

Efficacy and safety of ANGIPARS™ for the treatment of skin manifestations of scleroderma: a phase 2 clinical trial

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We aimed to evaluate the safety and efficacy of ANGIPARS™ in a phase 2 clinical trial. This study was performed as a phase 2 clinical trial without a control group between May 2007 and September 2008 in the Iranian Rheumatology Research Center on a group of volunteer patients that were diagnosed with scleroderma. Patients with the diagnosis of diffuse or limited scleroderma without the involvement of internal organs were given 100 mg ANGIPARS™ capsules three times a day for 6 months, followed by 2 capsules a day for a further 3 months. Follow-up continued for a year. At the baseline, modified Rodnan score, pain severity and number of pitting ulcers, number of perioral folds, finger to palm distance, and open-mouth area were assessed in each patient. The measurements were repeated on a monthly basis and their change from the baseline was calculated. Possible adverse effects were monitored at regular monthly intervals through a complete set of laboratory tests and clinical examination. Eleven patients including 10 females were recruited. The mean age was 39 years (SD= 10.2). No significant changes and no abnormality in laboratory measures were found during the study. Repeated measure analysis revealed a significant reduction in the modified Rodnan score (Mean reduction= 38%, P value < 0.001), finger to palm distance and number of pitting ulcers (mean reduction 33% & 87.5%, respectively, and P values < 0.001 & 0.003, respectively), and an increase in open-mouth area (mean reduction= 20.6%, P value= 0.041). The drug had no effect on the pain of the ulcers or on the perioral folds. ANGIPARS™ is efficient and safe for the treatment of the skin manifestations of scleroderma. Conducting a phase III placebo controlled randomized trial is recommended.

Keywords: ANGIPARS™, pitting ulcer, Rodnan score, scleroderma, skin manifestation.

Introduction

Systemic sclerosis (SSc), which is also known as scleroderma, is a multisystem connective tissue disorder. It is characterized by generalized microangiopathy, which results in the thickening of tissue and fibrosis. The disease often involves the internal organs [1, 2]. Systemic sclerosis has the highest rate of fatality among connective tissue disorders and 10-year survival of the disease is 55% [1]. Raynaud's phenomenon is the most frequent manifestation of vascular abnormalities in SSc. Abnormal reaction of blood vessels to stimuli results in digital ischemia and complications such as digital ulcers and necrosis [2, 3].

In a large cohort of patients with SSc, the frequency of digital ulcers was estimated at 48% at the beginning and 54% at a 7 year follow up [4]. Using a self-reported anonymous scleroderma questionnaire, Mawdsley reported that 46% of scleroderma patients had suffered from digital ulcers during the course of their disease [5]. During a 3-year QUINS study, a frequency of 25.1% was reported for digital ulcers in limited SSc [6]. It seems that the development of digital ulcers in scleroderma is multi-factorial. Factors such as ischemia caused by vascular disease (Raynaud's), sclerodactyly, dry skin, calcinosis, and local trauma all contribute to ulcer development. In addition to superimposed factors such as infection,

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epidermal thinning, skin being tightly stretched over joints and associated contractures, poor blood flow and tissue oxygenation mean digital ulcers do not heal. The digital ulcers are extremely painful and are associated with a significant reduction in the functions of the hands. Thus, introduction of new treatment for the ulcers plays a crucial role in the management of patients with Scleroderma and may help to improve the functioning of their hands. At present, there is a limited number of therapeutic options for the treatment of digital ulcers in patients with scleroderma [7].

Furthermore, skin fibrosis remains a therapeutic problem in SSc and there are limited treatments for the skin manifestations of scleroderma. The role of D-penicillamine remains controversial [8, 9]. Prostaglandin analogue infusion is still the treatment of choice for digital ulcers [10], and Bosentan as the second line drug has been used successfully in the management of Raynaud's phenomenon and digital ulcers. The evidence for Bosentan however, is limited to small non-randomized studies [11, 12] and some case reports [10, 13]. Some small studies have suggested clinical utilities for Methotrexate and mycophenolate (mofetil). Relaxin and minocycline have also been proposed for this purpose; however, their beneficial effects have not been tested in randomized controlled trials. Ultraviolet- A light therapy seems to be safe and effective for localized forms of scleroderma [1].

