Review Article

Morphea: Evidence-based recommendations for treatment

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ABSTRACT

Morphea is a rare fibrosing disorder of the skin. Evidence-based treatment strategies in morphea are lacking. This review summarizes the available data on morphea treatment and provides therapeutic strategies based on morphea subtypes. The Cochrane Library, Medline and Embase from inception until May of 2011 were searched using the key words "morphea" and "morphea treatment." Reference lists of the resultant articles, as well as relevant reviews, were also searched. This review focuses on randomized controlled trials, prospective interventional trials without controls and retrospective reviews with greater than five subjects.

Key words: Evidenced-based therapy, localized scleroderma, morphea, morphea treatment recommendations

INTRODUCTION

Morphea is a rare fibrosing disorder of the skin that may also involve the underlying muscle, connective tissue, bone and brain. The pathogenesis of morphea is incompletely understood, but results in an increase of collagen production and decrease in collagen destruction. Morphea typically goes through two stages: an active (inflammatory) stage and a "burnt out" stage. Treatment is targeted at the active phase, in the hope of stabilizing the size of current lesions and preventing the occurrence of new lesions. Anti-inflammatory and immunosuppressive agents are unlikely to improve the burnt-out phase of morphea and, therefore, should not be used for this phase of the disease. Treatment algorithms for morphea are lacking due to the relative paucity of treatment data. This article will review the strongest data in morphea treatment (randomized controlled trials, prospective trials and retrospective data with greater than five subjects) [Table 1]. Recommended treatment algorithms are provided for the following subsets of morphea: circumscribed morphea [Figure 1], linear morphea affecting the head or limbs [Figure 2]

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Table 1: Level of evidence

Intervention	Effective/ ineffective	Level of evidence
Weekly photodynamic therapy[1]	Ineffective	1
Twice-weekly intralesional subcutaneous interferon gamma[2]	Ineffective	1
Oral calcitriol[3]	Ineffective	1
Twice-daily topical 0.1% tacrolimus[4]	Effective	1
Low-dose UVA1, medium-dose UVA1, narrow-band UVB[5]	Effective	1
Weekly methotrexate and taper of oral prednisone[6]	Effective	1
Three times a week topical imiquimod[7]	Effective	2
Calcipotriol and betamethasone dipropionate twice-daily[8]	Effective	2
Twice-daily occluded calcipotriene[9]	Effective	2
UVA1[10-18]	Effective	2
PUVA[19,20]	Effective	2
Broadband UVA without psoralen[21,22]	Effective	2
Weekly methotrexate and taper of systemic steroids[23-25]	Effective	2
Mycophenolate mofetil[26]	Effective	2

*United States Preventive Services Task Force quality of evidence rating system[27]

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and generalized morphea (defined as four or more indurated plaques larger than 3 cm involving two or more body sites) [Figure 3].

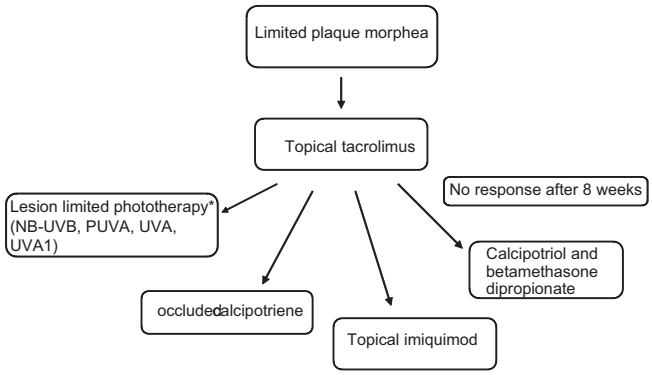

Figure 1: Treatment algorithm for limited plaque morphea. (Figure adapted from Fett N and Werth VP. Update on morphea. JAAD. 2011;64:217-242[28]), *Based on local availability

