# Evaluation of Corticosteroid and Methotrexate Therapy in the Treatment of Moderate to Severe Localized Scleroderma (Morphoea) –A 5 Year Study in a Teaching Hospital of North India

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## ABSTRACT

**Introduction:** Localized scleroderma is a rare disorder with not well recognized aetiology. Though considered to be a benign disorder it may result in a severe cosmetic disfigurement or even functional disability. There is no proven effective therapy for localized scleroderma so far making management of such cases challenging. Lack of evidence based treatment and standardization of evaluation methods may be reason for it. The Study was conducted to evaluate the role of corticosteroid and methotrexate therapy in our population with severe localized scleroderma (morphoea).

**Material and Methods:** All patients attending with OPD in Department of Dermatology SKIMS-MCH from Jan, 2014, to Jan, 2019, with clinical features suggestive of active, moderate to severe morphoea were enrolled in the study. A detailed clinical history was followed by a thorough clinical examination and calculation of LoSSI score. Patients were started on i/v methyl-prednisolone 30mg/kg monthly pulses as 3 consecutive doses for 3 months (maximum 1gm) and intramuscular MTX at 0.2 to 0.4 mg/kg/week (maximum 25 mg/week) for 12 months.

**Results:** A total of 21 patients were included in the study. Male: Female ratio was 1:3.2. Mean age was 21.19years. Linear morphoea was most common type (13 cases) followed by plaque morphoea (6 cases). There was a significant decrease in mean LoSSI score (from 15.19 to 6.62) at 4 months after completion of steroid methotrexate phase (value of *t* is -8.621425, value of *p* is < .00001). Mean LoSSI score after completion of 12 months of treatment was 0.94 (value of *t* is -9.644953, value of *p* is < .00001). The treatment was well tolerated.

**Conclusion:** The study suggests that systemic corticosteroids and methotrexate in combination is effective and well tolerated treatment for both adults and children with localized moderate to severe scleroderma.


**Keywords:** LoSSI, Morphoea, Methotrexate, Methyl-Prednisolone

## INTRODUCTION

The aetiology of localized scleroderma is not yet well recognized, but its multifactorial character seems obvious. The role of endothelial cell damage as an initiating factor in the aetiopathogenesis of localized scleroderma cannot be overruled. The main subtypes are plaque morphea, linear scleroderma (including scleroderma "en coup de sabre"), generalized morphea, and pansclerotic morphea. Though often considered to be a benign self limiting condition, the course of the disease is unpredictable. It may result in severe functional and cosmetic disability. There is no proven effective therapy for localized scleroderma so far making management of such cases challenging. Lack of evidence based treatment and standardization of evaluation methods may be reason for it. Numerous treatment regimens based on medications like penicillamine, antimalarial drugs, retinoids, calcitriol, cyclosporine, and interferon gamma, have reportedly been used for the treatment of LS, with varying degrees of success.[1,2,3,4] UVA 1 irradiation has shown limited success in linear and deep forms morphoea.[5] MTX has been used alone or in combination with oral or injectable corticotherapy with good results.[6,7,8,9,10,11] The study was conducted to evaluate the role of corticosteroid and methotrexate therapy in our population with severe localized scleroderma (morphoea).

## MATERIAL AND METHODS

All patients attending with OPD in Department of Dermatology SKIMS-MCH from Jan, 2014, to Jan, 2019, with clinical features suggestive of morphoea were enrolled in the study. After the approval of our study by ethical committee, informed consent was obtained from patients. A detailed clinical history was followed by a thorough clinical examination and calculation of LoSSI score.

**The inclusion criteria for the study were:**

1. Presence of active disease, defined by the presence of eryhematous or violaceous and/or new lesions.
2. Presence of moderate to severe disease, such as the involvement of deep tissue, crossing a joint, covering a large surface area, in cosmetically concerning locations
3. Failure of topical therapy failure.

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**Exclusion criteria were:**

1. Major concomitant medical conditions
2. Pregnancy and lactation
3. Contraindications to the study medication (i.e., elevation of transaminases, anaemia, positive viral serology, latent tuberculosis),.

Mayo Clinic Classification (in its simplified form) was used for classification of LoS.[12] According to this classification, there are five groups LoS, namely:

1. Plaque morphea,
2. Generalized morphea,
3. Bullous morphea,
4. Linear scleroderma - including subtypes that involve the head and face, linear scleroderma 'en coup de saber' (LScs) and progressive facial hemiatrophy (PFH),
5. Deep morphea.

