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Development of Consensus Treatment Plans for Juvenile Localized Scleroderma:

A roadmap toward comparative effectiveness studies in juvenile localized scleroderma

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Abstract

Objective—To develop standardized treatment plans, clinical assessments, and response criteria for active, moderate to high severity juvenile localized scleroderma (jLS).

Background—jLS is a chronic inflammatory skin disorder associated with substantial morbidity and disability. Although a wide range of therapeutic strategies have been reported in the literature, a lack of agreement on treatment specifics and accepted methods for clinical assessment of have made it difficult to compare approaches and identify optimal therapy.

Methods—A core group of pediatric rheumatologists, dermatologists and a lay advisor was engaged by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop standardized treatment plans and assessment parameters for jLS using consensus methods/nominal group techniques. Recommendations were validated in two face-to-face conferences with a larger group of practitioners with expertise in jLS and with the full membership of CARRA, which encompasses the majority of pediatric rheumatologists in the U.S and Canada.

Results—Consensus was achieved on standardized treatment plans that reflect the prevailing treatment practices of CARRA members. Standardized clinical assessment methods and provisional treatment response criteria were also developed. Greater than 90% of pediatric rheumatologists responding to a survey (67% of CARRA membership) affirmed the final recommendations and agreed to utilize these consensus plans to treat patients with jLS.

Conclusions—Using consensus methodology, we have developed standardized treatment plans and assessment methods for jLS. The high level of support among pediatric rheumatologists will support future comparative effectiveness studies and enable the development of evidence-based guidelines for the treatment of jLS.

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Introduction

Juvenile localized scleroderma (jLS) is a rare chronic inflammatory and fibrosing disorder associated with considerable morbidity (1, 2). Differences in disease subtype, duration, and long-term sequelae associated with jLS result in a more severe disease phenotype than is seen in adult-onset LS. For example, linear scleroderma, the most common jLS subtype, frequently affects muscle and bone in addition to skin, while the most common adult subtype, circumscribed superficial morphea (i.e., plaque morphea), is typically confined to the dermis (3, 4). Mean disease duration has been reported to be twice as long for jLS than adult-onset disease (13.5 versus 5.8 years) (5), and both relapsing and chronic-active disease are reported at relatively high frequency. Two recent pediatric studies documented recurrence rates of 28-44% at a mean of 16-20 months after discontinuing methotrexate, and a study of adults with childhood-onset disease reported a recurrence rate of 59% (6-8). Continuously active disease was reported in 30% of adults with childhood-onset LS (8), while another study reported active disease in 20% of jLS patients after 20 years (9). In addition, over 20% of jLS patients develop extracutaneous manifestations (ECM), including arthritis, seizures, and uveitis (4, 10).

Because jLS can present early in development and persist for years, the morbidity of jLS can be substantial. Children with jLS are at risk for major growth disturbance, including limb length differences, joint contractures, and facial atrophy. Review of a prospective registry of >100 jLS patients found that 38% had muscle atrophy, limb shortening, hemifacial atrophy, and/or joint contractures, and 25% had limited functional capacity (11). In a long term follow-up study of jLS patients, 25% reported mild to moderate disability after 20 years (9). Similarly, in a study of adults with childhood-onset LS, more than 50% reported permanent sequelae, including limited range of motion, deep tissue atrophy, and limb length differences (8).

Optimal therapy for jLS is not known. The lesions of jLS are characterized histologically by an early inflammatory stage followed by late stage fibrosis resulting in replacement of normal structures by abnormal collagen (1). A variety of therapeutic strategies for jLS have been proposed; however, the majority of published reports are case series with only a few comparative or placebo-controlled studies described (12-14). There is a profound lack of consensus on treatment among clinicians involved in the care of patients with jLS. To begin, there is a substantial division in therapeutic choices between subspecialty services receiving referrals for jLS, with pediatric rheumatologists treating disease beyond superficial circumscribed plaque morphea primarily with methotrexate (MTX) and systemic corticosteroids (CS), while dermatologists commonly utilize topical agents and phototherapy (6, 13, 15-18). Even more striking, when asked to detail their recommendations for treatment of a hypothetical patient with moderate to severe linear scleroderma, pediatric rheumatologists in the U.S. and Canada reported a nearly complete absence of agreement on details of the treatment regimens employed. Although more than 95% recommended MTX and CS for treatment in a linear scleroderma case vignette, when dose, route of administration, duration of treatment, and tapering or maintenance schedule were considered, there were 82 discrete MTX and 86 unique CS regimens described by 114 responders (Figure 1) ((15), and unpublished data). In effect, the majority of clinicians are following their own unique protocol for treatment of jLS, making it impossible to establish a valid comparison of outcomes.

An important limitation in the design and assessment of treatment studies in jLS, and a major source of variability in clinical practice, has been the lack of specific biomarkers and an absence of agreement on standards for quantifying disease activity and damage (19, 20). Although several clinical assessment methods have been published, including the DIET

(Dyspigmentation, Induration, Erythema, Telangiectasias) score, modified Rodnan Skin Score (mRSS), and Localized Scleroderma Skin Index (LoSSI) (21-23), all of these are severity measures, assessing activity and damage together, and each evaluates only a limited subset of the clinical parameters reported to reflect changes in disease state. Furthermore, the lack of validated treatment response criteria limits the ability of clinicians to make judgments regarding the efficacy of treatments.

In the interest of standardizing clinical practice and to establish a basis for the design and conduct of comparative effectiveness studies in pediatric rheumatic disorders, members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) have established a series of workgroups tasked with developing standardized clinical assessment and management plans (consensus treatment plans, CTPs). The aim is to develop CTPs that are consistent with best available evidence in the literature and differ only modestly from current practice for the majority of patients among the majority of participating clinicians, such that physicians will feel comfortable using the developed CTPs to treat their patients. Limiting practice variability in this fashion will allow comparison of data from diverse providers and enable the development of evidence-based standards of care.

