Childhood Arthritis and Rheumatology Research Alliance Consensus Clinical Treatment Plans for Juvenile Dermatomyositis with Persistent Skin Rash

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ABSTRACT. ***Objective.*** Juvenile dermatomyositis (JDM) is the most common form of idiopathic inflammatory myopathy in children. While outcomes are generally thought to be good, persistence of skin rash is a common problem. The goal of this study was to describe the development of clinical treatment plans (CTP) for children with JDM characterized by persistent skin rash despite complete resolution of muscle involvement.

Methods. The Childhood Arthritis and Rheumatology Research Alliance, a North American consortium of pediatric rheumatologists and other healthcare providers, used a combination of Delphi surveys and nominal group consensus meetings to develop CTP that reflected consensus on typical treatments for patients with JDM with persistent skin rash.

Results. Consensus was reached on patient characteristics and outcome assessment. Patients should have previously received corticosteroids and methotrexate (MTX). Three consensus treatment plans were developed. Plan A added intravenous immunoglobulin (IVIG) if it was not already being used. Plan B added mycophenolate mofetil, while Plan C added cyclosporine. Continuation of previous treatments, including corticosteroids, MTX, and IVIG, was permitted in plans B and C.

Conclusion. Three consensus CTP were developed for use in children with JDM and persistent skin rash despite complete resolution of muscle disease. These CTP reflect typical treatment approaches and are not to be considered treatment recommendations or standard of care. Using prospective data collection and statistical methods to account for nonrandom treatment assignment, it is expected that these CTP will be used to allow treatment comparisons, and ultimately determine the best treatment for these patients. (J Rheumatol First Release November 1 2016; doi:10.3899/jrheum.160688)

Key Indexing Terms:

PEDIATRIC DERMATOMYOSITIS/POLYMYOSITIS

THERAPEUTICS CLINICAL TREATMENT PLANS

Juvenile dermatomyositis (JDM) is the most common juvenile idiopathic inflammatory myopathy, affecting 2–3 per million children[1]. The most common features are a variety of typical skin rashes and muscle weakness, with reductions in

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endurance and impairment of physical function that can be severe. Other organ involvement is also possible, including pulmonary, gastrointestinal, and cardiac, and this involvement may contribute to morbidity and mortality[2].

In the past, before treatment with corticosteroids was standard, up to one-third of children with JDM died and another third experienced permanent disability[3]. Current treatment consists of corticosteroids and is often supplemented with other medications, such as methotrexate (MTX)[4]. This treatment approach has resulted in a marked reduction in mortality, to about 1%–2%[2]. However, morbidity remains common, and may include persistent weakness or physical limitation, rash, calcinosis, lipoatrophy, or chronic pulmonary disease.

For many patients, skin rashes persist despite complete resolution of muscle involvement. While possibly perceived as being less serious by healthcare providers, persistent skin rash is troubling and important to patients. It may be associated with pain, functional impairment, and poor self-image, and can interfere with normal psychosocial functioning. These observations have been demonstrated in adults with dermatomyositis[5], but have not been studied in children. Persistent rash may also be associated with features of skin damage, such as calcinosis and lipoatrophy[6,7]. Finally, it has been argued that persistent skin rash reflects ongoing systemic immune activation[8] and therefore warrants additional treatment.

A number of investigators have documented that persistent skin rash is common. Huber, *et al* found that 26 of 65 patients with JDM (40%) followed for more than 3 years (median 7.2 yrs) reported persistent rash[9]. More recently, Sanner, *et al* reported that 59% of children with JDM followed for a median of 16.8 years continued to have skin rash[10]. Thus, it is clear that persistent rash is a problem for a large number of children with JDM.

There is no agreement on standard treatment for children with persistent JDM skin rash. To date, no formal clinical trials have been conducted to study this issue, to our knowledge. Data are limited to a few case reports and small case series. A number of agents have been reported to be effective, including intravenous immunoglobulin (IVIG)[11,12], rituximab (RTX)[13], and tacrolimus[14], but these small, open-label studies cannot be used to guide treatment decisions.

