

Update on morphea

Part II. Outcome measures and treatment

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Learning Objectives

After completing this learning activity, participants should be able to recognize the need for a universally accepted validated outcome measure for the study of morphea therapies and compare the strengths and weaknesses of the currently available outcome measures, counsel their patients on the data available (and not available) for therapeutic options, and use the available treatment data and recommended therapeutic ladder when prescribing therapy.

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Morphea is a rare fibrosing disorder of the skin and underlying tissues. The underlying pathogenesis of morphea is not completely understood at this time, but ultimately results in an imbalance of collagen production and destruction. Evidence-based treatment options of morphea are limited secondary to the rarity of the disease, and the lack of universally used validated outcome measures. The most commonly used outcome measures are skin scores, computerized surface area measurement, durometer, cutometer, thermography, and ultrasound measurements. The Localized Scleroderma Cutaneous Assessment Tool is a promising recently validated skin scoring tool that allows differentiation between activity and damage, is sensitive to change, and requires no additional equipment. The most robust data in the treatment of morphea exists for methotrexate in combination with systemic steroids and ultraviolet A1. (J Am Acad Dermatol 2011;64:231-42.)

Key words: autoimmune connective tissue disorder; fibrosing disorders; localized scleroderma; morphea; scleroderma; systemic sclerosis.

Key points

- **Morphea is a fibrosing condition of the skin, subcutaneous tissue, underlying bone, and rarely, when present on the face and head, the underlying central nervous system**
- **Evidence-based therapies for morphea are lacking because of the rarity of the disease and the lack of universally used validated outcome measures**
- **Methotrexate in combination with systemic steroids and ultraviolet A1 light phototherapy are the two therapies for morphea with the most clinical data**

Morphea is a rare fibrosing disorder of the skin and underlying tissues that is equally prevalent in both children and adults. The underlying pathogenesis is incompletely understood, but is known to result in an imbalance of collagen production and destruction. Children are more likely to present with linear morphea, which can be disfiguring if present on the face and debilitating if it involves an extremity. Adults are more likely to present with circumscribed morphea, also known as plaque morphea, and have less associated morbidity. Evidence-based therapies for morphea are lacking (Table I). The source of this deficiency is multifaceted. Primarily, morphea is a relatively rare disease, which makes large randomized controlled

trials difficult to perform. Secondly, improvement is difficult to define. Outcome measures assessing lesion depth, surface area, hardness, elasticity, and activity all exist; however, a change in any one of these parameters has not been uniformly correlated with clinical improvement. Finally, the lack of evidence-based therapies for morphea is further

compounded by the absence of a uniform, validated outcome measure. The absence of an outcome measure makes intercenter collaboration and metaanalysis—required in the study of rare diseases—impossible to perform. Four randomized controlled studies of treatment options in morphea have been completed. Of these, two revealed negative results (subcutaneous interferon-gamma [IFN γ] and oral calcitriol performed as well as placebo), narrowband ultraviolet B light (NB-UVB) phototherapy was found to be as effective as low dose ultraviolet A1 light (UVA1) phototherapy, and occluded topical tacrolimus was more effective than placebo at treating active plaque morphea.¹⁻⁴ Methotrexate in combination with

systemic steroids and UVA1 phototherapy have been prospectively studied in a large number of patients with positive clinical outcomes. D-penicillamine, mycophenolate mofetil, cyclosporine, photophoresis, imiquimod, and calcipotriol in combination with betamethasone dipropionate have all reported to be effective in small prospective or retrospective studies.

CAPSULE SUMMARY

- Rare diseases require universally accepted validated outcome measures to allow for intercenter collaboration and metaanalysis.
- The Localized Scleroderma Cutaneous Assessment Tool is a promising recently validated skin scoring tool that allows differentiation between activity and damage, is sensitive to change, and requires no additional equipment.
- Randomized controlled trials assessing morphea therapeutics have concluded that narrowband ultraviolet B light phototherapy is as effective as low dose ultraviolet A1 light phototherapy, and that topical tacrolimus is an effective treatment for active plaque morphea.
- Methotrexate in combination with systemic steroids and ultraviolet A1 light phototherapy have the most evidence of efficacy in the treatment of severe morphea.