Methods

To address the aims of CARRA CTP project, a core workgroup (jLS Core) consisting of 10 board certified pediatric rheumatologists and 2 dermatology consultants, all with expertise and special interest in jLS, and 1 lay adviser (parent of child with jLS), was formed and charged with conducting this activity. As an initial step, the following were identified as necessary for the development of CTPs for jLS: 1) Identify the target population, including a definition of active disease; 2) Identify which medications and regimens to use; 3) Develop assessment tools for monitoring disease activity and damage; and 4) Define treatment response and failure. To achieve these goals, the jLS Core conducted monthly conference calls and web-based surveys from October 2009 to Aug 2011. The work of the jLS Core was reviewed and confirmed in two in-person consensus meetings with members of the CARRA LS Workgroup, and through a web-based survey of the physician members of CARRA (the membership of CARRA includes ~ 90% of pediatric rheumatology practitioners in North America).

The development of jLS CTPs was guided by the prior survey of all physician members of CARRA on jLS treatment (jLS CARRA survey) (15), and an in-depth literature review. The jLS CARRA survey indicated excellent agreement on use of MTX (93-100%) usually with CS (76%-97%) to treat moderate to high severity jLS, and identified four predominant treatment regimens utilized by CARRA physicians (15). These patterns are: MTX alone, MTX plus oral CS, MTX plus intravenous CS (IV CS), and MTX plus both oral and IV CS (combination CS). A literature review was conducted to evaluate current scientific evidence for systemic treatment of LS. Studies eligible for evaluation had to include >1 patient, with both pediatric and adult studies included. Levels of evidence were graded from A (randomized clinical trials) to D (Expert opinion without published supporting evidence) according to guidelines established by the Oxford Centre for Evidence Based Medicine (CEBM, www.cebm.net).

Monthly jLS Core surveys were conducted to establish the range of opinion on defined topics and guide the agenda for subsequent conference calls. For example, a survey on damage assessments asked members to specify from a list which features they felt indicated damage, which ECM should be included, and how to score them. This allowed the identification of items where consensus already existed, so that discussion could focus on non-consensus items. Consensus was defined as simple majority for non-medication items,

while consensus for medication dose, route, and duration of treatment required a minimum of 80% in agreement.

The goals of the project, literature review, preliminary CTPs and assessment measures were reviewed with the CARRA LS Workgroup at the 2010 CARRA Annual Scientific Meeting (Chicago, IL; 24 participants). Nominal group techniques were used to establish consensus on elements of the draft CTPs, as well as new concerns raised during the meeting. This process involves a presentation of individual agenda items for discussion, solicitation and documentation of input from each attendee, followed by voting to identify if a consensus had been reached (24). If consensus did not exist, then further discussion was conducted with references to current clinical practice and published treatment studies provided to ensure decisions were guided by best available evidence, followed again by a vote. This process was continued until consensus was achieved, or if this did not appear possible after several cycles the topics were referred back to the jLS Core group for post-conference discussion.

Subsequent Core group conference calls addressed the remaining tasks and non-consensus items, including the completion of CTPs and the development of clinical measures and treatment response criteria. The development of clinical measures was based upon mLoSSI and Localized scleroderma Clinical and Ultrasound Study group (LOCUS) work. The mLoSSI measure provides a global assessment of LS disease activity by assessing erythema, skin thickness, and new lesion/lesion extension in all affected anatomic sites, with the body divided into 18 sites (25). These parameters were found to have moderate to very high content validity and the overall measure has a large degree of responsiveness in active patients (25). LOCUS has recently completed a prospective study of 100 jLS patients in which a dozen clinical parameters were evaluated for their correlation with physician assessment of disease state to work towards developing an evidence-based weighted clinical disease activity measure (26).

The completed CTPs, as well as the clinical activity and damage measures, were reviewed by the CARRA LS workgroup, and then presented the CARRA membership in a web-based survey. Final review and discussion of the CTPs, assessments, and treatment response criteria were conducted with the LS Workgroup at the 2011 CARRA Annual Scientific Meeting (Miami, FL; 28 participants).

Results

Target population

The initial intent of the jLS Core was to develop separate CTPs for high and moderate severity patients. As severity levels for jLS have not been defined previously, the jLS Core developed provisional definitions for use in developing CTPs (see Supplemental Table 1). Briefly, high severity was defined as presentation with generalized or pansclerotic morphea, craniofacial linear scleroderma (en coup de sabre), or other subtype with evidence of high morbidity (e.g., CNS involvement, limb shortening, joint contracture). Moderate severity was defined as circumscribed deep morphea or linear scleroderma of the trunk or limb without evidence of high morbidity. Patients with low severity jLS, typically those with superficial circumscribed morphea (plaque lesions), are not routinely referred to pediatric rheumatologists but are managed primarily by dermatologists (15). Based on the jLS CARRA survey and a survey of jLS Core member treatment preferences, there was broad overlap in the therapeutic regimens specified for high and moderate severity patients. The jLS Core, therefore, elected to develop a single set of treatment plans for both high and moderate severity patients while excluding low severity disease.

Other characteristics of the target patient population defined by the jLS Core (Table 1) include diagnosis of LS by either a pediatric rheumatologist or pediatric dermatologist with subtype classification defined according to Padua Preliminary Classification Criteria (which excludes eosinophilic fasciitis)(27). As jLS can present at birth (28), no minimum age was defined. For the purposes of inclusion in future comparative effectiveness studies of jLS, maximum age parameters for use of these CTP were recommended as onset of symptoms before age 18 years and onset of treatment before age 21 years.