Studying treatment in children with JDM is challenging for a number of reasons. Given the low incidence, assembling adequate patient numbers for analysis of treatment effectiveness is very difficult, and more so when a disease subset such as persistent skin rash is being studied. The resulting need for large numbers of participating centers makes both costs and logistics of typical randomized treatment trials prohibitive. In addition, its low frequency makes JDM a lower priority for funding by national granting bodies. For these reasons, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) has pursued an alternative approach to studying treatments in children with rheumatic diseases. Using principles of comparative effectiveness research[15,16], CARRA members have developed a number of clinical treatment plans (CTP) in juvenile arthritis[17,18], juvenile systemic lupus erythematosus[19], juvenile localized scleroderma[20], and JDM[21,22]. These CTP were developed through consensus methods and are intended to reflect typical treatment approaches used by CARRA members for these illnesses. The CTP are not intended to be treatment recommendations or to represent gold standard or innovative treatment. The goal is that treating providers can choose a CTP that closely resembles their typical treatment approach. Data regarding patient characteristics and outcomes can be collected prospectively and ultimately analyzed using statistical methods that can account for biases introduced by nonrandom assignment of treatments. It is expected that the use of a limited number of CTP and prospective data collection will allow the comparison of treatments and help to determine optimal therapies.

Previously, CTP for children presenting with moderate JDM have been published[21,22] and a pilot study using these CTP is ongoing. The goal of the present study was to describe the development of CTP that were applicable to children with JDM characterized by persistent skin rash despite complete resolution of muscle involvement.

MATERIALS AND METHODS

CARRA is a North American organization consisting of pediatric rheumatologists and other medical and allied healthcare professionals with interests in research into pediatric rheumatic disease. The mission of this group is to "conduct collaborative research to prevent, treat and cure pediatric rheumatic diseases" (from CARRA Website: https://carragroup.org/about-us). Current membership is in excess of 400 individuals from more than 110 centers, and includes the majority of pediatric rheumatologists in North America.

Consensus information leading to the development of the CTP described in our work was drawn from a number of sources over several years. At each step, relevant literature was reviewed and presented to participants, as were results from previous consensus meetings and surveys. In addition, this process relied upon the experience and expertise of care providers to reflect an accurate representation of typical care provided in the pediatric rheumatology community.

The use of Delphi surveys in this process requires some discussion. Response rates for these surveys are difficult to estimate. The surveys were sent to the complete CARRA membership (about 400), but members were instructed to not complete the survey if they believed they lacked adequate expertise. It is unclear which nonrespondents considered themselves as lacking the appropriate expertise and which simply did not respond. Thus, the true denominator is unknown. However, minimum response rates can be calculated based on a denominator of 400.

1. 2011 CARRA Annual Meeting — Miami, Florida, USA. At this meeting, about 36 members of the CARRA JDM Committee discussed which JDM phenotype should be studied next. It was agreed that "skin rash" was a concern, and that both amyopathic and hypomyopathic disease should be included. It was also suggested that patients with "persistent skin rash" (i.e., patients with typical JDM with muscle and skin involvement who subsequently had persistent skin rash despite resolution of muscle involvement) were probably quite different from those with amyopathic or hypomyopathic disease and should probably be studied independently. There

was general discussion of patient characteristics, and a broad range of treatment options were discussed. These treatments included corticosteroids, MTX, hydroxychloroquine (HCQ), IVIG, azathioprine, cyclosporine, and biologic and topical agents, all in a wide range of doses and regimens. No definite consensus was reached at this meeting.

2. 2012 CARRA Annual Meeting — Las Vegas, Nevada, USA. Initially, about 50 members of the CARRA JDM Committee reviewed the results of the previous CARRA Annual Meeting. It was again agreed that patients with JDM with persistent skin rash should be studied separately from amyopathic/hypomyopathic JDM. Subsequently, a smaller group of 15 CARRA members met to start developing components of the CTP, including patient characteristics and candidate treatment regimens. The most commonly used treatments in North America were chosen for CTP development. Nominal group methods were used to come to consensus on each question, as summarized in Figure 1[23]. Consensus was defined *a priori* as ≥ 75%[21].

3. Delphi Survey 1 — Spring 2013. An electronic survey was sent to all CARRA members. The goals of this survey were to present the consensus results of the previous face-to-face meetings to the full CARRA membership, to determine whether the broader CARRA membership agreed (as with the face-to-face meetings, at least 75% agreement) with these consensus results, and to seek some clarification regarding issues that had not been satisfactorily addressed in the meetings. These issues included whether calcinosis or skin ulceration would influence potential participation in this CTP, and more complete delineation of other patient characteristics and treatment options. Complete responses were received from 97 CARRA members (73 pediatric rheumatologists, 7 internal medicine/pediatric rheumatologists, and 17 pediatric rheumatology fellows; minimum response rate 24.3%). Of these, 31% had 0–4 years, 26% had 5–10 years, and 43% had > 10 years of experience looking after patients with JDM. More than 82% of respondents considered themselves to be moderately or very experienced in the care of JDM.

