Jurnal RSMH Palembang
Journal Homepage: http://jurnalrsmh.com/index.php/JRP

Effect of Autologous Serum Therapy (AST) as Adjuvant Management in Morphea: A Pilot Study

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ARTICLE INFO

Keywords:
AST
DLQI
LoSCA
Morphea

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/jrp.v5i1.63

ABSTRACT

Morphea, or localized scleroderma, is a chronic autoimmune disease characterized by sclerosis of the skin, subcutaneous tissue, and bones. Morphea therapy targets the inflammatory component, cytokine release and collagen activation and deposition. The mechanism of action of autologous serum therapy (AST) is based on the principle of induction of desensitization or tolerance to pro-inflammatory signals. The patient's clinical improvement criteria were calculated using the localized scleroderma cutaneous assessment tool (LoSCAT) based on physical examination. This study used a one group pre-test – post-test experimental design on morphea patients at the Dermatology, Venereology, and Aesthetics (DVE) Polyclinic, Allergy and Immunology Subdivision in Dr. Mohammad Hoesin General Hosptial (RSMH) Palembang in May-October 2023. This study included 7 morphea patients who met the inclusion criteria for AST injection in 8 weeks duration. The Dermatology Life Quality Index (DLQI) assessment carried out before the AST and after the 8th AST showed that all patients experienced improvements in quality of life after 8 weeks. There was a decrease in LoSCAT scores in 5 patients (71.4%), while there was no change in LoSCAT scores in 2 patients (28.6%). Side effects of pain at the AST injection site in 3 patients (42.8%) were tolerable without painkillers, while other patients did not experience any side effects. The paired T-test statistical test on patients before AST and after AST treatment for 8 weeks showed that there was a significant difference in the mean DLQI and LoSCAT with p-value respectively 0.003 and 0.032. There is a significant difference in the mean DLQI and LoSCAT in study patients before AST and after AST for 8 weeks. There were side effects in the form of local pain at the AST injection area in 3 patients which were well tolerated without painkillers.

1. Introduction

Morphea, or localized scleroderma, is a rare, chronic autoimmune disease characterized by sclerosis of the skin, subcutaneous tissue, and underlying bone.[1,2] Clinical features of initial morphea lesions include erythematous to purple-black patches with post-inflammatory hyperpigmentation.[1] In many cases, localized scleroderma lesions become spontaneously inactive, but more severe cases lead to irreversible fibrosis of the skin and subcutaneous tissue.[3] Morphea commonly presents with systemic symptoms of malaise, headache, arthralgia, myalgia and positive autoantibody serology tests. The etiology of morphea is unknown but it is thought that the imbalance between collagen production and destruction triggers an autoimmune process.[1] Morphea therapy is aimed at the inflammatory component, cytokine release and collagen activation and deposition.[3]

Autologous serum therapy (AST) is one of the effective and promising adjuvant therapy for many autoimmune diseases, such as morphea when the autoimmune dysregulation become the main pathomechanism, resulting in permanent functional and cosmetic damage.[3,4] The mechanism of action of AST is based on the induced tolerance to pro-

inflammatory signals. It is gaining recognition for being one of the most cost-effective and minimal side effects to treat the morphea.[4] Clinical improvements of morphea can be objectively assessed through the localized scleroderma cutaneous assessment tool (LoSCAT) and patient-assessed Dermatology Life Quality Index (DLQI).[3]

The aim of this study is to determine the effect of AST as adjuvant therapy in reducing morphea disease activity measured by LoSCAT and DLQI. The second aim of this study is also to evaluate the side effects of AST in morphea patients.

2. Methods

This study was conducted as an experimental, add-on study without control group using one group pretest-posttest approach. The study was conducted at the DVE Outpatient Clinic of the Allergy and Immunology Subdivision of the Dermatovenereology and Aesthetic Medicine Department between May and October 2023. The population recruited was morphea patients visiting the DVE Outpatient Clinic, RSMH Palembang during the study period. The patients were included if they were willing to participate in the study signed informed consent after receiving detailed explanations of the study. The exclusion criteria were patients with clotting or bleeding disorders. The patient signed the consent declaration after thorough explanation and prior to the intervention.