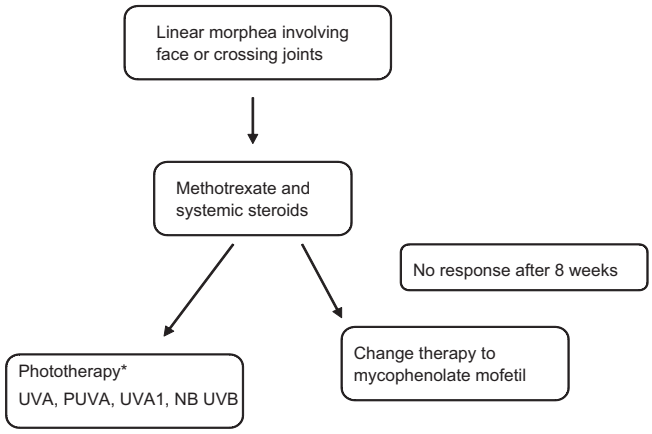

Figure 2: Treatment algorithm for linear morphea involving the face or crossing joints. (Figure adapted from Fett N and Werth VP. Update on morphea. JAAD. 2011;64:217-242[28]), *Based on local availability

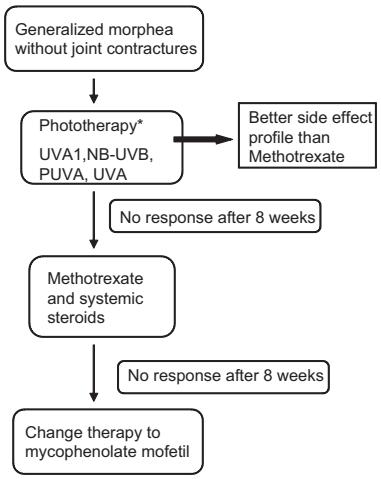

Figure 3: Treatment algorithm for generalized morphea. (Figure adapted from Fett N and Werth VP. Update on morphea. JAAD. 2011;64:217-242[28]), *Based on local availability

TRIALS OF TOPICAL TREATMENT

Randomized placebo-controlled trials of topical therapy

Two randomized placebo-controlled trials of topical therapy have been conducted. Kroft *et al*. assessed the efficacy of topical 0.1% tacrolimus in the treatment of plaque morphea.[4] Ten subjects were enrolled. Each subject had two or more active plaques of morphea, thereby serving as their own control. The plaques were separated by at least 15 cm. Subjects applied tacrolimus to one of the lesions and vehicle to the other. The primary outcome measures were change in surface area, change in durometer score (an assessment of skin hardness) and change in an investigator-derived clinical feature score made up of dyspigmentation, induration, erythema, telangiectasia and atrophy scales.[4] Plaques treated with topical tacrolimus had statistically significant reductions in both durometer scores and clinical feature scores when compared with placebo.[4] This suggests that topical tacrolimus is an effective treatment for an active (inflammatory) plaque morphea.

Batchelor *et al*. performed a randomized lesion-controlled trial of photodynamic therapy (PDT) in the treatment of morphea.[1] Seven subjects were enrolled and six subjects completed all treatments. After 6 weeks of weekly PDT treatments, no significant change was noted between treated and untreated lesions.[1] This suggests that PDT is not an effective therapy for an active plaque morphea.

Prospective pilot studies of topical therapy

The efficacy of thrice-weekly imiquimod in the treatment of morphea was assessed in a prospective pilot study of 12 subjects.[7] The primary outcome measure was an author-derived clinical score including dyspigmentation, induration, erythema and telangiectasias scales.[7] There was a statistically significant decrease in erythema and induration scores, both reflective of disease activity, at 6 months.[7] Dyspigmentation and telangiectasias scores, both reflective of damage, did not decrease over time.[7] This study is limited by the lack of a placebo group and by its long duration. It would not be unexpected for active plaques of morphea to burn out without intervention after a 6-month time lapse.

The efficacy of calcipotriol in combination with betamethasone dipropionate in the treatment of plaque morphea was assessed in a prospective pilot study of six subjects. Subjects were instructed to apply

the combination calcipotriol and betamethasone dipropionate once or twice a day to the active lesion. The authors reported an improvement in five of six subjects.[8] This study is limited by the lack of a placebo group. The results suggest that the combination of calcipotriol and betamethasone dipropionate once to twice daily may be an effective therapy for active plaque morphea.

Lastly, the efficacy of twice-daily occluded topical calcipotriene in the treatment of active plaque or linear morphea was assessed in a prospective pilot study of 12 subjects. The primary outcome measure was an author-derived skin score. Subjects were treated for a duration of 3 months. Twice-daily occluded calcipotriene resulted in a statistically significant decrease in erythema, dyspigmentation, telangiectasia and induration.[9] This study is limited by the lack of placebo. This study suggests that twice-daily occluded calcipotriene is an effective therapy for active plaque or linear morphea.