4. 2013 CARRA Annual Meeting — Chicago, Illinois, USA. Building on the results from the nominal group consensus meeting from the previous year and the first Delphi survey, 14 members of the CARRA JDM Committee (partial overlap with group from the previous year) met to attempt to reach consensus on questions that did not have it and additional questions that had not previously been addressed. Nominal group methods were used again, as described in Figure 1. Issues addressed included clarification of patient characteristics, the involvement of magnetic resonance imaging, medications to be included (but not dosing), and preliminary discussion of outcomes to be assessed.

5. Delphi Survey 2 — Spring 2014. A second electronic survey was sent out to all CARRA members to ensure general agreement (> 75%) with the proposed CTP and to clarify some final issues needed to complete the CTP. These issues included final decisions on patients with calcinosis and skin ulceration, medication dosing, and outcome assessment. Complete responses were received from 81 CARRA members (73 pediatric rheumatologists, 7 pediatric rheumatology fellows, and 1 allied health professional; minimum response rate 20.2%). Of these, 27% had 0–5 years, 25% had 6–10 years, 23% had 11–20 years, and 25% had > 20 years of experience treating JDM. All respondents looked after patients with JDM, with 54% caring for 1–10 patients and 46% caring for > 11 patients at any time.

6. 2015 CARRA Annual Meeting — Austin, Texas, USA. Eight members of the CARRA JDM Committee (partial overlap with previous groups) met to finalize the proposed CTP. First, the proposed CTP was presented. Then, using nominal group methods, the entire proposal was reviewed and discussed (Figure 1). This resulted in a number of changes. Clarification regarding the duration of skin rash after resolution of muscle disease was added. Clarification regarding the previous use of MTX and other medications was also added. The majority of the discussion was about the assessment of skin rash. The group agreed that while the use of a validated tool as a primary outcome was necessary, the collection of additional detail on the characteristics of the skin involvement was desirable and would facilitate future research.

This information was reviewed and summarized to develop CTP, which reflected consensus on typical treatments for patients with JDM with persistent skin rash.

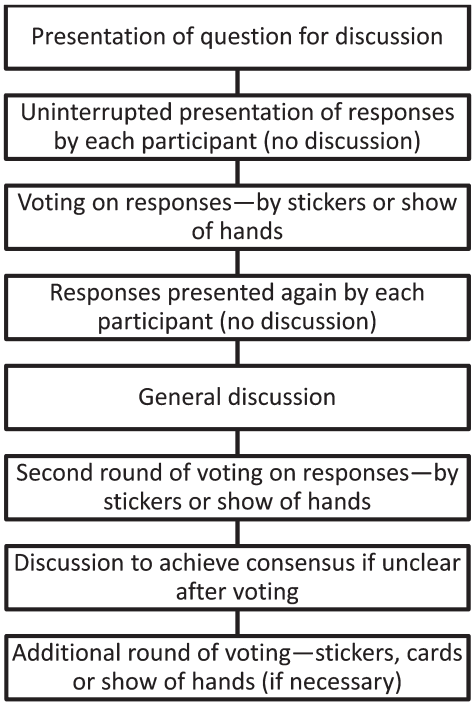

Figure 1. Summary of the process followed for achieving consensus for each question considered during the small group, face-to-face meetings.

RESULTS

Table 1 summarizes the characteristics of patients for whom these CTP are intended. In brief, patients should have persistent JDM skin rash for at least 3 months after previous muscle involvement has resolved. Skin involvement may have been persistent since diagnosis or recurred after initial resolution. The treating physician should be confident that patients do not have active myositis and have a "normal" Childhood Myositis Assessment Scale, taking into account factors such as age, contracture, and muscle damage. They should have received or currently be receiving appropriate treatment, which should include corticosteroids and MTX, and could additionally include HCQ and/or IVIG. Specifics of this initial treatment have been left to the treating health professional. Patients should not have extramuscular, extracutaneous organ involvement, ulcerative skin rash, or more than mild calcinosis (the definition of mild calcinosis being left to the judgment of the treating health professional). Patients with ulcerative skin rash or more than mild calcinosis were excluded because of concerns that these features may lead to different treatment approaches, and should be the focus of future CTP development.

The CTP are summarized in Table 2. It was agreed that 1 option was the initiation of IVIG therapy, assuming it was not already being used unsuccessfully to treat skin rash (Treatment A). In addition, there could be consideration

Table 1. Patient characteristics for JDM with persistent skin disease.