Patients were started on i/v methyl-prednisolone 30mg/kg monthly pulses for 3 months (dose given as 3 doses on three consecutive days, maximum 1gm) and intramuscular MTX at 0.2 to 0.4 mg/kg/week (maximum 25 mg/week). MTX was started at the dose of 0.4mg /kg and dose was adjusted as tolerated and continued for 12 months. Folic acid 5 mg PO was given daily except on the day of methorexate. Baseline CBC, KFT, LFT were done. Monitoring of CBC and LFT was done weekly for first month, two weekly for next two months, then monthly thereafter till completion of therapy.

**Clinical evaluation**

For assessment of skin involvement before and after treatment, a *LoSSI* (Localized Scleroderma (LS) Skin Severity Index) was used. The body is divided into 18 Cutaneous surface anatomic sites (head, neck, chest, abdomen, upper back, lower back, right and left — arms, forearms, hands/fingers, buttocks/thighs, legs and feet)

*The LoSSI* includes the sums of 4 separate activity scores as follows: (1) Area of involvement. 0: no involvement, 1: Upto 1/3, 2: 1/3 to 2/3, 3: more than 2/3 (1) **Erythema (ER)**: using the color of the lesion's edge. 0: no erythema; 1: slight erythema/pink; 2: red/clearly erythema; and 3: dark red or marked erythema/violaceous. (2) **Skin thickness (ST):** 0: normal skin thickness and freely mobile; 1: mild increase of thickness, mobile; 2: moderate increase of thickness; impaired skin mobility; 3: marked increase of thickness or no mobility of skin. (3) **New lesion/lesion extension (N/E):** new lesion development and/or enlargement of an existing lesion within the past month (score of 3). At study visits, patients were also classified as having 'active' or 'inactive' disease by the treating physician. Active disease was defined as the presence of new, enlarging and/or erythematous lesions, as these signs often prompt an increase or change in treatment. Inactive disease was defined as lack of these features. Initially and at study end, ultrasonography was performed with a digital 20-MHz ultrasound scanner, measuring both thickness and vascularity of a representative area. Skin biopsy specimens were obtained from a representative affected skin area to confirm the clinical diagnosis of morphoea by a different investigator (M.S.). Each biopsy specimen was stained with hematoxylin- eosin.

## STATISTICAL ANALYSIS

Data of clinical scores and values of biometrical assessment are given as mean±SD. After performing descriptive and explorative data analysis, pretherapeutic and post therapeutic evaluations were performed using the *t* test for paired samples (normal distribution). *P*_.001 was considered statistically significant.

## RESULTS

A total of 21 patients were included in the study. Male: Female ratio was 1:3.2. Mean age was 21.19 (range 3 to