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OUTCOME MEASURES**Key points**

- **Rare diseases require universally accepted validated outcome measures to acquire meaningful data**
- **Several outcome measures are currently used in morphea studies and include cutometer measurements, durometer measurements, thermography, ultrasound measurements, surface area assessment via**

Table I. Studied morphea therapies*

Treatment	Effective or ineffective	Level of evidence
Subcutaneous interferon gamma	Ineffective	IB
Oral calcitriol	Ineffective	IB
Topical tacrolimus	Effective	IB
Photodynamic therapy	Ineffective	IIA
NBUVB	Effective	IIB
UVA1 (low, medium, and high doses)	Effective	IIB
Broadband UVA	Effective	IIB
Imiquimod	Effective	IIB
PUVA	Effective	IIB
Calcipotriol in combination with betamethasone dipropionate	Effective	IIB
Methotrexate in combination with systemic steroids	Effective	IIB
D-penicillamine	Effective	III
Cyclosporine	Effective	III
Mycophenolate mofetil	Effective	III
Photophoresis	Effective	III

NBUVB, Narrowband ultraviolet B light phototherapy; PUVA, psoralen plus ultraviolet A light phototherapy; UVA1, ultraviolet A light phototherapy.

*Level of evidence rating scheme from Shekelle et al.⁶⁶

computerized imaging, and nonvalidated skin scores

- **The Localized Scleroderma Cutaneous Assessment Tool is a promising recently validated skin scoring tool that allows differentiation between activity and damage, is sensitive to change, and requires no additional equipment**

Validated outcome measures are necessary for meaningful data collection. The lack of evidence-based therapies for morphea is partially related to the absence of a universally used validated outcome measure. Defining an outcome measure for morphea is complicated by the difficulty in characterizing improvement. Based on clinical experience, lesions of morphea are thought to soften over time. However, this softening is not reliably reflected in change of lesion depth, hardness, or elasticity. Surface area is a notoriously unreliable outcome measure, and is unlikely to change as the lesions of morphea improve. An appropriate outcome measure needs to have good inter- and intrarater reliability and sensitivity to change. Several outcome measures for morphea are currently under investigation.

Skin scores

The first validated outcome measure in systemic sclerosis was the Rodnan skin score (RSS).⁵⁻⁷ The

scale was modified (and renamed the modified Rodnan skin score [mRSS]) to 17 anatomic areas (eliminating the toes, upper back, and combining the chest) and a score of 0 (normal skin) to 3 (severe thickening).⁶ Fingers and hands are heavily weighted in the mRSS, with the upper extremities totaling close to 50% of the total score. This bias is helpful in systemic sclerosis where patients universally have finger and hand involvement, but detrimental in morphea where finger and hand involvement is unexpected. The mRSS has not been validated for morphea.

Many authors use a self-created, nonvalidated skin score to report their experimental findings when studying morphea. The most commonly used nonvalidated skin score is the Modified Skin Score (MSS).⁸⁻¹² The MSS divides the body into seven anatomic regions (head and neck, trunk, arms, hands, fingers, and legs and feet). Each region is then scored on a 0 to 3 scale for degree of thickening and percent of involvement.⁸

A morphea-specific skin scoring system, the localized scleroderma skin severity index (LoSSI), has recently been validated by the Localized Scleroderma Clinical and Ultrasound Study Group (LOCUS).¹³ The index allows for measurement of skin erythema, thickness, and new lesions on a scale of 0 to 3 in each of 18 anatomic areas. The instrument was assessed including and excluding surface area. Surface area estimates resulted in poor inter- and intrarater reliability and poor sensitivity to change and therefore were eliminated from the tool, resulting in the modified LoSSI.¹⁴ The modified LoSSI (mLoSSI) has a reported interrater agreement of 0.70 and intrarater agreement of 0.77, and has been shown to be sensitive to change over a 10-week period.¹⁴ LOCUS has also recently validated the localized scleroderma skin damage index (LoSDI), showing high inter- and intrarater reliability.¹⁴ Arkachaisri et al¹⁴ recommends combining the LoSDI, LoSSI, and the Physician's Global Assessment (PGA) for activity and damage to compose the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT), as modeled after the cutaneous lupus erythematosus activity and severity index (CLASI).¹⁵ This tool would allow physicians to separate areas of activity from areas of damage, which has proven beneficial in the assessment of other autoimmune skin diseases.¹⁵ The LoSCAT appears to be the most promising outcome measure for morphea at this time, given its ease of use, ability to use in clinic without additional instruments or imaging, and good inter- and intrarater reliability.¹⁴ Further validation studies

including rare variants of morphea (particularly deep variants) are needed to assess the tool's full capabilities.