The AST was prepared by collecting approximately 5 mL of patient's blood and centrifuged at 2,500 rpm for 15 minutes. The separated serum was collected and stored into sterile container and injected intramuscularly into the gluteal region using a 22G needle. The AST injections were repeated every week for up to 8 weeks. Prior to the treatments, the patients were assessed with LoSCAT and DLQI to measure the activity of the disease. The second assessment of the LoSCAT and DLQI were conducted after 8th week of AST treatments to assess the outcomes of the therapy. In addition to the AST injections, the patients also received the standard systemic corticosteroid therapies. The data collected were processed and analyzed.

3. Results

This study included 7 morphea patients who met the inclusion criteria and received AST for 8 weeks. Six patients (85.7%) were female and 1 patient (14.3%) was male, with ages ranging from 32 to 61 years old.

Table 1. Distribution by gender and age

Patients	Gender	Age (Year)
Patient 1	Female	55
Patient 2	Female	41
Patient 3	Female	51
Patient 4	Female	37
Patient 5	Female	61
Patient 6	Female	53
Patient 7	Male	32

Dermatology life quality index (DLQI)

The Dermatology Life Quality Index (DLQI) is a holistic measure commonly used to determine the quality of life of patients with skin diseases. The higher the DLQI, the worse the effect of skin disease on the patient's quality of life. The DLQI assessments were conducted before the AST treatments and after 8 weeks of AST treatments. All patients showed improved quality of life after the 8th AST injection.

Table 2. DLQI score

Patients	DLQI Before AST	DLQI After 8th AST
Patient 1	6	5
Patient 2	15	13
Patient 3	14	11
Patient 4	18	14
Patient 5	10	9
Patient 6	16	13
Patient 7	11	10

The DLQI score was homogenous (p = 0.549), showing no significant DLQI score difference before the treatment was conducted. The DLQI score results was normally distributed (p = 0.852).

Table 3. DLQI homogeneity test before treatment

Group	*p value*
DLQI	0.549

*Levene test, p = 0.05

Table 4. DLQI normality test

Group	*p value*
DLQI	0.852

*Shapiro Wilk test, p = 0.05

Localized scleroderma cutaneous assessment tool (LoSCAT)

The LoSCAT score is an objective measure designed to quantify the morphea-induced skin activity and damage. The LoSCAT score in this study was used as the follow-up measure of the patients. The LoSCAT was assessed before the AST treatment started and after 8 weeks of the AST treatments. Higher LoSCAT score equals to higher morphea severity and skin damage. From the comparison between the LosCAT score before and after the 8th AST treatments, we were able to show the decrease of LoSCAT score in 5 patients (71.4%). Two patients (28.6%) showed no changes in LoSCAT score. Each morphea patient was documented through the photographs of the lesions before and after 8 weeks of AST treatments, with the follow-up results shown in Figures 1 A-H.

Table 5. LoSCAT Score

Patients	LoSCAT Before AST	LoSCAT After 8th AST
Patient 1	12	9
Patient 2	32	24
Patient 3	17	17
Patient 4	25	11
Patient 5	4	4
Patient 6	32	22
Patient 7	24	20

The LoSCAT score was homogenous (p = 0.356), showing no significant sdifference in the average LoSCAT score before the treatment. The LoSCAT score was normally distributed (p = 0.548).