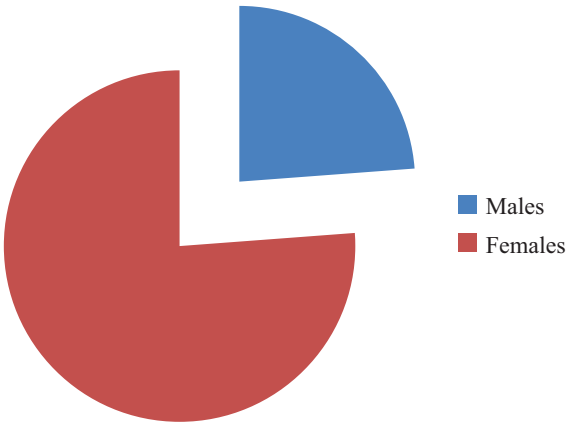


**Figure-1:** Gender Distribution of patients.

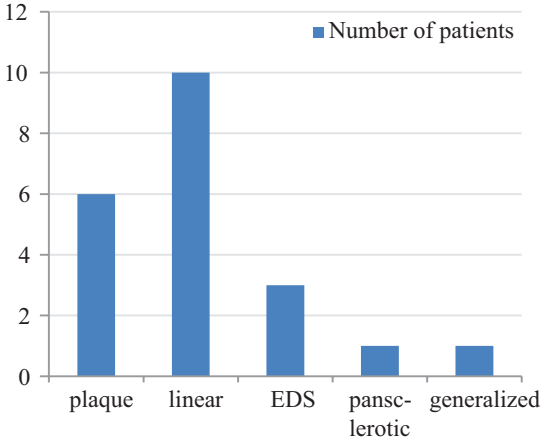


**Figure-2:** Clinical types of localized scleroderma

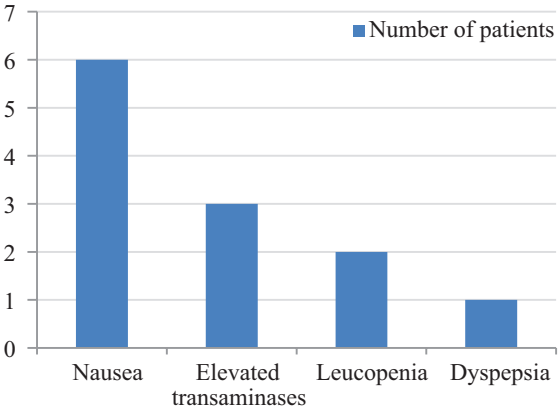


**Figure-3:** Side effects of the therapy

| No. | Age | Gender | Type | NFC | Sero-Markers | USG Skin | Previous treatment | Comorbidities |
|---|---|---|---|---|---|---|---|---|
| 1 | 6y | f | linear | normal | negative | Sugg. | - | - |
| 2 | 16y | f | EDS | normal | negative | Sugg. | 6DPs, Mtx | vitiligo |
| 3 | 18y | f | linear | normal | negative | Sugg. | MMF, T. steroids | Hypothyroid, obese |
| 4 | 20y | f | linear | normal | negative | Sugg. | | - |
| 5 | 9y | f | linear | normal | negative | Sugg. | Nb-UvB, oral steroids | - |
| 6 | 20y | m | EDS | normal | negative | Sugg. | - | - |
| 7 | 12y | m | linear | normal | negative | Sugg. | - | - |
| 8 | 9y | f | linear | Few megaloops | ANA + | Sugg. | Nb-UvB, T. steroids | Nuclear cataract |
| 9 | 58y | f | plaque | normal | negative | Sugg. | T. tacrolimus, vitamin E | hypertension |
| 10 | 60y | m | Generl-ized | Few megaloops | negative | Sugg. | - | diabetes |
| 11 | 35y | f | plaque | normal | negative | Sugg. | T. calcipotriol, steroids | - |
| 12 | 25y | f | linear | normal | negative | Sugg. | Minipulse Oral steroids, T. tacrolimus | - |
| 13 | 15y | m | plaque | normal | negative | Sugg. | - | - |
| 14 | 10y | m | linear | normal | negative | Sugg. | Minipulse Oral steroids, NB-UVB | - |
| 15 | 11y | f | plaque | normal | negative | Sugg. | T. steroids | - |
| 16 | 3y | f | pansclerotic | normal | negative | Sugg. | - | - |
| 17 | 8y | f | EDS | normal | negative | Sugg. | - | - |
| 18 | 35y | f | linear | normal | negative | Sugg. | - | - |
| 19 | 30y | f | linear | normal | negative | Sugg. | Pencillamine, T. steroids | PCOS |
| 20 | 20y | f | plaque | normal | negative | Sugg. | T. steroids | - |
| 21 | 25y | f | plaque | normal | negative | Sugg. | T. tacrolimus | PCOS, Gr 1 fatty liver |

(m=male, F= female, Y= years, EDS= en coup de sabre, ANA= antinuclear antibody, sugg.= suggestive, T.= topical, PCOS= polycystic ovarian syndrome, Gr 1= Grade 1)