Computer method

Zulian et al¹⁶ recently described a computerized method for assessing the skin lesions of morphea. Tegaderm is applied to the patient, overlaying the morphea lesion. The lesion is then palpated and the indurated component is outlined with a marker onto the Tegaderm. The surrounding erythema or violaceous hue is then assessed and also outlined on the Tegaderm with a different color marker. Specialized computer software is able to discern between the two colors and calculate the surface area of the total lesion, the inflammatory border, and the sclerotic center.¹⁶ Given the patient's height and weight, the software will also calculate the patient's body surface area (BSA) and then the lesion size to BSA ratio.¹⁶ Using the intraclass correlation coefficient two-way random effect model (ICC), the method has been validated for interrater reliability (0.95).¹⁶ Intrarater reliability was reported to be "acceptable."¹⁶ The measurement reportedly takes only 5 minutes per patient.¹⁶ This method is attractive in that it calculates surface area instead of relying on an estimation of the surface area. However, because morphea lesions do not shrink as they resolve, it is likely to be insensitive to improvement.

Durometer

A durometer is a handheld device that measures skin hardness. The measurement is dependent on edema, location, and patient sex and age. Seyger et al¹¹ evaluated the durometer as an outcome measure in patients with morphea. The durometer measurements had low inter- and intraobserver variability; however, they found poor correlation between durometer scores and a nonvalidated modified skin score (0.5).¹¹ Although the durometer's high reliability makes it an attractive outcome measure, its poor correlation with clinical skin scores and unknown sensitivity to change leave questions about its clinical utility.

Cutometer

A cutometer is a handheld device that, when connected to a computer with the appropriate software, is capable of measuring skin elasticity and relaxation. The measurement is dependent upon anatomic site, age, sex, and edema. The probe measures the rate at which it is able to pull skin in and the rate at which the skin

returns to baseline. Although cutometer readings are reported as results in morphea studies and appear to be sensitive to change, cutometer measurements have not been validated in morphea.^{17,18}

Thermography

Thermography captures infrared images of patients that are representative of the surface temperature of their skin. Performance of this measure requires a temperature-controlled room, a 15-minute period to allow patient skin temperature equilibration once in the temperature-controlled room, an infrared camera, a trained technician, and a skilled image interpreter. Areas are considered positive if they are 0.5°C warmer than the surrounding tissue. The criterion standard by which thermography is calibrated is the clinical appearance of the lesion and the lesion's behavior over time. Using the clinical examination as the criterion standard, Birdi et al¹⁹ reported a sensitivity of 100% and a specificity of 80%, and Martini et al²⁰ reported a sensitivity of 92% and a specificity of 68%. The false positives in both studies were noninflammatory lesions with considerable disease-induced atrophy. The authors speculate that the loss of subcutaneous tissue resulted in increased thermal conductivity of the epidermis, and reflects the underlying vascular plexus and not the disease activity.^{19,20} Given that thermography is incapable of distinguishing between active and quiescent disease, and that investigators trust their clinical exam above the results of the imaging, the imaging seems an expensive and cumbersome instrument that is unlikely to add relevant information to the examination of the patient.

Ultrasound

There are three recently published comprehensive reviews on the use of ultrasound as an outcome measure in morphea.^{21,22-24} Ultrasound is a noninvasive technique used to measure the depth of a lesion. Ultrasounds are manufactured with different frequencies, allowing a spectrum of resolution and penetration. Higher ultrasound frequencies produce superior resolution, but shallower penetration. Most studies performed in Europe use a 10- to 25-MHz ultrasound probe. When studied for use in morphea, these 10- to 25-MHz probes have proven to have good inter- and intrauser reliability, and are sensitive to changes in the clinical examination.^{9,10,25-29} The 10- to 25-MHz ultrasound is not available in the United States. Authors in the United States who wish to

use ultrasound as an outcome measure use a 10- to 15-MHz ultrasound. There are fewer studies of the validity of the 10- to 15-MHz ultrasound. However, the studies that have been performed show good inter- and intrareproducibility of measurements.^{29,30} To date, there are no studies assessing the correlation between 10- to 15-MHz ultrasound measurements and clinical examinations or the responsiveness of this ultrasound to clinical change.²¹

TREATMENT

Key points

- **Results of the four randomized placebo or standard therapy controlled studies assessing morphea treatment conclude the following:**

- **Subcutaneous interferon-gamma is not an effective treatment for plaque morphea (level IB evidence)**
- **Oral calcitriol is not effective for the treatment of morphea (level IB evidence)**
- **Narrowband ultraviolet B light phototherapy is as effective as low dose ultraviolet A1 phototherapy (level IB evidence)**
- **Topical tacrolimus is an effective treatment for active plaque morphea (level IB evidence)**

Four randomized placebo or standard therapy controlled studies have been performed assessing the efficacy of treatment in morphea. The first, published in 1997, assessed the efficacy of subcutaneous IFN γ in the treatment of active plaque morphea.¹ Twenty-four patients were randomized to receive 10 doses of IFN γ or placebo over 2 weeks and then weekly injections for an additional 4 weeks. The patients were then observed for a total of 18 weeks. Flu-like symptoms were more common in the interferon group than the placebo group. There was no statistically significant change between the groups when assessed for surface area involved, MSS, or a reduction in the total number of lesions. IFN γ is not an effective therapy for morphea.