Table 6. LoSCAT homogeneity test before treatment

Group	*p value*
LoSCAT	0.356

**Levene test, p* = 0.05

Table 7. LoSCAT normality test

Group	*p value*
LoSCAT	0.548

**Shapiro Wilk test, p* = 0.05

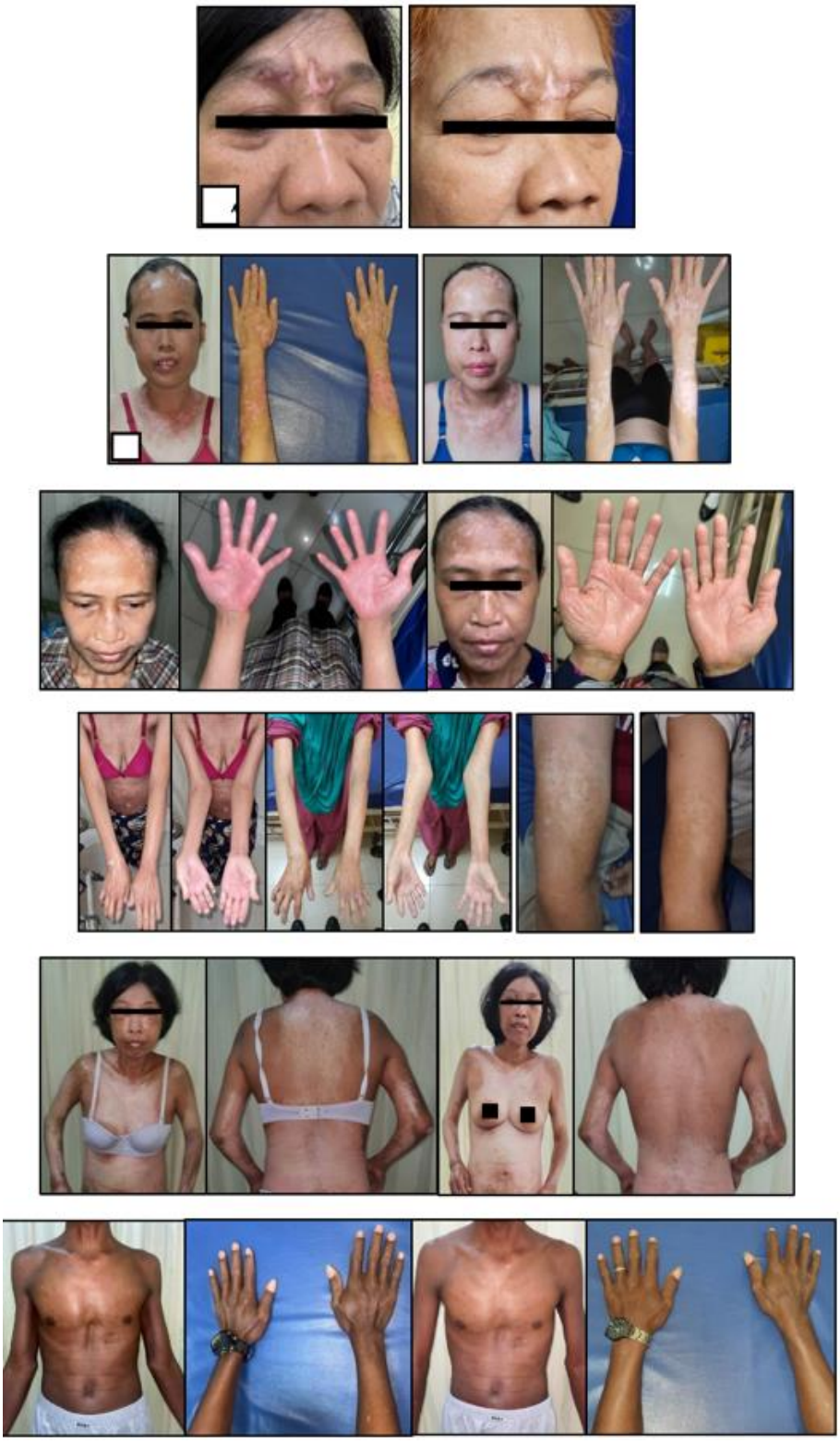

Figure 1. Morphea patients in this study (left) before AST, (right) after 8th AST. A. Patient 1, female 55 years old; B. Patient 2, female 41 years old; C. Patient 3, female 51 years old; D. Patient 4, female 37 years old; E. Patient 5, female 61 years old; F. Patient 6, female 53 years old; G. Patient 7, male 32 years old

Side Effects of AST

The side effects of AST treatments include pain, edema/hematoma, bleeding, and signs of infection. Local pain at the site of AST injection was observed in 3 patients (42.8%), although the pain was well tolerated without analgetics. The rest of the patients suffered no side effects.