**Table-1:** Demographic and baseline characteristics of patients with localized scleroderma (LS).

| | Duration | LoSSI at month | | | Side Effects | Activity after treatment | Follow up duration | Activity after follow up |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 4 | 12 | | | | |
| 1. | 0.5m | 12 | 5 | 0 | ↑transaminases | inactive | 15m | inactive |
| 2. | 6 m | 6 | 4 | 0 | - | inactive | 34m | relapse |
| 3. | 6 m | 14 | 6 | 2 | ↑transaminases | inactive | 47m | inactive |
| 4. | 4m | 17 | 8 | 0 | - | inactive | 9m | inactive |
| 5. | 1m | 33 | 15 | 7 | Nausea,Eosinophilia, cushingoid, cervical lymphadenopathy | inactive | 36m | relapse |
| 6. | 1.5m | 24 | 12 | 0 | - | inactive | 22m | inactive |
| 7. | 0.5m | 6 | 3 | 0 | - | inactive | 33m | inactive |
| 8. | 15m | 7 | 3 | 0 | Nausea | inactive | 17m | inactive |
| 9. | 22m | 19 | 10 | 4 | - | inactive | 9m | inactive |
| 10. | 1m | 21 | 9 | 0 | Nausea, leucopenia | inactive | 12m | inactive |
| 11. | 12m | 7 | 4 | 2 | - | inactive | 48m | inactive |
| 12. | 11m | 11 | 3 | 0 | dyspepsia | inactive | 91m | inactive |
| 13. | 7m | 15 | 5 | 3 | - | inactive | 44m | inactive |
| 14. | 19m | 25 | 7 | 0 | - | inactive | 11m | inactive |
| 15. | 22m | 21 | 6 | 0 | Nausea,↑transaminases | inactive | 10m | relapse |
| 16. | 0.5m | 16 | 7 | 2 | Nausea | inactive | 16m | inactive |
| 17. | 1m | 18 | 9 | 0 | - | inactive | 82m | inactive |
| 18. | 1m | 13 | 8 | 2 | Nausea | inactive | 26m | inactive |
| 19. | 36m | 9 | 3 | 2 | leucopenia | inactive | 74m | inactive |
| 20. | 5m | 7 | 3 | 0 | - | inactive | 8m | inactive |
| 21 | 1m | 18 | 9 | 0 | - | inactive | 39m | inactive |

(m= month, ↑= increased, LoSSI= Localized Scleroderma Skin Severity Index)

**Table-2:** Response of patients to the treatment and side effects.

60 years) (Fig. 1). There were 13 cases of linear morphoea (including 2 en coup de sabre), 6 plaque morphoea, one each of pansclerotic and generalized morphoea (Fig. 2). Only 2 patients had abnormal NFC showing megaloops. One patient had positive ANA. All patients had active morphoea on USG examination. Topical steroids (6), topical tacrolimus (3), Nb-UVB (3), oral steroids (2), dexamethasone pulses, methotrexate, D-pencillamine, topical.

calcipotriol, oral vitamin E were various treatments received by some patients prior to this therapy. (Table 1)

Mean duration of disease before starting treatment was 8.24(9.64) months. There was a significant decrease in mean LoSSI score (from 15.19 to 6.62) at 4 months after completion of steroid methotrexate phase (value of *t* is -8.621425, value of *p* is < .00001). Mean LoSSI score after completion of 12 months of treatment was 0.94 (value of *t* is -9.644953, value of *p* is < .00001). The treatment was well tolerated. 6 patients complained of nausea, which was managed conservatively. 3 patients had elevated transaminases, 2 leucopenia, 1 dyspepsia (Fig. 3). Levels returned to normal after reduction in dose of methotrexate. One patient was put on daily oral steroids, 1mg/kg after first month of methylprednisolone pulse as she developed new lesions. After 2 months of treatment she had cervical lymphadenopathy with eosinophilia and cushingoid features. CBC, PBF and Mantoux were normal. All treatment was stopped for 1 month and after resolution of symptoms was started on methotrexate only. The dose of methotrexate was reduced in other patient of EDS because of severe nausea to 0.2mg/kg. All patients had inactive disease after 12 months of treatment. After a mean follow up period of 32.52 (24.80) months (ranged from 8 months to 91 months) 3 had relapse. (Table 2)

## DISCUSSION

Male to female ratio in our study was 1:3.2 which is consistent with other studies.[13] Topical treatment is recommended for more superficial and limited forms of morphoea. Of the various treatment options available narrowband ultraviolet B light (NBUVB) 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.[2,3,14,15] Methotrexate in combination with systemic steroids and ultraviolet A1 light phototherapy have the most evidence of efficacy in the treatment of severe morphea.[15] Methotrexate (MTX) with or without corticosteroids (CS) in various regimens and modes of administration was reported to be an effective systemic therapy in pediatric and adult LS with varied success.[6,7,8,9,16,17] Earlier open-label studies of monotherapy in adults reported 67% efficacy with oral MTX[8] and 82% efficacy of oral CS as monotherapy for LS.[17] MTX can be used alone or in combination with oral or injectable corticotherapy.[6,7,8,9,10,11] The recommended dose is 1mg/kg/week, subcutaneously, and the maximum recommended dose is 25mg/week. 0.4-1 mg/day or 5mg/week of folic acid should be supplemented to the diet.[18] Most studies report an 80% improvement rate with this therapeutic regimen.[8,9] The use of corticosteroids alone is effective, but the risk of relapse is higher.[18] However, studies over the past 10 years in children have reported benefit with about 90% efficacy from combined MTX and CS, and have greatly influenced the manner in which pediatric rheumatologists treat LS.[6,7,10]

