbows, then thighs, buttocks, back, arms</td>
<td>2154</td>
<td>230</td>
<td>190</td>
</tr>
<tr>
<td>2</td>
<td>7/F</td>
<td>6 mo</td>
<td>7 yr</td>
<td>Proximal myopathy especially in upper limb, neck muscle weakness, dysphonia, positive gower’s sign</td>
<td>Skin rash (face, elbows, knees), gottron papules, photosensitivity</td>
<td>Weight loss, cataract, joint contractures, skin ulceration, calcinosis, recurrent skin infections, hirsutism</td>
<td>9 mo after Diagnosis</td>
<td>Shoulders, elbow, wrist, hands, thighs, knees, ankles, back, lower abdomen</td>
<td>1231</td>
<td>451</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>4 yr</td>
<td>2 mo/M</td>
<td>5 yrs</td>
<td>Myalgia, muscle tenderness, Generalised weakness, upper and lower limb proximal weakness, upper limb distal weakness, muscle atrophy</td>
<td>Heliotrope rash, scalp dermatitis, edema of hands, pocktleroderma, scarring Gottron’s papules</td>
<td>Fever, arthralgia, weight loss, malaise, skin ulcers, skin infection, abnormal nailfold capillary pattern, recurrent chest infections</td>
<td>1 yr 4 mo after Diagnosis</td>
<td>hands, wrist, knee, ankle, shoulder, neck</td>
<td>1427</td>
<td>864</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>3 yr</td>
<td>7 mo/M</td>
<td>4 yrs</td>
<td>Generalized muscle weakness, inability to stand, muscle atrophy, dysphonia</td>
<td>Generalised skin rash especially facial and over elbows, knee, edema over face, eyelids, hands, forearm, feet gottron papules</td>
<td>Growth failure, fever, GI symptoms, contractures, calcinosis, convulsions, arthritis</td>
<td>13 mo after diagnosis</td>
<td>Shoulders, elbow, wrist, hands, thighs, knees, ankles, back</td>
<td>2532</td>
<td>653</td>
<td>153</td>
</tr>
</tbody>
</table>
**Table 2. Summary of rituximab treatment.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical features and calcinosis at start of Rituximab</th>
<th>Treatment before Rituximab</th>
<th>Concurrent treatment with Rituximab</th>
<th>Regimen (course, dose)</th>
<th>Side effects of rituximab</th>
<th>2 year after rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe disability, difficult swallow, failure to thrive, compliance with treatment, calcinosis (cutaneous, dystrophic)</td>
<td>CS, HQ, MTX, PMD, Infliximab, AZT, IVIG, MMF, Warfarin</td>
<td>MTX, IVIG, Low dose CS</td>
<td>Weekly for 4 doses 375 mg/m² once weekly for 4 doses</td>
<td>Fever for 5 days (unknown cause), febrile UTI (one month later), local reactions, leucopenia (mild)</td>
<td>Complete remission, absent calcinosis, no new lesions, no contractures or joint limitation</td>
</tr>
<tr>
<td>2</td>
<td>Growth failure, Joint contractures, recurrent chest infections, dysphonia, calcinosis, skin ulcerations</td>
<td>CS, HQ, MTX, CC, CP, IVIG</td>
<td>CP, CS, HQ</td>
<td>One course (0, 14 days), 375 mg/m²</td>
<td>Hypotension, generalised skin rash (allergic), Cellulitis</td>
<td>Partial disease remission, arrested calcinosis progression, no new lesion, limited joint movement at left MCPs, distal 4th and 5th PIP</td>
</tr>
<tr>
<td>3</td>
<td>Growth failure, Joint contractures, recurrent chest infections, upper and lower limb proximal weakness, upper limb distal weakness, muscle atrophy, calcinosis, skin ulcerations</td>
<td>CS, MTX, HQ, IVIG, Cyclosporin, PMD</td>
<td>MTX, Cyclosporin CS</td>
<td>One course (0, 14 days), 375 mg/m²</td>
<td>Flushing Hypogammaglobulinemia Hypersensitivity reactions, Herpesvirus infection Febrile episodes</td>
<td>Partial disease remission, decreased calcinosis sites, and density progression, no new lesion</td>
</tr>
<tr>
<td>4</td>
<td>Joint contractures, recurrent chest infections, upper and lower limb proximal weakness, muscle atrophy, calcinosis, skin ulcerations, skin infections and gangrene</td>
<td>CS, MTX, HQ, IVIG, AZT, PMD, RTX</td>
<td>MTX, AZT, CS</td>
<td>2 courses (0, 14 days); 375 mg/m², 8 months apart</td>
<td>Sinus/ear infection Joint pain/swelling, Pneumonia/lower respiratory tract infection</td>
<td>Partial disease remission, decreased calcinosis sites, and density progression, no new lesion, Flexion contractures at left ankle, left elbow, and right knee</td>
</tr>
</tbody>
</table>