TRIALS OF SYSTEMIC TREATMENT

Randomized controlled trials of systemic therapy

Two negative randomized placebo-controlled trials have been conducted: the assessment of subcutaneous intralesional interferon gamma in the treatment of morphea and oral calcitriol. The efficacy of subcutaneous intralesional interferon gamma in the treatment of active plaque morphea was assessed by Hunzelmann *et al*.[2] Twenty-four subjects were randomized to receive either 14 doses of interferon gamma over 6 weeks, or placebo.[2] The primary outcome measures were a change in skin surface area, change in an author-derived skin score and change in the number of lesions.[2] There was no statistically significant change between the interferon-treated group and the placebo group at 18 weeks.[2] This suggests that interferon gamma is not an effective therapy for morphea.

The second negative study, published in 2000, evaluated the effectiveness of oral calcitriol as a therapy for morphea.[3] Twenty subjects were randomized to oral calcitriol or placebo for 9 months.[3] The primary outcome measure was an author-derived skin score. The placebo group had a greater decrease in their skin scores than the calcitriol group.[7] This suggests that oral calcitriol is not an effective treatment for morphea.

Two positive randomized controlled trials assessing morphea therapy have been published.

The first, published in 2006, randomized 62 subjects to receive low-dose ultraviolet A1 (UVA1; 340–400 nm), medium-dose UVA1 and narrow-band ultraviolet B (NB-UVB) therapy for morphea.[5] Subjects were treated for eight consecutive weeks. The UVA1group received a total dose of 800 J/cm^2, the medium-dose UVA1 group was given a total dose of 2000 J/cm^2 and the narrow-band UVB group was started at 0.1 J/cm^2 for skin type 2 and 0.2 J/cm^2 for skin type 3 and was increased by 0.1–0.2 J/cm^2 as tolerated, with maximum doses of 1.3 J/cm^2 for skin type 2 and 1.5 J/cm^2 for skin type 3.[5] Outcome measures were an author-derived skin score (the modified skin score, or MSS), scores on a visual analog scale, changes in the histological appearance and 20 MHz ultrasound measurements. All three groups had a statistically significant decrease in skin scores.[5] Comparison of the skin score changes between treatment arms revealed that the medium-dose UVA1 group showed statistically significant improvements in skin score compared with the NB-UVB, but was equivalent to the low-dose UVA1 group.[5] Low-dose UVA1 and NB-UVB groups also had equivalent improvement in skin scores.[5] This study is limited by the lack of a placebo group, but suggests that low-dose UVA1, medium-dose UVA1 and narrow-band UVB may all be effective therapies for morphea.

The second trial published in 2011 is a double-blind randomized study of combination of 3 months of 1 mg/kg/day oral prednisone and 1 year of weekly oral methotrexate compared with 3 months of oral 1 mg/kg/day prednisone in children with active linear, generalized or mixed variant morphea.[6] Seventy subjects were randomized in a two to one fashion, resulting in 46 subjects treated with prednisone and methotrexate and 24 subjects treated with prednisone alone.[6] The outcome measures were time to disease relapse and comparison of "responders" in each group.[6] Responders were defined as children who had a skin surface ratio of less than one (this proportion accounts for the normal growth of the children), a 10% decrease in thermography measurement and no new lesions.[6] There was a statistically significant prolongation in time to relapse in the methotrexate-treated group, suggesting that the combination of oral prednisone and methotrexate is an effective therapy for active morphea.

Prospective trials of systemic therapy

Three prospective trials of the therapeutic effects of methotrexate in combination with systemic corticosteroids in morphea have been performed.[23-25] These studies assessed the response of morphea to methotrexate treatment in a total of 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 subjects received bursts of high-dose intravenous methylprednisolone as well. The outcome measures in the adult studies were change in mean skin score and change in mean ultrasound thickness.[23,24] Both adult studies revealed a statistically significant decrease in mean skin score and mean ultrasound measurements when compared with baseline.[23,24] Nine of the 10 children were reported to improve based on clinician assessment.[25] These three prospective studies suggest that treatment of morphea with systemic methotrexate and steroids is effective.