Patients should have:
1. Skin involvement consistent with JDM that is not improving (static or worsening) at least 3 mos after previous muscle involvement is resolved. Skin involvement may have been persistent since diagnosis or recurred after initial resolution.
2. Resolution of muscle involvement is defined as:
a. In the judgment of the treating provider, the patient should have no active myositis.
b. CMAS should be "normal" — this will depend on the judgment of the treating provider, and should take into account age, contractures, muscle damage, and other factors that could limit the maximum attainable CMAS.
c. Muscle enzymes should be normal or elevations in muscle enzymes are attributed to other explanation (e.g., MTX, liver disease, etc.).
d. Muscle MRI is recommended, but not required. If MRI has been done, there must be no evidence of active myositis.
3. Received previous or current treatment with corticosteroids and MTX.
Patients may have:
1. Mild calcinosis.
2. Nailfold capillary abnormalities.
3. Received previous or current HCQ.
4. Received previous or current IVIG.
Patients should not have:
1. Significant organ involvement that would influence treatment decisions or outcomes. This would include, but not be limited to, parenchymal lung disease, cardiac disease, or gastrointestinal vasculitis.
2. Other medical conditions that would influence outcome.
3. Calcinosis that is considered to be more than "mild" by the treating provider.
4. Ulcerative skin disease.

JDM: juvenile dermatomyositis; CMAS: Childhood Myositis Assessment Scale; MTX: methotrexate; MRI: magnetic resonance imaging; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulin.

Table 2. Clinical treatment plans for patients with juvenile dermatomyositis with persistent skin disease.

Treatment A (if not previously treated with IVIG for skin disease)
IVIG: 2 g/kg (maximum 70 g) every 2 weeks × 3 doses, then monthly.
Treatment B
Mycophenolate mofetil: 10 mg/kg/dose bid pr 600 mg/m^2/dose bid, whichever is greater, maximum dose 1500 mg bid.
Treatment C
Cyclosporine: at least 3 mg/kg. Higher doses may be used at the discretion of the treating provider, with appropriate monitoring of blood pressure and renal function.
1. Current medications, including IVIG, may be continued in arms B and C.
2. Daily corticosteroids may be continued during all arms.
a. Should not be in excess of 2 mg/kg/day, maximum 60 mg.
b. Dose of corticosteroid may be weaned at discretion of treating provider.
c. Patients starting arm A may move to arms B or C if there is an inadequate response or toxicity.
d. Pulse corticosteroids may be used at discretion of treating provider.

IVIG: intravenous immunoglobulin.

toward restarting IVIG if it had been used previously, but discontinued. However, it was recognized that IVIG therapy may not be possible or appropriate for a number of reasons, including intolerance, lack of availability, lack of venous access, or care provider preference. Other therapeutic options were mycophenolate mofetil (MMF; Treatment B) or cyclosporine (Treatment C). In addition, appropriate sun avoidance and sunscreen use were recommended for all patients, as per the expert treating provider. Information about duration of treatment or when to declare a treatment ineffective were not addressed during this process, and were left to the judgment of the treating clinician.

Table 3 summarizes the recommended outcome measures to be collected. It was agreed that these should follow those described in previous JDM CTP publications, with the addition of an assessment of skin rash[21,22]. As with the assessments in the moderate JDM CTP, recommended data collections were at 1, 2, 6, 12, and 18 months, although

Table 3. Outcomes to be assessed for patients with juvenile dermatomyositis with persistent skin disease at baseline and followup.

Initial
1. Basic
a. Cutaneous Disease Activity VAS from the MDAAT
b. PGA of disease activity
c. Patient/parent's global assessment of disease activity
d. PGA of skin disease activity
e. Patient/parent's global assessment of skin disease activity
f. CMAS
g. CHAQ
h. Manual Muscle Testing
i. MRI, if done
j. Muscle enzymes, preferably several of ALT, AST, LDH, CK, aldolase
2. Expanded, basic plus items below
a. Other autoantibodies, myositis-specific and myositis-associated
b. Full PRINTO or IMACS core set
Followup
1. Basic
a. Cutaneous Disease Activity VAS from the MDAAT
b. PGA of disease activity
c. Patient/parent's global assessment of disease activity
d. PGA of skin disease activity
e. Patient/parent's global assessment of skin disease activity
f. CMAS
g. CHAQ
h. Manual Muscle Testing
i. Muscle enzymes, preferably several of ALT, AST, LDH, CK, aldolase
2. Expanded, basic plus item below
a. Full PRINTO or IMACS core set