The second, published in 2000, evaluated the effectiveness of calcitriol as a therapy for morphea.² Patients were randomized to receive 0.75 mcg/day calcitriol for 6 months and then 1.25 mcg/day for an additional 3 months or placebo for 9 months.² A skin score was used as the primary outcome measure. The placebo group had more improvement in their skin scores than the treatment group, disproving calcitriol as an effective therapeutic for morphea.²

The third, published in 2006, assessed the efficacy of low dose UVA1 (340–400 nm), medium dose UVA1 and NBUVB phototherapy for morphea.³ Sixty-four consecutive white patients were recruited, randomized, and treated three times weekly for 8 weeks. Patients randomized to the low dose UVA1 group received a total dose of 800 J/cm², the medium dose UVA1 group was given a total dose of 2000 J/cm², and the NBUVB group started at 0.1 J/cm² for Fitzpatrick skin type II and 0.2 J/cm² for Fitzpatrick skin type III and was increased by 0.1 to 0.2 J/cm² as tolerated with maximum doses of 1.3 J/cm² for Fitzpatrick skin type II and 1.5 J/cm² for Fitzpatrick skin type III. Outcome measures were the MSS, scores on a visual analog scale, change in histologic appearance, and 20-MHz ultrasound measurements. There was a statistically significant decrease in the MSS in all groups.³ Pre- and posttreatment biopsy specimens were available in 36 patients, with only the NBUVB group showing a statistically significant decrease in skin thickness.³ Pre- and posttreatment ultrasound results were available in 48 patients. Only the medium dose UVA1 group had a statistically significant decrease in corium thickness by ultrasound measurement.³ When the treatment arms were compared, the medium dose UVA1 group showed statistically significant improvements in skin score compared to the NBUVB, but not when compared to the low dose UVA1 group.³ The low dose UVA1 and NBUVB groups showed equivalent improvement in skin scores.³ The authors concluded that NBUVB could be considered a safe, efficacious, and readily available treatment option for morphea.³

The fourth, published in 2009, assessed the efficacy of topical 0.1% tacrolimus in the treatment of plaque morphea.⁴ Ten patients with two or more active plaques of morphea separated by at least 15 cm were recruited for the study. The patients applied tacrolimus to one of the lesions and petroleum jelly to the other. The primary outcome measures were change in surface area, change in durometer score, and change in a clinical feature score (dyspigmentation, induration, erythema, telangiectasia, and atrophy).⁴ There was no statistically significant change in surface area involved between the petroleum jelly- and tacrolimus-treated lesions.⁴ Both durometer scores and clinical feature scores had a statistically significant reduction when compared to placebo.⁴ The authors concluded that topical tacrolimus effectively decreases skin thickness,

dyspigmentation, induration, erythema, telangiectasia, and atrophy when applied twice a day for 12 weeks.⁴

Methotrexate

Key points

- **Retrospective studies on 119 patients with morphea treated with methotrexate (usually in combination with systemic steroids) report a combined success rate of 80%**
- **The efficacy of methotrexate in combination with high dose systemic steroids is supported by three prospective trials**
- **Methotrexate in combination with systemic steroids is supported by level IIB data**
- **Randomized placebo controlled studies are needed to assess the efficacy of methotrexate in combination with systemic steroids**

In the last 4 years, four retrospective reviews on the use of methotrexate have been carried out on a total of 119 patients with morphea.³¹⁻³⁴ Sixty-seven of these patients received methotrexate in combination with systemic corticosteroids.³¹⁻³⁴ Methotrexate doses ranged from 0.3 to 0.4 mg/kg per week in children and 15 to 25 mg per week in adults.³¹⁻³⁴ Systemic corticosteroids were given via intravenous pulse and then transitioned to oral. Ninety-four of the 119 patients (79%) reportedly improved with treatment.³¹⁻³⁴ In studies using methotrexate without systemic steroids, results varied when compared to the patients that received methotrexate in combination with steroids.^{31,33} Because of the retrospective and uncontrolled nature of these studies, it is difficult to say if those patients not treated with steroids were similar to those patients who were. If steroid treatment was reserved for patients with more severe involvement (and therefore a worse overall prognosis), then it is conceivable that those patients not treated with steroids (those with a milder course) would have a better outcome based on the natural course of their disease and not based on the intervention. The primary outcome measure was the treating physician's documented clinical impression.³¹⁻³⁴