ANGIPARS™ is a herbal drug containing *Mellilotus Officinalis* dried extract and is effective in the treatment of diabetic foot ulcers [14]. The safety of the product was established by conducting a complete set of preclinical studies and in-vivo and in-vitro tests for acute and subacute toxicities as well as genotoxicity [15-17]. Previous clinical studies have shown the efficacy and safety of the drug in the treatment of diabetic foot ulcers [18-21] and pressure sores [22, 23] with some immunomodulatory effects being observed for the drug [18]. In previous studies, the possible known mechanism for ANGIPARS™ has been described as angiogenesis and has been said to improve microcirculation [19, 20, 22, 23]. In this study we aimed to evaluate the safety and efficacy of ANGIPARS™ for the treatment of the skin complications of scleroderma including skin involvement, and the healing of digital ulcers.

Materials and Methods

Patients

This study was conducted as a phase 2 clinical trial

without a control group between May 2007 and September 2008 in the Iranian Rheumatology Research Center on a group of volunteer patients with the diagnosis of scleroderma. Ethical approval was obtained from the Ethics Committee of Endocrinology and Metabolism Research Center affiliated with Tehran University of Medical Sciences. All patients gave written informed consent before taking part in the study. The patients were not paid to participate in the study, nor did they pay anything for medication or lab tests.

Patients with diagnosis of diffuse or limited scleroderma, according to the American College of Rheumatology's criteria with skin involvement who had not had adequate response to the current treatments of scleroderma were enrolled into the study. Inadequate response in SSc patients was defined as less than a 10% improvement in Rodnan Score during the standard course of treatment. For sample size estimation, we aimed at recruiting 14 patients in order to demonstrate at least 20% of the therapeutic effects [18]. Only those who had Raynaud's phenomenon and positive anti-centromere or Anti-SCL-70 antibodies were included in the study. Patients with life threatening conditions, osteomyelitis, other systemic and autoimmune diseases, involvement of internal organs such kidney, lung and heart, or presence of infection at the site of the ulcer were all excluded. The diagnosis of scleroderma was confirmed by two rheumatologists.

Baseline characteristics such as skin thickness, finger to palm distance, pain severity and number of pitting ulcers, and number of perioral folds and open-mouth area were obtained by a rheumatologist at the beginning of the study. Finger to palm distance was measured in centimeters and can be described as the gap between tip of the index finger and palmar area while patient was trying to close his or her fist. The perioral folds were counted while the mouth was closed. For a simple calculation, open-mouth area was calculated by multiplying its maximum horizontal and vertical diameters. All patients were photographed in every session.

The possible adverse effects of the drug were monitored using a complete set of laboratory tests including complete blood counts (CBC), blood urea nitrogen (BUN), creatinin (Cr), erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (PTT), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (Alp), serum albumin (Alb), total serum protein (Total Pr), amylase, serum

sodium (Na), potassium (K), calcium (Ca), magnesium (Mg) and phosphorous (P). The physician also examined the patients and asked about symptoms at each visit to check for any possible side effects.

Patients underwent a course of treatment with ANGIPARS™, which included a herbal extract prepared and delivered by ParsRoos Co. (Tehran, Iran). We chose the ANGIPARS™ dose based on our experience of its use in diabetic foot ulcer patients. ANGIPARS™ capsules (each capsule contains 100 mg active agent) were prescribed for 9 months. Patients received 3 capsules per day for the first 6 months and 2 capsules per day for the remaining three months. They were followed up for an additional 3 months following the end of the treatment. The instructions for the use of ANGIPARS™ advise to take the drug after a meal to prevent gastric discomfort. As most of the patients with scleroderma suffer from dysphagia and gastric problems, and with our previous experience that showed ingestion of ANGIPARS with a half full stomach is tolerated much better, the subjects were instructed to ingest the capsules 0.5-1 hour after a meal.

Patients were visited for a follow-up 10 times at the hospital clinic by the same physician during a 12 month study period in accordance with an agreed protocol. Visits were carried out monthly during the first 6 months and at slightly longer intervals thereafter. The patients were informed of the possible complications and were asked to consult our clinic immediately if any such complications developed.

The patients were taking part in standard treatments and their previous medication continued throughout the study, so ANGIPARS™ was added to the patients' treatments. According to the study's protocol, the patients were allowed to take medications where it was deemed necessary by a responsible physician. If any changes in patients' treatments related to the scleroderma, it was recorded. All the participants had chronic and stable cases of scleroderma and no significant changes in their treatment protocol occurred during the study. All of the physical examinations were performed by the same rheumatologist.

End points

The main end points of the study were the safety and efficacy of the drug in reducing skin thickness measured by the modified Rodnan score 24. Skin thickness was marked from 0 (normal) to 3 (severe) at 17 different body sites by a single assessor (Rheumatologist) who was unaware of each patient's score at the previous session. The marks were then

summed to obtain the modified Rodnan score (with a maximum possible score of 51). The number of perioral folds, pitting ulcers, finger to palm distance, pain of pitting ulcers (as measured by the visual analogue scale), and open-mouth area were also recorded as other outcomes to assess the changes of the skin involvement and efficacy of the ANGIPARS™.