VAS: visual analog scale; MDAAT: Myositis Disease Activity Assessment Tool; PGA: physician's global assessment; CMAS: Childhood Myositis Assessment Scale; CHAQ: Childhood Health Assessment Questionnaire; MRI: magnetic resonance imaging; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; PRINTO: Pediatric Rheumatology International Trials Organization; IMACS: International Myositis Assessment and Clinical Studies Group.

clinical assessments may be more frequent[22]. There was extensive discussion about the use of a measure of skin disease activity as a primary outcome. While it was acknowledged that there are a number of tools developed and validated for the assessment of skin disease in JDM, it was noted that none of these have been generally accepted[24,25,26,27,28,29]. For this reason, it was decided that the cutaneous disease activity visual analog scale from the Myositis Disease Activity Assessment Tool would serve as the primary outcome[30]. This was a consensus decision supported by 91% of respondents in the first Delphi survey and 84% of respondents in the second Delphi survey. As noted previously, during the spring 2015 meeting, it was agreed that additional detail should be collected regarding the characteristics and degree of skin rash.

DISCUSSION

We have presented a set of consensus treatment plans for children with JDM who have persistent skin rash despite complete resolution of muscle involvement. This is a surprisingly common problem, and may occur in 40%–59% of cases[9,10]. Like previous CTP developed by CARRA for JDM and other rheumatic diseases, these treatment plans do not constitute treatment recommendations or optimal clinical care. Rather, they represent common treatment approaches taken by experienced pediatric rheumatologists. The goal of developing these treatment plans is to provide treating clinicians with a number of options, one of which would be the same as or very similar to their typical approach for patients such as those described here. The use of treatment plans would help to minimize variation across treatment approaches. Prospective collection of data regarding patient characteristics, course, and outcome could then be used to compare these approaches. Given that the choice of a specific treatment plan by a provider for specific patients would not be random, each CTP would need to be used with sufficient frequency to be analyzed and statistical techniques would be needed to account for patient differences that are associated

with which CTP was chosen. For example, it is possible that patients with more severe disease would receive treatment that was perceived to be more aggressive. In this way, data from a large number of patients could be aggregated to help evaluate how to best treat these patients, without the difficulties and costs associated with formal randomized clinical trials in the treatment of a rare condition.

As with any publication, there are some limitations relevant to the understanding of our work. We have described a minimum response rate to our Delphi surveys of between 20% and 24%, and a much smaller number of treating providers participated in the nominal groups. This appears to be a low response rate. However, the surveys were sent to the full CARRA membership of about 400, many of whom either do not see patients or did not feel that they had adequate expertise in JDM to respond. For this reason, the response rate among those with expertise in JDM is likely much higher; we cannot estimate this value. However, given that nearly 100 North American treating providers did participate, and that those with the most JDM experience are likely to have responded, we believe that we have met our goal of describing the most common treatment approaches.

Patients being treated with MMF (Treatment B) or cyclosporine (Treatment C) may have already failed treatment with IVIG (Treatment A). Thus, it is possible that the patients receiving Treatment B or C will be more resistant to treatment. This will tend to bias the results against these treatments, and will need to be carefully accounted for in our analysis, along with other variables that may differ between the groups.

Despite the involvement of a large number of pediatric rheumatologists in this consensus process, it is likely that some treating providers would not completely agree with the CTP described here. It is also true that we could not incorporate all treatment options into our work, particularly less common regimens such as cyclophosphamide, RTX, or other biologic therapies. For these reasons, these treatment plans may not be relevant for some providers and some patients. However, it is expected that these treatment plans would represent a reasonable approximation of typical treatment for the majority of patients with this phenotype by the majority of providers. It should also be reiterated that these treatment plans do not represent recommendations, nor should they be considered as a standard of care. They do not replace clinical judgment or decision making between the treating provider and patient. These treatment plans also do not reflect other factors that may affect clinical decision making, such as medication cost and availability, or insurance coverage.

We present a set of treatment plans complementary to the growing number of treatment plans that have been developed by the disease-specific committees of CARRA. Our work will be used to facilitate an improved understanding of treatment approaches for the subset of patients with JDM with persistent skin rash. In the future, the best of these treatment plans will be compared with additional approaches in an iterative fashion, with the goal being to identify treatment approaches associated with the best outcomes for our patients.

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