Three prospective trials of the therapeutic effects of methotrexate in combination with systemic corticosteroids in morphea have been carried out.^{9,12,35} These studies assessed the response to treatment in 24 adults and 10 children. Adults were treated with 15 mg of

methotrexate a week, with doses adjusted based on clinical response. Children were treated with 0.3 mg/kg per week, with doses adjusted to response as well. All patients were treated with bursts of high dose intravenous methylprednisolone. Both adult studies showed statistically significant improvement in the mean MSS and mean ultrasound measurements when compared to baseline.^{9,12} Nine of the 10 children were reported to improve based on clinician assessment.³⁵

The above retrospective and prospective studies of the use of methotrexate in morphea have also reported disease flaring with therapy cessation. It is difficult to interpret these results, given the lack of a control group, but authors have inferred that flaring with cessation of therapy supports the efficacy of methotrexate in the treatment of morphea.

In conclusion, although randomized placebo controlled studies assessing the efficacy of methotrexate in morphea are lacking, several prospective and retrospective studies support its effectiveness in combination with systemic steroids.

Ultraviolet light

Key points

- **Ultraviolet A1 light, broadband ultraviolet A light, psoralen plus ultraviolet A light phototherapy, and narrowband ultraviolet B light phototherapy all provide benefit to patients with morphea**
- **High dose ultraviolet A1 light is likely the most effective ultraviolet light therapy for morphea; however, it is not widely available in the United States and requires long exposure times**
- **The level of evidence for Ultraviolet A1 light, broadband ultraviolet A light, psoralen plus ultraviolet A light phototherapy, and narrowband ultraviolet B light phototherapy is level IIB**
- **Further studies on the efficacy of broadband ultraviolet A light and narrowband ultraviolet B light phototherapy are needed to expand treatment options for morphea in the United States**

Interest in the use of UVA as a therapeutic modality for morphea was sparked by an article published by Kerscher et al in 1994.³⁶ Two patients with morphea were treated with psoralen plus ultraviolet A light phototherapy (PUVA), tapered over 15 weeks for a total of 30 treatments.³⁶ Both

patients had clinical improvement, reduction in skin thickness measured by 20-MHz ultrasound, and a reduction in sclerosis on histopathologic examination.³⁶

Kerscher et al³⁶ then postulated that psoralen may not be a necessary adjunct in this treatment, and went on to treat 10 morphea patients with UVA1.³⁷ Patients were treated with 20 J/cm² per day irradiations over 6 weeks, for a total of 24 treatments, and a total UVA1 dose of 480 J/cm². All 10 patients showed clinical improvement, a reduction in skin thickness measured by 20-MHz ultrasound, and a reduction in sclerosis on histopathologic examination.³⁷

The exact mechanism of action of ultraviolet therapy in the treatment of morphea is unknown. Most authors have focused on using UVA1, given its ability to penetrate more deeply into the skin and clinical efficacy in the absence of systemic medication. UVA1 causes apoptosis of epidermal Langerhans cells and T cells.³⁸⁻⁴⁰ UVA1 also affects fibroblasts, increasing synthesis of collagenases and decreasing synthesis of collagen.^{39,40} It is also thought to impair collagen cross linking. UVA1 also affects levels of local cytokines. It causes a decrease in interleukin-6, which decreases collagen and glycosaminoglycans, a decrease in transforming growth factor-beta (TGFβ), which decreases fibroblast growth, and an increase in IFNγ, which increases matrix metalloproteinase-1.³⁹⁻⁴¹ A review of the literature reveals agreement among authors that UVA1 is efficacious in the treatment of morphea. What is lacking is agreement on the correct dosing regimen or frequency, total exposure, and whether UVA1 is effective in patients with darker skin tones (ie, Fitzpatrick skin types ≥ IV).^{42,43}