Since 1995, 121 subjects with morphea have been prospectively treated with UVA1.[10-18] Subject ages ranged from 3 to 73 years and disease duration ranged from 6 months to 20 years. Subjects with linear, plaque and deep morphea were included in these studies. Seventy of the 121 subjects were treated with low-dose UVA1, at doses of 20 J/cm^2/day tapered over 5–20 weeks, with total irradiation ranging from 600 to 800 J/cm^2. Of these 70 subjects treated with low-dose UVA1, 90% reportedly improved based on changes in clinical examination, an author-derived skin score, changes in ultrasound measurement, changes in cutometer measurements, skin biopsies or a combination of these outcome measures.[10,11,13-15,17] Two studies compared medium-dose UVA1 (70 J/cm^2/treatment with a total dose of 2100 J/cm^2) and high-dose UVA1 (130 J/cm^2/treatment with a total dose of 3900 J/cm^2) to low-dose UVA1 (20 J/cm^2/treatment with a total dose of 600 J/cm2).[12,15] All three treatment modalities showed improvement in outcome measures, with suggestion that the duration of improvement was more prolonged with higher doses.[12,15]

Thirty subjects with morphea have been prospectively treated with psoralen in combination with UVA (PUVA).[19,20] Of these 30 subjects, 80% had improvement in skin scores.[19,20]

Seventy-five subjects with morphea have been prospectively treated with broadband UVA without psoralen.[21,22] Broadband UVA doses ranged from 5 J/cm^2/treatment with a total of 100 J/cm^2 of irradiation to 20 J/cm^2/treatment with a total of 400 J/cm^2 of irradiation, with equivalent improvements in both groups.[22] Of these 75 subjects, 77% were reported to have "fair" or better response to therapy based on clinical assessment.[21,22] These studies suggest that broadband UVA therapy and PUVA may be effective treatments for morphea.

Retrospective trials of systemic therapy

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.[29-32] Of these 119 patients, 67 received methotrexate in combination with systemic corticosteroids, and 52 received methotrexate without systemic steroids.[29-32] Methotrexate doses ranged from 0.3 to 0.4 mg/kg/week in children and 15 to 25 mg/week in adults.[29-32] Systemic corticosteroids were given via intravenous pulse and then transitioned to oral. Seventy-nine percent of the 119 patients reportedly improved with treatment.[29-32]

Mycophenolate mofetil (MMF) has been retrospectively assessed as a treatment for pansclerotic, generalized, linear and mixed variant morphea in children.[26] All these subjects had failed to improve with corticosteroids, methotrexate or a combination of the two.[26] The primary outcome measures were clinician assessment of improvement and change in thermography. Nine of 10 patients reportedly improved with MMF therapy.[26] This study is limited by its retrospective nature and lack of a placebo group. MMF has been shown to have anti-proliferative and anti-fibrotic properties in *in vitro* and *in vivo* experiments.[33-39] MMF therapy has resulted in a statistically significant improvement in skin scores in subjects with diffuse systemic sclerosis and improvement in retroperitoneal fibrosis.[36,39]

RECOMMENDED TREATMENT ALGORITHMS

Before making decisions about treatment options, patients with morphea need to be counseled on the prognosis of their disease process. It is important for patients to enter into therapy knowing that morphea is not life-threatening and does not progress to systemic sclerosis. Patients with linear morphea are at risk for facial deformity, limb length discrepancy and contractures. Patients need to balance the risks of systemic therapy with the risk of untreated disease. Patients with plaque morphea and superficial

generalized variants will generally be left with hyperpigmentation as the only sign of prior disease. Patient's expectations should also be managed. Patients need to recognize that the involved skin will never look completely normal. They must be counseled that treatment is aimed at active disease in the hopes of preventing enlargement of already-present lesions and the development of new lesions. Burnt-out disease is unlikely to improve with immunosuppression and, therefore, the risks of these medications are not warranted in burnt-out disease.

Patients with limited plaque morphea are at very low risk of facial deformity, limb length discrepancy and contractures and therefore should be treated with topical agents whenever possible. Based on the available data, active limited plaque morphea should be primarily treated with topical tacrolimus twice daily. If no response is seen after 8 weeks, therapy may be changed to lesion limited-phototherapy (NB-UVB, BB-UVA, UVA1, or topical psoralen and UVA), twice-daily occluded calipotriene, a combination of calcipotriol and betamethasone dipropionate once to twice a day or thrice-weekly topical imiquimod. Topical steroids, the most commonly utilized therapy for active limited plaque morphea, may be effective but, to date, we do not have data supporting their efficacy.