deposits in thighs and buttocks. The dose of prednisolone was increased to 2 mg/kg/day and Methotrexate was started (0.3 mg/kg/day) weekly with folic acid. IV methylprednisolone was also given 30 mg/kg for 3 consecutive days. She continued in remission for one year with reduction of steroids but calcinosis was not improving.

Due to decreased clinical disease activity, the family used to be not so compliant with use of medications so the child presented with active disease with skin rash and muscle weakness with malnutrition. At this time she was given IVIG and restarted on methotrexate, hydroxychloroquine and later mycophenolate mofetil. However, calcinosis was further progressed, so Pamidronate was started at dose of 1 mg/kg/day for 3 consecutive days every 3 months and continued for one year. As no improvement in calcinosis, Warfarin was also given at a dose of 0.5 mg daily for 6 months but there was no observed response and infliximab was introduced but immediately discontinued due to anaphylaxis. Rituximab was added to concurrent treatment because of persistent muscle weakness and skin manifestations with physical disability and frequent school absence. 4 doses of rituximab were given of 375 mg/m²/week.

She was continued on her medications: methotrexate, prednisolone, hydroxychloroquine and 4 years later she had no disease activity and no calcinosis.

**Case 2:**

7 years old female child who was referred to pediatric rheumatology clinic 6 months after symptoms of muscle weakness and fatigue.

When she was seen for the first time by pediatric rheumatologist, she was showing typical features of JDM (proximal myopathy, skin manifestations and elevated muscle enzymes with no calcinosis), she was started on methylprednisolone, prednisone and methotrexate.

Calcinosis was diagnosed 15 months later and was mainly seen in knees, thighs, elbows and both elbows and shoulders. It was hard and tender mainly in lower limbs. As the general disease activity was not well responding to the above management, she was given also IVIG and cyclophosphamide intravenously (0.5 - 1 g/m²) monthly, discontinued after 20 months of treatments as there was no adequate improvement in disease activity.

Together with persistent disease activity, calcinosis continued to be more extensive and causing multiple contractures so she was unable to walk or even stand. She also got multiple skin ulcerations with infection at both ankles and right elbow. At this stage, she was given methylprednisolone and continued on Prednisone, Methotrexate, hydroxychloroquine and started on Pamidronate for one year which had little effect on calcinosis.

One year later, she was started on rituximab due to persistent disease activity and functional disability. The first dose of rituximab was associated with generalized skin rash and hypotension which was managed by decreasing infusion rate, however, this did not occur with the second dose.

2 weeks after 2nd dose, she had severe cellulitis and thigh abscess required hospital admission and drainage of abscess.
6 months later, calcinosis was improving with lesions becoming less hard, less painful and tender although functional disability was still present.

3 years later, Calcinosis showed further improvement with no new lesions and existing lesions became smaller (Figure 1), non painful and non tender.

**Case 3:**

This male child was diagnosed at age of 5 years, and seen in pediatric rheumatology clinic 8 months later, he was on prednisone and methotrexate with inactive disease clinically (no skin rash and normal muscular examination), he continued to be in remission for approximately 9 months when he presented with skin rash and muscle weakness, increasing muscle enzyme levels with multiple areas of clacinosis at shoulders, elbows, thighs and ankles. Lesions were quite hard but not painful. He was managed with IVIG, prednisolone 2 mg/kg/day, methotrexate, hydroxychloroquine. This was associated with decreasing disease activity but calcinosis continued and became more extensive with multiple new lesions and contractures in both elbows and knees and skin ulcers at ankles, elbows and finger tips.

After 18 months, the disease was not completely controlled with cyclosporine, cyclophosphamide so Rituximab course was started which was followed by a febrile illness which required admission to hospital 2 weeks later. He also developed herpes infection 3 months later.

4 years after rituximab course, JDM was in partial remission with marked improvement in calcinosis as lesions became much less clinically and by X-ray, lesions were not painful, non tender and no contractures secondary to calcinosis.