Table 8. AST Side Effects

Patients	AST Side Effects
Patient 1	No side effects
Patient 2	No side effects
Patient 3	No side effects
Patient 4	Local pain
Patient 5	Local pain
Patient 6	Local pain
Patient 7	No side effects

Corticosteroid Therapy

Corticosteroids become the chosen therapy for the management of morphea. Systemic and topical corticosteroids is effective in morphea, especially when administered during the active phase of the disease. In addition to AST adjuvant therapy, the study patients received a variety of corticosteroid therapy for morphea.

Table 9. Corticosteroid Therapy

Patients	Corticosteroid Therapy
Patient 1	Mometasone furoat 0.1% cream
Patient 2	Methylprednisolone 4 mg tablet
Patient 3	Methylprednisolone 4 mg tablet + desoximethasone 0.25% cream
Patient 4	Methylprednisolone 8 mg tablet
Patient 5	Clobetasol propionate 0.05% cream
Patient 6	Clobetasol propionate 0.05% cream
Patient 7	Clobetasol propionate 0.05% cream

Effect of AST on DLQI

This study was conducted to determine the effect of 8 weeks of AST treatments on DLQI of morphea patients. The DLQI score was found to be significantly lower after the 8 weeks of AST treatments (12.86 ± 4.10 vs. 10.71 ± 3.09; p = 0.003).

Table 10. Effect of AST on DLQI before AST and after 8th AST

Assessment	Treatment		*p value*
	Before AST	After the 8th AST	
DLQI	12.86 ± 4.10	10.71 ± 3.09	0.003

*Paired T-test, p = 0,05

Effect of AST on LoSCAT

This study was conducted to determine the effect of 8 weeks of AST treatments on LoSCAT score in morphea patients. The LoSCAT score was significantly lower after 8 weeks of AST treatments (20.86 ± 10.43 vs. 15.29 ± 7.43; p = 0.032).

Table 11. Effect of AST on LoSCAT before AST and after 8th AST

Assessment	Treatment		*p value*
	Before AST	**After the 8th AST**	
LoSCAT	20.86 ± 10.43	15.29 ± 7.43	0.032

*Paired T-test, p = 0,05

4. Discussion

Morphea, also known as localized scleroderma, is a rare inflammatory disease of the skin and subcutaneous tissue. Morphea is as frequent in in children as in adults. Morphea covers a wide spectrum of clinical variants, ranging from solitary skin lesions with minimal complaints to severe skin manifestations (e.g. generalized or linear morphea). Clinical manifestations of morphea are commonly limited to the skin and subcutaneous tissues. Extracutaneous involvement is reported in about 22% of linear and generalized morphea and more common in pediatric population. The extracutaneous manifestations may include joint contractures, limb growth disorders, and other extracutaneous disorders.[7]

Morphea is a rare disease with an incidence of less than 3 per 100,000 people and women have a susceptibility 5 times higher than men.[2,3] Between 2016-2021, our institution only received 12 morphea patients, consisting of 7 women and 5 men ranging from 1-57 years old. During the study period (May-October 2023), 6 female patients (85.7%) and 1 male patient (14.3%) were examined, with an age range of 32 to 61 years.

The etiology of morphea is still unclear. The interplay between genetic, environmental, and autoimmune factors are likely involved in the pathogenesis of morphea. The strongest genetic association of morphea is found with HLA class II allele DRB1*04:04 and HLA class I allele HLA-B*37. Various environmental factors, such as trauma and frictions, may also trigger morphea. Radiation exposure may result in local secretion of interleukins 4 and 5, which in turn induces TGF-β-mediated fibrogenesis. Auto-antibodies, such as antinuclear antibodies (ANA), anti-single-stranded DNA (SS-DNA), and anti-histone antibodies, are also commonly found in morphea patients, supporting the hypothesis of autoimmune dysregulation in morphea. Several cohort studies have shown that family members of morphea patients are prone to other autoimmune diseases.[7]