The CTPs as developed and presented here are intended for patients with currently active disease regardless of prior therapy or disease duration. Because there are no established definitions for active jLS disease, the jLS Core generated a definition based upon features cited in the literature. Core members were asked to select and rank clinical features to be included in a definition of active disease from a list of parameters that had been used to evaluate treatment response or were cited as indicative of a change in disease state. This resulted in a two tier system of activity features (Table 2), with one level containing parameters that Core members agreed were individually sufficient to indicate disease activity, and the other containing parameters that members thought were not specific or severe enough on their own; a minimum of two parameters from this second level would be required for a patient to be considered to have active disease.

Consensus Treatment Plans (CTPs)

The jLS Core group identified 15 published studies that provided supporting evidence for MTX as an effective treatment for LS. These were rated using CEBM evaluation criteria; there was one level A (16), 4 level B (17, 29-31), and 10 level C papers (6, 10, 32-39). The majority of those reports also indicated a beneficial role for systemic CS at the onset of therapy, and include the four predominant treatment patterns of MTX and CS used by CARRA members (15). An additional level B study reported that solo CS treatment was effective, but had a high rate of immediate relapse following discontinuation of CS (40).

The jLS Core group worked to develop CTPs specifying the first 12 months of therapy for the predominant MTX and CS regimens utilized by CARRA members: MTX alone, MTX plus oral CS, MTX plus intravenous CS (IV CS), and MTX plus both oral and IV CS (combination CS). Although jLS Core and CARRA members commonly treat jLS patients for longer than 12 months, the jLS Core group felt there was insufficient information to specify duration of treatment beyond 1 year. The use of topical treatments for jLS among rheumatologists is variable. The jLS Core did not address topical therapy in development of the CTPs and defers their use in conjunction with a CTP to the judgment of the treating physician. Details of the CTPs developed by the jLS Core are summarized in Table 3 and described below.

Methotrexate (MTX): CTP A, B, and C—MTX is included in CTPs both as monotherapy (CTP A) and in combination with CS (CTP B and C). The jLS Core recommended that all patients on MTX follow the same guidelines. The most commonly specified dose of MTX in the jLS CARRA survey was 1 mg/kg/week (39% of survey respondents), with a majority favoring subcutaneous administration (77.8%) (15). The jLS Core and 2010 LS Workgroup unanimously approved a recommended maximum weekly dose of 25 mg administered subcutaneously. Supplementation with folic acid (0.4 to 1 mg per day) or folinic acid (5 mg weekly) is recommended.

Intravenous Corticosteroid (methylprednisolone, IV CS): CTP B—There was ready agreement among jLS Core and jLS CARRA survey respondents on a standard dose for IV CS therapy (methylprednisolone, 30 mg/kg/dose, maximum dose of 1000 mg) to be

given in conjunction with weekly MTX (15). The schedule most commonly specified by jLS CARRA survey respondents (43%) was 3 doses of IV CS given on consecutive days once per month (3 doses/month) (as per Uziel, et al. 2000 (17)). Alternative schedules named by respondents included 1 dose/week (25%) and 3 doses/week (25%) (15). The jLS Core group was divided on the use of 3 doses/month versus 1 dose/week, with discussion primarily related to logistic issues (e.g., local institution and insurance policies, patient preferences). Ultimately, the jLS Core group included both regimens in the CTP, with individual patients expected to follow a single schedule for the duration of IV CS treatment.

Although the first report on the use of IV CS for jLS specified a duration of 3 months (17), many clinicians reported using longer durations of IV CS therapy. Two jLS Core group members (RL and EP) reported their extended experience with the 3-month protocol, indicating the vast majority of patients who received 3 months of IV CS treatment have not relapsed or required additional CS. Because of the lack of published data showing a benefit to longer or shorter duration of IV CS use, the jLS Core group agreed to specify 3 months as the standard duration for IV CS treatment. As the CTPs represent standardized versions of current practice and are not guidelines, physicians can elect to treat their patient with IV CS for longer periods if they feel the patient has had an inadequate response after 3 months. By initially following a standardized treatment plan and assessing the patient with standardized outcome measures, data can be collected to determine the plan's efficacy and direct future enhancements. The 2010 LS Workgroup unanimously endorsed this schedule.

Oral Corticosteroid (prednisone or prednisolone): CTP C—For oral CS used in conjunction with MTX, the most common initial oral CS doses specified in the CARRA jLS treatment survey were 1 mg/kg/day (48%) and 2 mg/kg/day (31%) (15). Two prospective studies of MTX and oral CS treatment were discussed in depth and form the basis of the oral CS CTP (16, 31). In the first study, subjects were treated with oral CS at 2 mg/kg/day (maximum of 60 mg) for a minimum of 2 weeks. Once a clinical response was achieved (defined as absence of new/expanding lesions, and decrease in erythema and skin thickness), the CS dose was tapered to a target of 1 mg/kg/day by 8 weeks, and to zero by 12 months (31). In the second study, subjects were treated with oral CS at 1 mg/kg/day without tapering for 3 months (16). Both studies showed efficacy. All of the CARRA LS Workgroup attendees and the majority of jLS CARRA survey respondents favored a regimen with scheduled tapering of CS similar to the first study above and detailed in Table 3. The CTP allows for a more rapid taper of oral CS after the initial two weeks of treatment if the patient is judged by their treating physician to have achieved inactive disease.