Statistical analysis

Statistical analysis was carried out using SPSS (SPSS Inc., Chicago IL. version 11.5). Quantitative data was expressed as mean±standard deviation. The study variables were tested for normality by the Kolmogorov- Smirnov test. Repeated measure analysis was performed to analyze the data gathered over the study period. P values of below 0.05 were considered to be statistically significant.

Results

Twelve patients, including 11 females (92%), met the inclusion criteria and were enrolled into the study. The mean age of the patients was 39 years old (ranging from 21 to 53 years). The mean duration of the disease was 8.3 years (ranging from 2.5 to 18 years) at the time of enrolment. One patient was dropped due to severe dysphagia and malabsorption after 4 months as she became incapable of swallowing the medication (Table 1).

Table 1. Characteristics of study subjects

Characteristics	Value
Gender (Women)	91.6%
Age groups	
< 30 year	25%
30-40 year	25%
40 year	50%
Mean duration of illness	8.4 (SD=4.8)*

* This variable is normally distributed (Kolmogorov-Smirnov P value = 0.626).

Repeated measure analysis revealed a significant reduction in the modified Rodnan score, finger to palm distance, and number of pitting ulcers, and revealed an increase in the open-mouth area. The drug did not have any effect on the pain of the ulcers or the number of perioral folds. The results have been summarized in Table 2 (all the variables were normally distributed).

Analysis of laboratory measures did not show any significant changes and no abnormal results arose during the course of the study (Table 3).

WBC, white blood cell, Hb, hemoglobin, Plt, platelet, ESR, erythrocyte sedimentation rate, CRP, C-reactive protein, PT, prothrombin time, PTT, partial thromboplastin time, SGOT, serum glutamic

ANGIPARS™ for scleroderma

Table 2. Summary of clinical assessment

	Follow up visit											P value
	1	2	3	4	5	6	7	8	9	10	11	
RS	25.9 ± 9.5	22.9 ± 9.3	18.9 ± 8.0	17.4 ± 7.0	14.8 ± 7.8	13.6 ± 8.0	15.0 ± 9.4	12.5 ± 4.8	15.1 ± 9.7	16.2 ± 10.6	16.2 ± 10.3	<0.001
MS (cm ²)	14.1 ± 2.4	15.1 ± 2.8	16.7 ± 3.3	17.4 ± 3.6	17.0 ± 4.3	16.4 ± 3.3	16.4 ± 3.9	16.9 ± 3.9	17.9 ± 3.3	16.2 ± 3.1	17.0 ± 3.4	0.041
FPD (cm)	3.3 ± 2.0	3.3 ± 2.0	3.1 ± 2.0	3.0 ± 1.8	3.0 ± 1.7	3.1 ± 1.7	2.5 ± 1.9	2.6 ± 2.0	2.8 ± 2.1	2.6 ± 1.9	2.2 ± 2.1	<0.001
PU (Number)	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.8 ± 0.4	0.4 ± 0.5	0.1 ± 0.4	0.09 ± 0.3	0.3 ± 0.5	0.1 ± 0.4	0.003
VAS-Pain	3.5 ± 4.1	2.8 ± 3.7	2.8 ± 3.5	2.5 ± 3.6	2.0 ± 3.6	1.7 ± 2.5	2.0 ± 3.4	0.9 ± 1.3	0.4 ± 1.4	1.6 ± 2.5	1.3 ± 2.4	0.180
Perioral fold (Number)	8.0 ± 5.8	8.0 ± 6.5	8.2 ± 6.4	7.9 ± 6.4	7.8 ± 6.0	8.7 ± 6.8	8.4 ± 6.1	7.2 ± 6.7	9.4 ± 6.6	9.2 ± 6.8	9.7 ± 6.7	0.218
Weight (Kg)	56.1 ± 2.6	55.6 ± 12.8	55. ± 12.3	54.5 ± 13.1	56.0 ± 12.5	56.8 ± 13.0	57.0 ± 13.4	57.1 ± 13.3	56.6 ± 12.6	55.1 ± 12.7	59.3 ± 13.6	0.340

Table 3. Results of the laboratory tests for the subjects during the course of the study