In morphea with well-demarcated lesions, topical treatments commonly showed excellent therapeutic response. First-line treatments for superficial morphea include topical corticosteroids and topical tacrolimus for 3-4 weeks. For more extensive lesions and deep morphea, the first-line treatment is ultraviolet A1 (UVA1) phototherapy, although this treatment is not effective for morphea with subcutaneous tissue, muscle, or bone involvements. Patients who are unable to receive phototherapy can be treated with high-potency topical corticosteroids, intralesional corticosteroids, or topical tacrolimus.[7]

Rapidly progressive morphologic lesions require prompt treatment with a combination of systemic corticosteroids and methotrexate. Systemic corticosteroids, either oral or intravenous, have shown to be effective in controlling morphea. The symptoms of morphea nevertheless may reappear after the corticosteroid treatment is stopped. For rebound patients, a combination of methotrexate and systemic corticosteroids is considered to be the first-line treatment. Mycophenolate mofetil can also be used as an alternative to methotrexate. Both methotrexate and mycophenolate mofetil can cause significant side effects in patients and highly contraindicated in pregnant women. The morphea treatments require contraceptives measures, careful considerations of drug interactions, and toxicity monitoring to improve patient adherence and

reducing the harmful side effects.[7]

In allergic, inflammatory, infectious, and autoimmune disorders, AST treatments has become a promising adjuvant therapy option.[4] AST therapy is a cost-effective adjuvant therapy with minimal side effect to control the autoimmune diseases.[4,8] Desensitization and tolerance to proinflammatory signals expressed in plasma are the main mechanisms of AST treatments.[8] Autoimmune factors mainly circulate in serum (as opposed to the not cellular components of the whole blood). In addition, sera can also be stored for several hours without clumping and finer needles are able to be used, reducing patient discomfort and improving treatment compliance.[4,8,9]

The DLQI consists of 10 questions covering six aspects: symptoms/complaints, daily activities, leisure time, work/school, personal relationships, and medication. Each answer is scored from "very much" (3) to "not at all" (0), and the total score is in the range of 0-30; with higher scores indicate worse quality of life.[9] In this study, DLQI was decreased in all study participants after 8 weeks of AST administration, indicating an improvement in quality of life in all study patients. Our analysis showed a significant difference in the decrease in DLQI after the 8th weeks of the AST treatments. Our study is consistent with Yu et al. reporting QoL improvements after 8 weeks of AST treatments.[9]

The morphea activity and damage can be assessed using LoSCAT scale, consisting from LoSAI (a modification of mLoSSI) and LoSDI. For LoSAI scale, the morphea lesions are assessed for the disease activity based on the degree of erythema (0-3), induration of the lesions (0-3), and the presence of new lesions or old lesions enlarged (0 or 3) in the past month.[11,12] Total LoSAI is the sum of scores from lesions in 18 body regions, ranging from 0 to 162, with higher scores indicating more severe morphea activity. For LoSDI scale, morphea lesions are scored based on skin damage, namely degree of dyspigmentation (0-3), dermal atrophy (0-3), subcutaneous atrophy (0-3) and central thickness (0-3). The total LoSDI is based on the sum of scores from lesions in 18 body regions. The LoSDI ranges from 0 to 216, with higher scores indicating higher severity.[3,10,11] Our study showed significant decrease of the mean LoSCAT after 8 weeks of AST treatments.

Three patients (42.8%) in this study reported minor side effects of AST treatments, including well-tolerated local pain on the site of the AST injection. Our study is thus in line with the Fintaru et al. regarding AST side effects (local pain at the injection site for 12-24 hours).[13] To assess the long-term outcome of therapy in morphea patients (e.g., disease relapse or changes in the extent of skin damage), the follow-up should be conducted for at least 5 years.10 Therapeutic success in morphea patients is defined as the resolution of erythema (usually within 2 to 3 months), softened skin lesions (12 months or more), no widespread lesions, and no new lesions.[1]

5. Conclusion

There were significant differences in mean DLQI ($p = 0.003$) and mean LoSCAT ($p = 0.032$) in all study patients before AST and after AST for 8 weeks. There were side effects of local pain on the AST injection area in 3 study patients (42.8%) which were well-tolerated.

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