Since 1995, 121 patients with morphea treated prospectively with UVA1 have been reported in the literature.^{10,17,18,27,28,37,44-46} These patients ranged in age from 3 to 73 years and had morphea based on clinical and histologic findings with a range of duration from 6 months to 20 years. Patients with linear, plaque, and subcutaneous morphea were included in these studies. When stated, the patients were predominantly white. The majority of the patients had been treated with topical steroids before treatment and the treatment washout period ranged from 4 weeks to 6 months. Not all studies stated that actively inflamed morphea lesions were required. The majority of these patients were treated with low dose UVA1, at doses of 20 J/cm² per day tapered over 5 to 20 weeks, with total irradiation ranging from 600 to

800 J/cm² (70/121 patients). Ninety percent of these patients were reported to improve on the basis of the clinical examination, skin score, ultrasound measurements, cutometer measurements, skin biopsy specimens, or a combination of these outcome measures.^{10,27,37,44-46} Two of these studies compared medium dose UVA1 (70 J/cm² per treatment with a total dose of 2100 J/cm²) and high dose UVA1 (130 J/cm² per treatment with a total dose of 3900 J/cm²) to low dose UVA1 (20 J/cm² per treatment with a total dose of 600 J/cm²).^{28,46} Treatment with medium dose UVA1 resulted in a longer duration of the statistically significant change in ultrasound measurements.⁴⁶ Patients treated with medium dose UVA1 had similar changes in a clinical skin score when compared to patients treated with low dose UVA1.⁴⁶ Both medium dose UVA1 and low dose UVA1 resulted in a statistically significant change in clinical skin score when compared to placebo.⁴⁶ Patients treated with high dose UVA1 showed statistically significant changes in clinical skin score, skin thickness by 20-MHz ultrasound measurement, cutometer measurements, and histologic examination when compared to those patients treated with low dose UVA1.²⁸

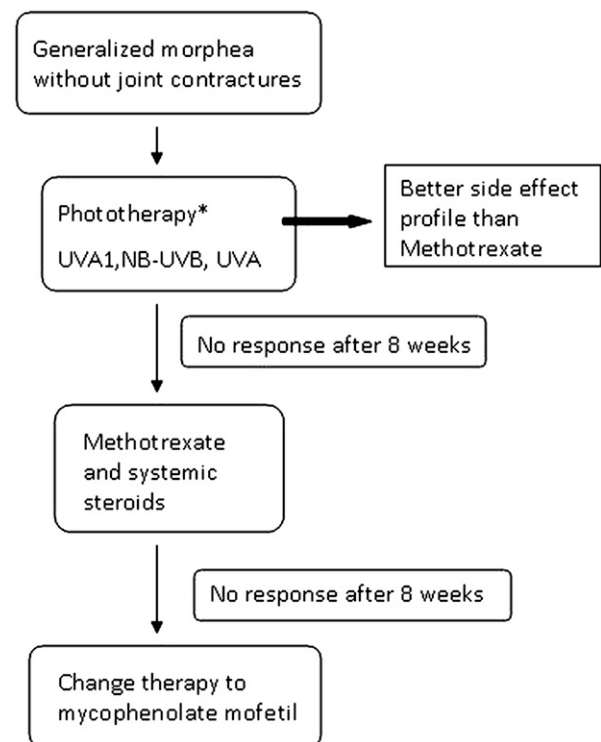
The majority of patients in these studies are of Fitzpatrick skin types I through III, because of the demographics of the countries in which these studies were carried out, and because UVA1 was presumed to be less efficacious in darker skin types. In 2008, Jacobe et al⁴² published a retrospective review of 101 patients spanning Fitzpatrick skin types I through V who were treated with high dose UVA1.⁴² Patient diagnoses spanned morphea, systemic sclerosis, graft versus host disease, atopic dermatitis, nephrogenic systemic fibrosis, granuloma annulare, pityriasis rubra pilaris, and urticaria pigmentosa. No difference in UVA1 therapy efficacy was noted across the five skin types when all disease subtypes were assessed. Forty-seven of the patients had morphea, and again, no difference in efficacy of therapy was noted across the five skin types.⁴² This is in contrast to a 2008 molecular-based prospective trial carried out by Wang et al.⁴³ Wang et al⁴³ made several interesting observations. First, skin type was predictive of the amount of decline of type 1 and type 3 collagen and the increase of matrix metalloproteinases after treatment with high dose UVA1 (ie, the lighter the skin type, the more dramatic the changes and the darker the skin type, the less dramatic the changes).⁴³ Secondly, they noted a statistically significant reduction in collagen 1 and 3

production after one treatment of high dose UVA1, that was not seen in patients treated with three high dose UVA1 sessions before measurement.⁴³ These findings lead them to suggest that UVA1 be provided in pulse therapy, to prevent tanning and increase efficacy, as well as in low doses, for similar reasons.⁴³