Patients with linear morphea of the head and neck or limbs are at significant risk of facial deformity, limb length discrepancy and contractures and should, therefore, be treated with systemic therapy. Based on the available evidence, methotrexate in combination with a short course of systemic steroids is first-line therapy. If the patient does not show improvement after 2–3 months, therapy can be switched to phototherapy (NB-UVB, PUVA, UVA or UVA1) based on availability. If phototherapy is not available or impossible for the patient because of the time commitment required, I recommend a trial of MMF. The evidence for MMF in the treatment of morphea is weak; however, it is not weaker than the evidence for the use of other systemic immunosuppressives such as cyclosporine, imatinib, d-penicillamine, cyclosphosphamide, tumor necrosis factor-alfa inhibitors or extracorporal photopheresis,[40-46] and it has a more favorable side-effect profile than these treatment modalities. MMF may also have anti-fibrotic properties based on the *in vitro* and *in vivo* studies discussed above. It is with consideration of the data, MMF's more favorable side-effect profile and anti-fibrotic properties that I recommend it in patients with potentially deforming disease who fail methotrexate and steroids.

Patients with generalized morphea may have superficial or deep variants. In patients without lesions that cross joints, phototherapy is an appropriate first option. At this point, there is not enough data to recommend one type of phototherapy over another. There is data supporting the use of NB-UVB, PUVA, UVA and UVA1. Phototherapy has a more favorable side-effect profile than methotrexate and systemic steroids, which is why I favor it as a primary therapy in this subset of patients. If the patient has not improved after 2–3 months, then switching therapy to methotrexate in combination with systemic steroids is a next step. If, after an additional 2–3 months the patient has not improved, I recommend a trial of MMF.

In conclusion, additional trials of therapeutic options for patients with morphea are needed. Randomized trials focusing on comparison of the efficacy of different types of phototherapy with the addition of a placebo group would be particularly useful. Randomized placebo-controlled trials assessing additional systemic agents in those patients recalcitrant to methotrexate in combination with steroids are also necessary.

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Multiple Choice Questions

1. The _____ phase of morphea responds to treatment with anti-inflammatory agents.
   a. Burnt out b. Active/inflammatory
   c. Quiescent d. Post-inflammatory hyperpigmentation

2. The following treatment has been found to be ineffective in the treatment of morphea in a randomized placebo controlled trial
   a. Oral calcitriol b. Twice daily topical 0.1% tacrolimus
   c. UVA1 d. Methotrexate

3. The following treatment has been found to be effective in the treatment of morphea in a randomized placebo controlled trial.
   a. Oral calcitriol b. Mycophenolate mofetil
   c. Methotrexate d. Photodynamic therapy

4. All of the following are subtypes of morphea except:
   a. Linear b. Generalized
   c. Circumscribed d. Systemic

5. All of the following have the same level of supporting data in the treatment of circumscribed morphea except:
   a. Topical tacrolimus b. PUVA
   c. Occluded calcipotriene d. Calcipotriol and betamethasone diproprionate

6. Based on data from a randomized placebo-controlled trial in children, first line treatment of linear morphea involving joints and head is
   a. Topical tacrolimus b. Mycophenolate mofetil
   c. UVA1 d. Methotrexate in combination of systemic steroids

7. UVA1 includes the following wavelengths
   a. 280-340nm b. 340-400nm
   c. 400-460nm d. 460-520nm

8. Prior to making decisions about treatment options, patients with morphea need to be informed of the following:
   a. Morphea is a life threatening disease that requires aggressive immunosuppression
   b. Morphea progresses to systemic sclerosis
   c. Patients with linear morphea are at risk for facial deformity, limb length discrepancy and contractures
   d. All subtypes of morphea carry the same amount of morbidity and therefore all subtypes should be treated similarly

9. Morphea patients need to be informed that the main goal of therapy is
   a. To make all morphea lesions disappear, leaving behind normal skin
   b. To preventing enlargement of already present lesions and the development of new lesions
   c. Prevent progression to systemic sclerosis
   d. Prevent death from uncontrolled morphea

10. The following morphea therapies are supported with level 1 evidence
    a. PUVA b. Oral calcitriol
    c. Mycophenolate mofetil d. Twice daily topical 0.1% tacrolimus

Key
1. b, 2. a, 3. c, 4. d, 5. a, 6. d, 7. b, 8. c, 9. b, 10. d