Combination IV and Oral CS—The jLS Core and LS Workgroups were not able to reach consensus on a combination IV and oral CS CTP. As the literature does not offer objective evidence of a benefit of combination over single route CS treatment, the jLS Core decided not to pursue development of a combination CS CTP at this time.

Mycophenolate Mofetil (MMF)—There is very limited data regarding treatment of jLS that is unresponsive to methotrexate with or without corticosteroids. There is one level C paper supporting use of MMF for jLS (41). Despite the limited data, many CARRA members have used MMF for jLS and there was significant interest in developing a MMF CTP as an option for jLS patients who fail to achieve control on one or more of the MTX-based treatment plans, or as an alternative therapy for patients who are MTX-intolerant. In the interest of limiting practice variation among physicians who use MMF, and promoting a more rapid acquisition of valid comparative data, the jLS Core developed an MMF CTP based upon FDA dosing recommendations for pediatric renal disease (Table 3). The treating physician is encouraged to use MMF with or without CS according to the schedule of the corresponding MTX-based CTPs (alone, IV CS, or oral CS) and to employ the same

assessment methods. Several of the patients in the published jLS MMF study were also treated with MTX (6/10 patients), with no clear difference in efficacy or toxicity (41). The jLS Core defers to the treating physician's discretion whether MMF should be given alone or with MTX.

Assessment methods

Activity measure—The jLS Core group reviewed the literature on current LS assessments and preliminary data provided by LOCUS (S. Li, personal communications) and decided to develop a disease activity measure based on both LoSSI and LOCUS results. The parameters selected (Table 4) have been found to correlate significantly with physician assessment of disease activity in both LoSSI and LOCUS datasets (23, 25, 26). The scoring range for skin thickness is based upon the mRSS (0-3, where 0 is normal and 3 is hidebound) (22). The jLS Core group defined scoring ranges for the other parameters based upon LoSSI and LOCUS work, and a review of jLS lesion photographs.

Damage measure—A clinical damage measure to score skin and subcutaneous tissue damage was developed in a similar fashion (Table 4). Scoring parameters were selected that showed significant correlation with physician assessment of damage in LoSDI and LOCUS studies (26, 42)(and unpublished data, S. Li, personal communication). In addition to skin parameters, the damage measure captures extracutaneous involvement as an independent value in order to better evaluate the potential differential risk of these sequelae among patients in the different CTPs. The list of ECM included was based on published data (4). Scoring ranges were developed for arthritis and joint range of motion, as these were thought to be closely related to the degree of skin disease. Other ECM are to be scored as present or absent. More study is needed to determine relative scoring weights for the different damage features (skin, subcutaneous tissue, and ECM) before a composite damage score can be generated.

Scoring atlas—To assist with use of the disease activity and damage measures, a scoring atlas was generated consisting of photographs of jLS lesions representing each scoring level for each visible parameter (erythema, violaceous color, atrophy, depigmentation, etc.). Individual images were selected by consensus opinion from a collection provided by LS Core group members. Candidate images that did not reach consensus with regard to the proposed score were discarded. This atlas, which will be distributed to clinicians via the CARRA network, is intended as a guide to facilitate and aid standardization of scoring among treating physicians, some of whom may have had limited experience with jLS patients. Ease of use of the disease activity and damage scoring measures, as well as the utility of the scoring atlas, were piloted at the 2011 LS Workgroup following a brief tutorial. Comments from participants indicated these tools were helpful and simplified the scoring of complex patients.

Treatment response criteria—To support the development of future comparative effectiveness studies, the jLS Core group felt it was critical to develop provisional treatment response criteria for jLS. Following a review of examples from other fields, the jLS Core group elected to follow the structure of treatment response criteria for juvenile idiopathic arthritis (Pedi30) (43). The format of the Pedi30 takes into account multiple outcome variables, and its overall structure is familiar to pediatric rheumatologists. The Pedi30 requires patients to have 30% improvement in 3 of 6 outcome variables without worsening by >30% in any one outcome variable. To adapt this to jLS, the jLS Core proposed that improvement be defined as 30% improvement in at least 3 of 7 outcome variables and the absence of any parameter from a list of treatment failure markers (Table 5).

To define the criteria items, the jLS Core group identified features they considered to be more specific to treatment response or failure (e.g., erythema, lesion size, PGA), and eliminated those that could be readily related to normal disease evolution (e.g., pigmentation, atrophy, fibrosis). It is important to recognize that patients may have many lesions in various stages of development. The scoring of clinical measures is based upon the worst or highest level of the parameter in any lesion within each affected anatomic site. The treatment response criteria require that the total score for specific parameters across all affected anatomic sites decrease by 30% to rate the patient as “a responder.” As these criteria are focused on evaluating efficacy of treatment for skin features, consideration of ECM was restricted to those considered to have a course similar to skin disease, namely arthritis and restricted joint range of motion. Information about development or change in other ECM would be collected in the clinical damage measure, but not used to define treatment response or failure in the current iteration of these measures. Furthermore, because jLS lesions can be slow to respond to treatment, a determination of treatment failure criteria should not be applied prior to the patient completing two months of treatment.

Physician Survey on Consensus Treatment Plans

The members of CARRA were asked to evaluate the proposed CTPs in a web-based survey. Sixty-seven percent of members replied to the survey (142/218), with 134 (respondents) indicating that they were in active practice and treat jLS. Over 90% of respondents agreed with the target population definition and proposed assessments, with 94% of respondents expressing willingness to use at least one of the CTP to treat their patients. Respondents estimated, in total, they would treat 464 jLS patients using these CTP over a 12-month period, with 31% of these patients likely to be treated with MTX alone, 36% with MTX plus IV CS, and 23% with MTX plus oral CS (Figure 1c). The remainder of expected cases (10%) would be treated with MMF.