Though methotrexate has been used in number of fibrotic disorders its mechanism of action is not fully understood. Methotrexate (MTX) is an antimetabolite drug that competitively inhibits dihydrofolate reductase and leads to impaired DNA and nucleotide synthesis.[20] Additional mechanisms may be involved in MTX's immunomodulatory action, such as decreased proinflammatory cytokine production, extracellular adenosine release and inhibition of antigen-induced T-cell activation.[21] Number of authors have suggested that MTX may have an anti-fibrotic action but there are no studies to prove it.[8,22] A possible mechanism of MTX in modifying morphea is by interfering with cytokine expression. Decreased levels of circulating soluble interleukin-2 receptors and decreased serum levels of interleukin-6 and interleukin-8 after MTX treatment have been reported both in juvenile and in adult rheumatoid arthritis, while their increased levels have been related to an active phase in morphea.[23,24,25,26] Suppression of the JAK/STAT pathway has recently shown to be likely principal anti-inflammatory and immunosuppressive mechanism-of-action of low-dose MTX which is independent of dihydrofolate reductase (DHFR).[27]

Seyger MM et al used low dose methotrexate (15mg/week) in 9 patients for 24 weeks. Beneficial effect was seen in all patients with no serious side effects.[8] in a study by Uziel Y et al

10 patients were put on methotrexate 0.3 to 0.6 mg/kg/week in addition to intravenous methylprednisolone 30mg/kg for 3 days monthly for 3 weeks. Though the treatment was well tolerated and effective the duration of treatment was not fixed.[7] Kreuter A et al evaluated the efficacy of pulsed high-dose corticosteroids (I/V methylprednisolone 1000mg for 3 days monthly for 6 at least months) combined with orally administered low-dose methotrexate (15mg/week) therapy in patients with severe localized scleroderma (LS). 13 out of the 14 patient had significant improvement, 1 discontinued, treatment was well tolerated.[9] Torok et al recruited Thirty-six patients with active LS were recruited and started them on oral prednisone 2 mg/kg/day (maximum 60 mg/day) and subcutaneous (SC) MTX at 1 mg/kg/week (maximum 25 mg/week). Prednisone was tapered and kept at 0.25 mg/kg/day for 12 months. MTX SC was continued for 24 months, and then switched to oral administration to complete 36 months of therapy. None of their patients had a flare within the 36 months of therapy on combination MTX SC and high-dose oral CS.[28] The results of our study are comparable with above studies. Three relapse cases in study could be because of low dose methotrexate given in one patient because of methotrexate intolerability and high LoSSI score in other two. Such patients may have required methotrexate for longer duration, as treatment was fixed for 12 months in our

study. All our patients had inactive disease at 4 months. The treatment was generally well tolerated and side effects where mild and managed conservatively.

In 2012 a core group of pediatric rheumatologists and dermatologists were engaged by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop standardized treatment plans, clinical assessments, and response criteria for active, moderate to high severity juvenile localized scleroderma (jLS). The consensus methotrexate dose was 1mg/kg/week (maximum 25mg, Subcutaneous preferred), Intravenous methyl-prednisolone was 30mg/kg for 3 days monthly for 3 months and oral corticosteroid was 2mg/kg (maximum 60mg/day). Three consensus treatment plans were put forward and choice of plan is based on physician judgment of best care. CTP A is MTX alone, CTP B is MTX+ IV CS and CTP C is MTX+ Oral CS.[29]

Over 20% of patients with LoS develop extracutaneous manifestations such as arthritis, seizures, and uveitis.[30,31] None of our patients had any associated arthritis or neurological abnormality. The most frequent neurological involvement associated with scleroderma reported are complex partial seizures, though there is no correlation of severity of brain changes with skin condition [32,33,34] However vitiligo, hypothyroidism and nuclear cataract each were seen in three of our young patients with morphoea as seen in other studies.[35,36,37] The other associated comorbidities found were hypertension, type2 diabetes mellitus, polycystic ovarian disease in adult patients with morphoea.

## CONCLUSION

The study suggests that systemic corticosteroids and methotrexate in combination is effective and well tolerated treatment for both adults and children with moderate to severe localized scleroderma.

### Drawbacks

It was not a case-control study. Borrelia serology was not assessed due to high cost factor.

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