Unfortunately, although proven efficacious in the treatment of morphea, UVA1 is not widely available in the United States. UVA1 is also inconvenient in that it requires 30 to 60 minutes of exposure per treatment, a time commitment that is difficult to make three times per week. The relative unavailability of UVA1 and inconvenient prolonged treatment times have led authors to investigate the use of broadband UVA in the treatment of morphea, both with and without psoralen. Thirty patients with morphea have been prospectively treated with PUVA.^{26,47} Eighty percent of them reportedly showed improvement via skin score with or without ultrasound measurement.^{26,47} Seventy-five patients with morphea have been prospectively treated with broadband UVA.^{48,49} Approximately 77% of these patients were reported to have “fair” or better clinical response to therapy.^{48,49} These patients also showed normalization of dermal collagen on histologic examination.^{48,49} Treatments ranged from 5 J/cm² per treatment with a total of 100 J/cm² of irradiation to 20 J/cm² per treatment with a total of 400 J/cm² of irradiation, without statistically significant changes in outcome between these groups.⁴⁹ This suggests that when UVA1 therapy is not locally available, broadband UVA therapy or PUVA may be used.

It is interesting to note that between 20% and 80% of patients with morphea have positive anti-nuclear antibody (ANA) titers. None of the discussed studies excluded patients with positive ANA titers. Of the over 400 patients included in this review, none of them were reported to have problems related to photosensitivity. Therefore, although patients with morphea may have positive ANA titers, they are unlikely to have photo-induced disease.

In conclusion, UVA1, broadband UVA, PUVA, and NB-UVB provide benefit to patients with morphea. High dose UVA1 is likely the most effective option. However, the long-term side effects of photodamage and carcinogenesis may make low dose UVA1 a safer yet still effective option. Given the paucity of UVA1 treatment options in the United States, and the reported benefits of broadband UVA and NB-UVB, these wavelengths of irradiation should be further studied in the treatment of morphea patients.



* Based on local availability

Fig 1. Treatment algorithm for generalized morphea.

Other systemic agents

Key points

- **Use of D-penicillamine is supported by level III evidence**
- **The addition of mycophenolate mofetil to methotrexate and systemic steroids, the use of cyclosporine, and the use of photophoresis are all supported by level III evidence**

D-penicillamine in doses of 2 to 5 mg/kg per day has been reported in case series to be an effective treatment for morphea, but is rarely used given its unfavorable side effect profile.⁵⁰

Mycophenolate mofetil (MMF) was been retrospectively assessed as a treatment adjunct in children with morphea.⁵¹ The majority of these children were already taking, and continued taking, methotrexate and systemic steroids while being treated with MMF.⁵¹ The primary outcome measures were subjective clinical improvement and thermography. Nine of 10 patients reportedly improved with the addition of MMF to their regimen.⁵¹ In an in vitro human lung fibroblast model, MMF inhibited type 1 collagen expression, enhanced the expression of matrix metalloproteinase-1, and altered fibroblast

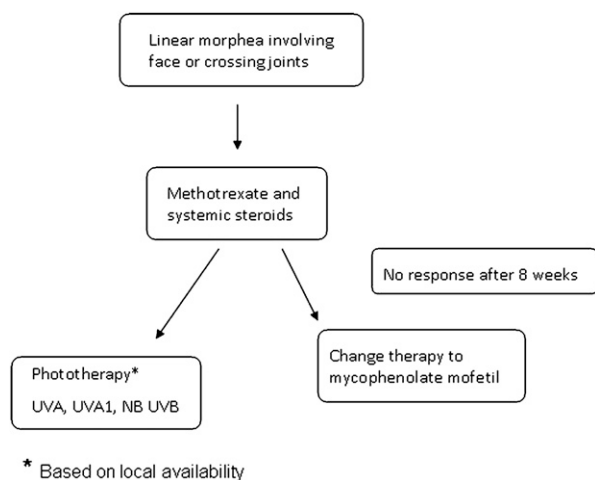


Fig 2. Treatment algorithm for linear morphea involving the face or crossing joints.