Discussion

This is the first effort in pediatric rheumatology to develop consensus derived standardized treatment plans for the initial 12 months of treatment of active juvenile localized scleroderma of moderate or high severity. These CTPs represent a major advance in the process to develop evidence-based treatment for jLS, as prior work showed enormous variation in methods of assessment and the specifics of treatment regimens (Figure 1a and 1b) (15). These CTPs are consistent with the current scientific evidence, and specify the use of MTX alone, or with CS administered orally or IV; a fourth provisional CTP based on MMF was developed as an option for patients intolerant to MTX, or who fail to respond to treatment in a MTX-based CTP. The high level of support (94%) from CARRA members for these plans, and large number of jLS patients (>450) whom CARRA members indicate they would treat with these CTP, suggests that this effort was successful in developing a practical approach to the standardization of care of jLS patients that will be of value to the pediatric rheumatology community.

It is important to emphasize that these CTPs are not meant to be guidelines or prescriptive instructions as the available data are too limited to enable such recommendations. Instead, these CTPs are intended to reflect and standardize current clinical practices, thus limiting variability in medication use and methods of assessment and making it feasible to evaluate treatment strategies in future comparative effectiveness studies. The authors emphasize that these CTPs are not intended to cover treatment of all patients with jLS; patients with overlap syndromes or more severe ECM may not be appropriate patients for these CTPs. Use of these CTPs is at the discretion of treating physicians, and the treating physician should diverge from the CTP if it is felt to be in the patient's best interest.

There are several limitations to this work. The developed CTPs address only the first 12 months of treatment, and they do not include a CTP for combination oral and intravenous corticosteroid treatment, a treatment specified as preferred by about 25% of CARRA members in the initial jLS treatment survey (15). However, results from the 2011 CARRA survey indicate that the majority of CARRA members found the proposed CTPs to be acceptable for treating their current and future patients. Of note, these plans do not differentiate between new onset and relapsing jLS. While it is possible that treatment response will differ between these two groups, most published studies have included patients who had received prior treatment without evidence of such a difference (6, 16, 17). The developed CTPs also do not address all jLS treatment and management issues, such as treatment of ECM, and we were not able to develop separate treatment plans for moderate and high severity patients. It is hoped that future studies utilizing these CTPs will promote investigation of the utility of separate treatment recommendations for high and moderate severity jLS or new and recurrent disease, as well as for management of extracutaneous manifestations.

A major difficulty with this project was the lack of a gold standard or validated biomarker for disease assessment. The clinical assessments developed in this effort aim to quantify multiple cutaneous clinical features, but, as with any assessment scheme, there can be ambiguity in application of the scoring methods. Although images are an imperfect representation of actual clinical findings, we expect that the scoring atlas developed by the jLS Core group will help with standardization and use of these measures. Efforts to evaluate the validity of these measures and further develop training and practice tools are in progress.

Finally, we expect implementation of CTPs for jLS to be an ongoing and iterative process, where alternate regimens and novel treatments can be evaluated against those already studied to enable evaluation of comparative effectiveness. The clinical measures and treatment response criteria presented here should also be considered a work in progress, and will need to be evaluated and modified as dictated by study findings. We anticipate these collaborative efforts will enable the community to move forward toward identification of optimal evidence-based treatments for jLS, thereby minimizing the risk for severe, persistent morbidity, and improving the long-term outcome of these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Fett N, Werth V. Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol*. 2011; 64:217–28. [PubMed: 21238823]

2. Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV Jr, et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. *J Rheumatol.* 2006; 33(5):1004–13. [PubMed: 16583463]
3. Nelson A. Localized Scleroderma Including morphea, linear scleroderma, and eosinophilic fascitis. *Curr Probl Pediatr.* 1996; 26:318–24. [PubMed: 8922521]
4. Zulian F, Vallongo C, Woo P, Russo R, Ruperto N, Harper J, et al. Localized Scleroderma in Childhood is Not Just a Skin Disease. *Arthritis Rheum.* 2005; 52:2873–81. [PubMed: 16142730]
5. Marzano A, Menni S, Parodi A, Borghi A, Fuligni A, Fabbri P, et al. Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases. *Eur J Dermatol.* 2003; 13:171–6. [PubMed: 12695134]
6. Weibel L, Sampaio M, Visentin M, Howell K, Woo P, Harper J. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol.* 2006; 155:1013–20. [PubMed: 17034534]
7. Mirsky L, Chakkittakandiyil A, Laxer R, O'Brien C, Pope E. Relapse after systemic treatment in paediatric morphoea. *Br J Dermatol.* 2011 in press.
8. Saxton-Daniels S, Jacobe H. An evaluation of long-term outcomes in adults with pediatric-onset morphea. *Arch Dermatol.* 2010; 146:1044–45. [PubMed: 20855712]
9. Peterson L, Nelson A, Su W, Mason T, O'Fallon W, Gabriel S. The epidemiology of morphea (localized scleroderma) in Olmstead County 1960-1993. *J Rheumatol.* 1997; 24:73–80. [PubMed: 9002014]
10. Christen-Zaech S, Hakim M, Afsar F, Paller A. Pediatric morphea (localized scleroderma): review of 136 patients. *J Am Acad Dermatol.* 2008; 59:385–96. [PubMed: 18571769]
11. Wu E, Rabinovich E, Torok K, Li S, Fuhlbrigge R, Investigators C. Description of the Localized Scleroderma Subgroup of CARRAnet [abstract]. *Arthritis Rheum.* 2011; 63(10 (Supplement)):S787–88.
12. Chung L, Lin J, Furst D, Fiorentino D. Systemic and localized scleroderma. *Clin Dermatol.* 2006; 24:374–92. [PubMed: 16966019]
13. Fett N, Werth V. Update on morphea. part II. Outcome measures and treatment. *J Am Acad Dermatol.* 2011; 64:231–42. [PubMed: 21238824]
14. Santos Vilela F, Carneiro S, Ramos-e-Silva M. Treatment of Morphea or Localized Scleroderma: Review of the Literature. *J Drugs Dermatol.* 2010; 9:1213–19. [PubMed: 20941945]
15. Li S, Feldman B, Higgins G, Haines K, Punaro M, O'Neil K. Treatment of pediatric localized scleroderma: results of a survey of North American pediatric rheumatologists. *J Rheumatol.* 2010; 37:175–81. [PubMed: 19918041]
16. Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A, et al. Methotrexate treatment in juvenile localized scleroderma. *Arthritis Rheum.* 2011; 63:1998–2006. [PubMed: 21305525]
17. Uziel Y, Feldman B, Krafchik B, Yeung R, Laxer R. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr.* 2000; 136:91–5. [PubMed: 10636981]
18. Zwischenberger B, Jacobe H. A systematic review of morphea treatments and therapeutic algorithm. *J Am Acad Dermatol.* 2011; 65:925–41. [PubMed: 21645943]
19. Hunzelmann N, Scharffetter Kochanek K, Hager C, Krieg T. Management of localized scleroderma. *Semin Cutan Med Surg.* 1998; 17:34–40. [PubMed: 9512105]
20. Zulian F. New developments in localized scleroderma. *Curr Opin Rheumatol.* 2008; 20:601–7. [PubMed: 18698185]
21. Dytoc M, Ting P, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphoea. *Br J Dermatol.* 2004; 153:815–20. [PubMed: 16181467]
22. Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol.* 1995; 22:1281–85. [PubMed: 7562759]
23. Arkachaisri T, Pino S. Localized scleroderma severity index and global assessments: a pilot study of outcome instruments. *J Rheumatol.* 2008; 35:650–7. [PubMed: 18322985]

24. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Seminars in arthritis and rheumatism*. 2011; 41(2):95–105. [PubMed: 21420149]
25. Arkachaisri T, Vilaiyuk S, Li S, O'Neil KM, Pope E, Higgins GC, et al. The localized scleroderma skin severity index and physician global assessment of disease activity: a work in progress toward development of localized scleroderma outcome measures. *J Rheumatol*. 2009; 36(12):2819–29. [PubMed: 19833758]
26. Li S, Torok K, Pope E, Stewart K, Higgins G, Rabinovich C, et al. Development of a clinical disease activity measure for juvenile localized scleroderma [abstract]. *Arthritis Rheum*. 2011; 63(10 Supplement):S955–56.
27. Laxer R, Zulian F. Localized scleroderma. *Curr Opin Rheumatol*. 2006; 18:606–13. [PubMed: 17053506]
28. Zulian F, Vallongo C, de Oliveira S, Punaro M, Ros J, Mazur-Zielinska H, et al. Congenital Localized Scleroderma. *J Pediatr*. 2006; 149:248–51. [PubMed: 16887444]
29. Kreuter A, Gambichler T, Breuckmann F, Rotterdam S, Freitag M, Stuecker M, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. *Arch Dermatol*. 2005; 141:847–52. [PubMed: 16027298]
30. Seyger M, van den Hoogen F, de Boo T, de Jong E. Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol*. 1998; 39:220–25. [PubMed: 9704833]
31. Torok KS, Arkachaisri T. Methotrexate and Corticosteroids in the Treatment of Localized Scleroderma: A Standardized Prospective Longitudinal Single-center Study. *J Rheumatol*. 2012 Epub ahead of print.
32. Beltramelli M, Vercellesi P, Frasin A, Gelmetti C, Corona F. Localized severe scleroderma: a retrospective study of 26 pediatric patients. *Pediatr Dermatol*. 2010; 27:476–80. [PubMed: 20796242]
33. Fitch P, Rettig P, Burnham J, Finkel T, Yan A, Akin E, et al. Treatment of pediatric localized scleroderma with methotrexate. *J Rheumatol*. 2006; 33:609–14. [PubMed: 16511930]
34. Kawashima H, Watanabe C, Kashiwagi Y, Sato S, Ioi H, Sasamoto M, et al. Therapy of childhood generalized morphea: case reports and reviews of the literature of Japanese cases. *Pediatr Int*. 2006; 48:342–45. [PubMed: 16732809]
35. Osminina M, Geppe N, Tougarinova G, Rabieva G, Kostina Y. Efficacy and safety of methotrexate treatment of juvenile localized scleroderma. *Pediatric Rheumatology*. 2008; 6(Suppl 1):230.
36. Cox D, O'Regan G, Collins S, Byrne A, Irvine A, Watson R. Juvenile localised scleroderma: a retrospective review of response to systemic treatment. *Ir J Med Sci*. 2008; 177:343–6. [PubMed: 18941862]
37. Kroft E, Creemers M, Van Den Hoogen F, Boezeman J, De Jong E. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. *Br J Dermatol*. 2009; 160:1075–82. [PubMed: 19210503]
38. Walsh J, Martini G, Woo P, Black C, Murray K. Evaluation and treatment of childhood onset localised scleroderma 1988 - 1999. *Arch Dis Child*. 2000; 82(Suppl 1):A44.
39. Hedrich C, Flebig B, Hahn G, Suttrop M, Gahr M. Presentations and treatment of childhood scleroderma: localized scleroderma, eosinophilic fasciitis, systemic sclerosis, and graft-versus-host disease. *Clin Pediatr*. 2011; 50:604–14.
40. Joly P, Bamberger N, Crickx B, Belaich S. Treatment of severe forms of localized scleroderma with oral corticosteroids: follow-up study on 17 patients. *Arch Dermatol*. 1994; 130:663–4. [PubMed: 8179352]
41. Martini G, Ramanan A, Falcini F, Girschick H, Goldsmith D, Zulian F. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology*. 2009; 48:1410–13. [PubMed: 19713439]
42. Arkachaisri T, Vilaiyuk S, Torok K, Medsger T Jr. Development and initial validation of the localized scleroderma skin damage index and physician global assessment of disease damage: a proof-of-concept study. *Rheumatology*. 2010; 49:373–81. [PubMed: 20008472]