**Case 4:**

This male child presented to pediatric rheumatology clinic and diagnosed 10 months after onset of JDM symptoms. His disease was not completely controlled with IV and oral steroids and methotrexate as well as IVIG. Calcinosis started approximately 13 months after diagnosis, symmetrically in both shoulders, elbows with progressive increase in size and density on X-ray, thighs, knees and ankles. This was associated with frequent ulcerations induced by trauma and skin infections for which he was admitted two times. Although there was clinical and laboratory improvement in disease activity, there was progressive calcinosis which led to contractures in elbows, knees and ankles causing functional impairment.

Pamidronate was given intravenously for 3 consecutive days every 3 months for one year at a dose 1 mg/kg/day.

Due to persistent disease activity despite of immunosuppressive therapy, rituximab was added at a dose 375 mg/m² at 0 and 14 days, a second course was given 8 months later.

This child was admitted 2 weeks after the 2nd course of rituximab due to pneumonia but did not require ICU care.

There was gradual improvement in skin calcinosis mainly at ankles and significant improvement at left knee and right elbow but contractures were not completely recovered at left ankle, left elbow, and right knee despite of physiotherapy. He reported did not report any pain related to calcinosis in unresolved
lesions. At her visit 2 years later, she showed no more new calcifications (Figure 1).

4. Discussion

Calcinosis, a well-recognized sequela, is considered one of the features by which JDM differs from adult dermatomyositis as it generally occurs in 10% - 70% of children with JDM [1]. Although it is not one of the diagnostic criteria, its progression may contribute to increased morbidity [8] and even mortality in JDM patients as it may continue even if the disease was controlled [9]. Its pathogenesis in JDM is not yet clearly explained but it consists of abnormal or pathological deposition of hydroxyapatite calcium and phosphate in soft tissue in patients who has generally normal calcium and phosphorus blood levels.

As a part of the idiopathic inflammatory process, the release of inflammatory mediators like interleukin 1β and IL-6 [10], TNF-α and their presence in the milk of calcium may indicate a major role in pathogenesis of calcinosis [11].

Figure 1. Calcinosis in case 2 (upper) and case 4 (lower) involving subcutaneous tissue and muscles of thighs and legs (left) and marked improvement 2 years after rituximab therapy (right).
Calcinosis may involve only skin and subcutaneous tissue and presents clinically as cutaneous or subcutaneous plaques or nodules or may have popcorn-like appearance on X-ray.

Calcium deposits may extend deeper into muscular fascia and tendons leading to disturbance in muscle function or may have a wide spread distribution leading to formation of exoskeleton [11] [12].

Different factors were related to development or severity of calcinosis in JDM including genetic or environmental factors. [13], early age of JDM onset [14] and delayed presentation, diagnosis or treatment [15]. It was also related to disease control, chronicity and the presence severe skin involvement [13]. However in a study of 34 cases of JDM, no risk factors for calcinosis were found [1].

Calcinosis in JDM presents generally between 1 - 3 years after diagnosis although it may presents at diagnosis or many years later [1].

All our 4 cases had polycyclic and chronic course and calcinosis was present at diagnosis in case 1.

Up to date, there is no generally accepted specific treatment for calcinosis in JDM and this treatment remains a challenge.

Calcinosis may regress or completely resolve spontaneously [16] [17], improves with JDM treatment or may require specific management to decrease its disabling effects.

Different therapeutic regimens were used to treat calcinosis in JDM. Their use to treat calcinosis was based mainly upon case reports, articles or institutional experience.

These treatments include; antinflammatory medications like IVIG, thalidomide and colchicine, drugs that interfere with calcium or phosphorus metabolism like Calcium channel blockers (e.g. diltiazem), probenicid, bisphosphonate (e.g. pamidronate, alendronate, etidronate) and biologic agents.

However, their use to treat calcinosis was associated with controversial therapeutic effects as some of them resulted in improvement of calcinosis in some case reports but showed no efficacy in others and several different treatments may be used in one patient [18].

Pamidronate, a bisphosphonate, which acts by reducing osteoclast activity and reduces bone resorption was reported to be effective in treatment of calcinosis in JDM.

A. Marco Pouche et al. reported complete clearance of calcinosis in one patient and significant improvement in 2 other patients with JDM [13]. 2 further case reports showed improvement of severe debilitating calcinosis in a 7 and 14 year children after treatment with pamidronate for 2 years [19] [20].

In our patients, cyclic pamidronate infusion was used in 3 patients at a dose 1 mg/kg/day for 3 consecutive days every 3 months, it was continued for at least one year. There was no satisfactory effect. Similarly, there was no improvement in calcinosis in 10 year old child after 5 doses of 3 monthly infusions as reported by Al-mayouf et al. [21].