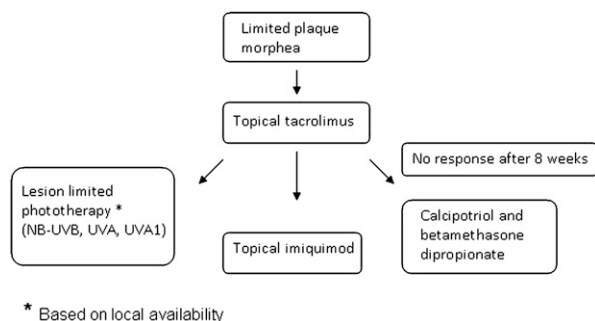


Fig 3. Treatment algorithm for limited plaque morphea.

migratory and contractile functions.⁵² MMF has also been shown to down regulate profibrotic cytokines TGF β 1, smad 2 and 3, and inhibit smooth muscle cell proliferation in arterials.^{53,54} These combined effects may inhibit fibrosis in humans. A recently conducted prospective trial of MMF in the treatment of diffuse cutaneous systemic sclerosis resulted in statistically significant improvement in skin scores.⁵⁵

There are two case reports of benefit of cyclosporine in the treatment of morphea in children in the literature.^{56,57}

Inspired by the success of extracorporeal photopheresis in the treatment of systemic sclerosis reported by Knobler et al,⁵⁸ Neustadter et al⁵⁹ recently reported clinical improvement in a patient with generalized morphea after extracorporeal photopheresis.

TOPICAL THERAPY

Key points

- **The use of imiquimod to decrease erythema and induration of morphea lesions is supported by level IIB evidence**

- **The combination of calcipotriol in combination with betamethasone dipropionate is supported by level IIB evidence**
- **The ineffectiveness of photodynamic therapy is supported by level IIA evidence**

Dytoc et al⁶⁰ assessed the value of thrice weekly imiquimod in the treatment of morphea in 12 patients. The lesions were scored with a clinical scale assessing dyspigmentation, induration, erythema, and telangiectasia.⁶⁰ *P* values were not presented for the change in total skin score, likely reflecting nonsignificance. However, there was a statistically significant change in erythema and induration scores at 6 months.⁶⁰ Dytoc et al⁶⁰ postulate that the increase in interferon-gamma produced by imiquimod is the underlying mechanism of action.

Calcipotriol in combination with betamethasone dipropionate was reported to have efficacy in the treatment of morphea in a prospective study of six patients with plaque morphea.⁶¹

In an open-label prospective study of 12 patients with active plaque or linear morphea, twice daily occluded topical calcipotriene used for 3 months resulted in a statistically significant decrease in erythema, dyspigmentation, telangiectasia, and induration.⁶² Batchelor et al⁶³ recently carried out a prospective, lesion-controlled study of photodynamic therapy in the treatment of morphea. After 6 weeks of weekly treatments, no significant change was noted between treated and untreated lesions.

OTHER THERAPIES

Key point

- **The effectiveness of physical therapy in the treatment of morphea has never been studied**

Physical therapy

Physical therapy is often recommended in patients with morphea, particularly the linear limb, generalized, and pansclerotic variants that can cause joint contractures.^{64,65} Physical therapy outcomes have not been studied in patients with morphea. However, physical therapy does not appear to exacerbate the disease and may be of value in preserving range of motion and minimizing joint contractures.

CONCLUSIONS

Morphea is a rare, clinically heterogeneous disease process defined by increased collagen deposition. Morphea is distinguished from systemic sclerosis by its lack of sclerodactyly, Raynaud phenomenon, and nailfold capillary changes. Central nervous system fibrosis most commonly affects those

children with head and neck involvement. Children with head and neck morphea should have regular ophthalmologic examinations to monitor for asymptomatic involvement that may lead to irreversible damage if not aggressively treated. The pathogenesis of morphea is likely multifactorial, involving genetic factors and environmental exposures, culminating in small vessel damage, the release of profibrotic cytokines, and a disruption of the balance of collagen production and destruction. Few randomized placebo controlled studies assessing morphea therapy have been published. To date, methotrexate combined with systemic corticosteroids and UVA1 have the most convincing data supporting their use. Both of these medications should be reserved for those patients with extensive involvement, facial involvement, or involvement across joints. For patients with limited involvement, treatment with topical tacrolimus is supported by a randomized placebo controlled trial. Noncontrolled prospective trials support the use of occluded calcipotriene, calcipotriol in combination with betamethasone dipropionate, and imiquimod in the treatment of limited morphea. The authors have included suggested treatment algorithms for morphea subtypes (Figs 1 to 3). To allow for collaboration and metaanalysis, therapeutic trials in the treatment of morphea would benefit from the universal use of a validated outcome measure. To date, the LoSCAT is the only validated skin scoring tool for morphea. Further validation studies of the LoSCAT are needed, but its application appears promising.

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