43. Giannini E, Ruperto N, Ravelli A, Lovell D, Felson D, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum.* 1997; 40:1202–9. [PubMed: 9214419]

Significance and Innovations

Juvenile localized scleroderma (jLS) is a rare chronic inflammatory and fibrosing disorder that is the major form of scleroderma in the pediatric population. Because jLS presents in young children and can dramatically affect limb and/or craniofacial growth, it is associated with high morbidity and lifelong disability.

There are no established guidelines for the treatment of jLS. Assessment of therapeutic approaches reported in the literature has been hindered by a lack of consensus as to the methods of assessment and definitions of response.

This report documents the generation of standardized treatment and clinical assessment plans for active, moderate-to-high severity jLS through a consensus process among expert practitioners.

Standardized treatment plans will enable the identification of optimal evidence-based treatments for jLS and, thereby, improve the long-term outcome of these patients.

Figure 1. Standardization of corticosteroid and methotrexate treatment regimens for juvenile localized scleroderma

Distribution of initial corticosteroid (CS) and methotrexate (MTX) treatment regimens for jLS based upon surveys of CARRA members conducted before (upper circles) and after (lower circles) development of jLS CTP. The size of each wedge is proportional to the number of respondents specifying this regimen.

Current Practice: The CS piechart depicts the 59 initial CS regimens specified for treating a jLS linear scleroderma of limb case vignette (15). Each oral CS dose and intravenous (IV) CS dosing regimen is represented by a different color, with the different shades representing differences in duration of treatment and/or tapering schedule. Different CS types and dosing amounts or schedules are separated by tick marks with the different types/doses indicated above the wedge. For the combination CS treatment (IV + P), only the IV dosing regimen is listed, with different shades representing differences in prednisone dose, prednisone duration and/or IV CS duration. Oral prednisone (P) doses are in milligrams per kilogram of body weight per day. The MTX piechart depicts the 58 MTX regimens specified for the first 12 months of treatment for the same linear scleroderma case vignette (15). Each colored wedge represents a different dose, route and/or duration of treatment for the first 12 months of therapy. Different dosing amounts are separated by tick marks with the dose indicated above the wedge. The values of 0.3 to 1.0 represent milligrams (mg) of MTX per kilogram of patient's body weight. The values of 10 to 20/m² represent mg of MTX per meter squared of patient's surface area.

Consensus Treatment Plans: The CS piechart shows the distribution of CS CTPs that CARRA members estimated they would use to treat future jLS patients. The survey did not ask members to specify which of the two IV CS dosing regimens they would use so this wedge is shaded both purple and green. All of the MTX based CTPs specify the same dosing regimen of MTX administered subcutaneously every week for the first 12 months of treatment. This dosing regimen was unanimously agreed upon by jLS core and LS Workgroup members, and was endorsed by 94% of CARRA responders in 2011 survey. Abbreviations: d= day, IV = intravenous, kg = kilograms, mg = milograms, mo = month, P = prednisone; wk = week.

Table 1
Identification of the jLS target population[/]

Patient should have:

- i. LS diagnosed by a Pediatric Rheumatologist or Pediatric Dermatologist according to Padua Preliminary Classification criteria (27)
- ii. Active disease (defined in Table 2)
 - 1. No minimum disease duration
- iii. Treatment with systemic therapy indicated in the opinion of the treating physician
- iv. Age <18 y at onset of disease
 - 1. No minimum age
- v. Age <21y at onset of treatment

Patient should not have:

- i. Eosinophilic fasciitis
 - ii. Another defined systemic rheumatic disease (e.g., systemic sclerosis, systemic lupus erythematosus, juvenile dermatomyositis, or juvenile idiopathic arthritis)
 - iii. Intolerance to study medications
-

[/]These criteria are defined solely for the purpose of directing potential comparative effectiveness studies in jLS and are not intended to qualify or disqualify patients for any specific treatment

Table 2
Active disease definition for comparative effectiveness studies

Patients can have either one item from Group 1 or 2 from Group 2 to qualify as having active disease.

Group 1:	
1	New lesion(s) within the prior 3 months, documented by clinician
2	Extension of an existing lesion within the prior 3 months, documented by clinician *
3	Erythema of moderate or marked level in lesion or an erythematous lesion border
4	Violaceous lesion or border color
5	Documentation of active or progressive deep tissue involvement; documentation can be by clinical examination, photographs, MRI, or ultrasound.
Group 2:	
1	Patient or parent report of new lesion OR extension of existing lesion occurring within the prior 3 months. NOTE: This ONLY applies for new patients (i.e., first visit to clinician's office).
2	Lesion warmth
3	Mild erythema of lesion
4	Marked or moderate induration of lesion border
5	Worsening hair loss in scalp, eyebrow, or eyelashes; documented by clinician
6	Elevated creatine kinase level in the absence of other source
7	Lesion biopsy showing active disease (i.e., inflammation and progressive tissue fibrosis, microvasculature occlusion, and increased connective tissue macromolecules (eg. collagen, glycosaminoglycans, tenascin, fibronectin))

* Lesion extension observed in serial photographs or tracings, or documentation of 30% difference in lesion size (maximum length × width).