Colchicine is an anti-inflammatory drug was reported to result in suppression
of inflammation due calcinosis in dermatomyositis. Nevertheless, more recent reports did not show evidence of efficacy in treatment of calcinosis in JDM patients [21] [22] [23].

Two of our patients received colchicine at a dose of 1 mg/day to treat calcinosis for at least 7 months duration but it was discontinued because of no effect and GI symptoms.

Warfarin, an anticoagulant, was suggested to play a role in preventing calcinosis [24] by inhibiting the production of the calcium binding amino acid; gamma glutamic acid which was found in high concentrations in involved tissues [25].

T Cukierman et al. evaluated the effect of low dose warfarin on calcinosis in 3 cases of systemic sclerosis, 2 patients showed rapid response and complete clearance of calcinosis within 2 months of treatment [26].

2 further case reports also showed the possible effect of warfarin on treatment of calcinosis [27] [28].

In contrast to the previous case reports, warfarin at a dose of 0.5 mg was given for 6 months to one of our patients (patient 1) but no clinical effect on calcinosis was observed. Failure of warfarin in treatment of calcinosis was reported by Lassoued K et al. who used warfarin for 1 year in 6 patients with calcinosis [29].

Furthermore, there were no clear benefits of warfarin in treatment of calcinosis in 5 patients reported by Moore et al. Other similar reports showed same result [21] [30] [31].

In our 4 cases, the introduction of rituximab was due to refractory JDM and its complications.

We did not expect that it will have a major effect on calcinosis as—up to our knowledge—there were no reports describing its specific efficacy on calcinosis in JDM.

Rituximab is one the biologic agents which are increasingly used in treatment of rheumatologic diseases.

It is a chimeric (murine-human) monoclonal antibody which depletes CD20 positive B cells which are abundant in muscles and peripheral blood of patients with active myositis. Its efficacy in management of dermatomyositis were shown in different trials and case reports; in 2005, Levine et al. reported major clinical improvement in 7 patients with dermatomyositis after treat with rituximab [32].

In 2013, a randomized double blind-placebo phase trial to assess the efficacy of rituximab in 200 patients with myositis (including 48 children) showed that 83% of patients achieved the predetermined definition of improvement by 44 week and there was significant steroid sparing effect after treatment with rituximab. Although this study failed to achieve the primary end point, authors concluded that rituximab had an effect [6].

A recent literature review of 48 publications revised 485 patients with refractory myositis who were treated with rituximab till July 2015, the rate of response to rituximab was found to be 78.3% [33].

In contrast to these reports and review, with exception of patient 1, there was
no major clinical effect of rituximab on muscle strength and skin features in our patients.

Most of reports about the effectiveness of rituximab in treating myositis did not assess its efficacy on calcinosis, however it was found that early and aggressive treatment of JDM may result in complete regression of calcinosis [1].

Although it may has a different mechanism of action, rituximab was associated with regression of calcinosis in other rheumatological conditions [1] [14] [34] [35] [36], however rituximab cannot be yet recommended for treatment of calcinosis [37] since there are no evidence based studies supporting its efficacy and the availability of other less expensive therapies which were shown to be effective in case reports.

We cannot clearly determine if improvement in calcinosis was due rituximab alone or due combination of rituximab with other conventional DMARDs, however, our patients did not show improvement in calcinosis except after rituximab introduction.

A major concern with rituximab therapy is its side effects especially in children. These side effects include infusion reactions especially at the first infusion [38] which can be reduced with appropriate premedication regimens, reactivation of viral infections like herpes, hepatitis and CMV, hypogammaglobinemia [38] and rarely fatal progressive multifocal leukoencephalopathy [39].

2 patients experienced mild to moderate infusion related reactions in the first infusion which were managed by decreasing infusion rate and antihistamine only. One patient had lower respiratory tract infection which required hospital admission. However there was no life threatening side effects in our patients.

There are several weak points in our study as it is a retrospective and most of data were taken from routine clinical practice notes which caused missing of some important clinical, laboratory and radiological data. For example, latest X rays of patient 1—who had complete clearance of calcinosis—and patient 3 were missed.

5. Conclusion

In our cohort of 4 patients with JDM and severe calcinosis, there was significant improvement and/or clearance of calcinosis after rituximab therapy when used with other DMARDs. Further clinical studies are required to evaluate the efficacy of rituximab in JDM-associated calcinosis.

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