Table 3
jLS Consensus Treatment Plans

Decision to treat and choice of plan is based on physician judgment of best care

Medications*		CTP A	CTP B	CTP C
		MTX alone	MTX + IV CS	MTX + Oral CS
MTX	Dose:	1mg/kg/week SC, max 25 mg	1mg/kg/week SC, max 25 mg	1mg/kg/week SC, max 25 mg
	Frequency:	Weekly	Weekly	Weekly
	Duration:	12 months	12 months	12 months
CS		None	Methylprednisolone	Prednisone
	Dose:	-	30 mg/kg/dose IV, max 1 gm	2 mg/kg/day PO, max 60 mg
	Frequency/	-	Schedule 1:	Divided BID
	Duration:		3 consecutive daily doses/month × 3 months	Minimum 2 weeks Maximum 4 weeks
			Schedule 2: 1 dose/week × 12 weeks	
Taper schedule -			None	Taper targets (% initial dose): Week 8: 50% (divided BID) Week 16: 25% (daily) Week 24: 12.5% (daily) Week 48: Off CS

* Notes:

MTX route: Subcutaneous (SC) preferred to optimize bioavailability, oral if SC not practical

IV CS dosing: Use either Schedule 1 or Schedule 2 for duration of treatment.

Schedule 1: 3 consecutive days per month × 3 months (9 doses)

Schedule 2: 1 day per week × 12 weeks (12 doses)

Oral CS dosing:

Minimum criteria for tapering is lack of progression/worsening (physician overall impression)

Taper targets are maximum values at the end of 8, 24 and 48 weeks of treatment. The specific method or path of taper is left to physician judgment. BID = two times per day.

MMF CTP: MMF to be used in addition to or as replacement for MTX per physician preference.

It is suggested that patients start on one of consensus plans (i.e. Regimen A, B or C) at the time of change/addition of MMF.

MMF Dosing: <1.25 m²: 600 mg/m² BID, 40-50 kg or 1.25-1.5 m²: 750 mg BID

>50kg or >1.5 m²: 1000 mg BID

Table 4**Clinical assessments**

Score in each involved anatomic site; body divided into 19 anatomic regions: scalp, face, neck, chest, abdomen, back, buttocks, hand, forearm, arm, foot, leg, thigh (right and left for limb areas). Numbers in parentheses represent scoring equivalents for clinical impressions

Clinical Activity Parameters:	Scoring levels
Erythema:	None (0), mild (1), moderate (2), marked (3)
Violaceous color:	None (0), lilac ring or violaceous center (1)
Development of new lesion:	Absent (0)/Present (1)
Change in lesion size:	Smaller (-1), unchanged (0), larger (1)
Skin induration: lesion edge:	None (0), mild (1), moderate (2), marked (3)
Lesion warmth:	Absent (0)/Present (1)
Waxy, white/yellow lesion:	Absent (0)/Present (1)
Clinical Damage Parameters	Scoring levels
Dermal Atrophy:	None (0), shiny (1), visible vessel (2), cliff-drop (3)
Subcutaneous tissue atrophy:	None (0), mild (1), moderate (2), marked (3)
Hyperpigmentation:	None (0), mild (1), moderate (2), marked (3)
Hypopigmentation:	None (0), mild (1), moderate (2), marked (3)
Skin thickness: lesion center:	None (0), mild (1), moderate (2), marked (3)
Extracutaneous involvement:	Scoring levels
Arthritis:	Number of affected joints
Other joint limitation:	0-4 for most joints
All other ECM	Absent (0)/Present (1)
	1 Eye involvement
	2 Neurological involvement
	3 Hair loss (indicate site: scalp, eyebrow, eyelashes, other)
	4 Raynaud Phenomenon
	5 Fascia or Muscle involvement (documented by biopsy or imaging)
	6 Gastroesophageal reflux
	7 Esophagitis (documented by endoscopy)
	8 abnormal PFT (will need to specify findings)
	9 abnormal CXR/CT (will need to specify findings)
	10 Dyspnea or cough
	11 Vasculitic rash
	12 Arrhythmia
	13 Dental or other oral problems from ECDS/PRS
	14 Deep Breast tissue involvement
	15 Other (specify)

Table 5
Treatment Response and Failure Criteria

Treatment Response Criteria: Decrease by 30% in 3 of following, and absence of any outcome variable from Treatment Failure Criteria. Numerical scores for each parameter are defined in Table 4.

- 1 Erythema (overall level)
- 2 Violaceous color (overall level)
- 3 Lesion Size: Obvious change on serial photos or >30% decrease in area (calculated as maximum width × maximum length or from serial tracings)
- 4 Physician Global Assessment of disease activity
- 5 Patient/parent Global Assessment of overall disease
- 6 Induration (overall level)
- 7 Extracutaneous manifestations:
 - a. Arthritis: Any one of these parameters: number of affected joints, swelling (0-3), limited range of motion (0-3), pain with motion (0-1)
 - b. Other limitation of joint range of motion/contracture

Treatment Failure Criteria: Presence of any one outcome variable indicates failure.

- 1 Development of New lesion: Must have erythema, violaceous color, or induration
- 2 Extension of Existing lesion: Must have erythema, violaceous color, or induration *
- 3 Development or worsening of arthritis *OR* worsening joint range of motion
- 4 Persistent or increased erythema (overall level)
- 5 Persistent or increased violaceous color (overall level)

* Extension can be documented as obvious change on serial photos or >30% decrease in area (calculated as maximum width × maximum length or from serial tracings)