Variable	1	2	3	4	5	6	7	8	9	10	11	P value
WBC (×10 ⁶ /l)	9041.6 ± 2843.0	8808.3 ± 2832.7	8166.6 ± 2433.9	7816.6 ± 4391.52	8600.0 ± 2056.8	7945.4 ± 2040.7	7736.3 ± 1886.9	7854.5 ± 2070.9	8136.3 ± 2486.4	9118.1 ± 4418.5	9209.0 ±	
Hb (g/dl)	12.2 ± 1.0	12.6 ± 1.1	12.4 ± 1.0	12.6 ± 1.0	12.6 ± 1.0	12.8 ± 1.3	12.6 ± 0.9	12.1 ± 1.2	12.3 ± 1.3	12.4 ± 1.3	12.8 ± 1.5	
Ht (×10 ⁶ /l)	338000 ± 99364.1	330000 ± 96297.2	349000 ± 122370.02	98000 ± 80255.0	300000 ± 72772.7	311000 ± 74398.0	339000 ± 86090.6	363000 ± 129202.3	335000 ± 90709.7	356000 ± 109773.8	-	
SR (mm/hr)	17.1 ± 16.6	23.4 ± 19.3	22.1 ± 18.9	20.5 ± 12.6	27.1 ± 15.6	19.8 ± 13.0	18.9 ± 13.9	21.8 ± 13.2	24.0 ± 23.0	18.6 ± 11.1	19.4 ± 11.5	
RP (mg/l)	5.9 ± 7.0	9.9 ± 22.1	6.7 ± 9.6	6.0 ± 10.0	11.7 ± 15.8	8.5 ± 8.9	9.9 ± 11.7	10.0 ± 11.6	9.2 ± 11.0	8.2 ± 11.3	7.7 ± 11.5	
T (sec)	12.7 ± 0.7	12.2 ± 0.8	12.9 ± 0.9	13.2 ± 1.2	13.1 ± 1.2	14.5 ± 1.2	14.5 ± 1.2	13.9 ± 0.7	14.0 ± 1.0	13.9 ± 1.0	13.6 ± 0.8	
TT (sec)	36.1 ± 3.6	33.0 ± 7.2	36.4 ± 6.2	35.0 ± 6.0	36.1 ± 5.7	37.6 ± 8.4	39.6 ± 8.5	41.7 ± 8.5	41.6 ± 7.1	42.3 ± 5.3	42.6 ± 5.7	
GPT (units/l)	17.4 ± 10.3	15.5 ± 7.4	18.6 ± 11.8	20.5 ± 13.0	19.2 ± 10.6	21.3 ± 10.3	22.9 ± 14.0	26.8 ± 32.1	27.0 ± 35.1	19.5 ± 17.2	15.0 ± 7.9	
GOT (units/l)	19.6 ± 7.8	18.7 ± 4.9	21.0 ± 5.7	20.0 ± 6.1	21.1 ± 5.5	22.9 ± 7.2	21.8 ± 7.5	23.5 ± 12.1	21.5 ± 13.0	20.4 ± 6.8	18.0 ± 4.9	
ALP (units/l)	142.0 ± 32.8	158.8 ± 40.9	163.1 ± 46.4	181.0 ± 48.5	190.8 ± 48.0	198.7 ± 52.9	207.7 ± 48.9	198.0 ± 42.4	191.7 ± 34.6	190.3 ± 44.8	182.3 ± 43.5	>0.05
Amylase (units/l)	64.0 ± 20.3	71.5 ± 26.1	77.3 ± 21.1	79.5 ± 29.5	83.6 ± 33.0	84.5 ± 32.8	88.2 ± 33.1	90.7 ± 26.7	94.4 ± 38.5	91.1 ± 27.0	86.9 ± 31.0	
Alb (g/dl)	4.7 ± 0.2	4.7 ± 0.3	4.7 ± 0.3	4.7 ± 0.4	4.8 ± 0.2	4.9 ± 0.3	5.1 ± 0.4	5.2 ± 0.3	4.8 ± 0.5	4.7 ± 0.4	4.4 ± 0.3	
total pr (g/dl)	6.7 ± 0.4	6.8 ± 0.3	6.8 ± 0.2	6.9 ± 0.5	7.2 ± 0.6	7.4 ± 0.5	7.8 ± 0.6	7.7 ± 0.6	7.6 ± 0.7	7.3 ± 0.6	6.9 ± 0.4	
Na (mEq/l)	141.5 ± 1.4	140.5 ± 2.4	142.2 ± 1.4	142.0 ± 1.5	140.3 ± 3.0	142.1 ± 1.5	139.2 ± 2.4	139.4 ± 2.2	139.0 ± 1.6	139.3 ± 2.3	139.4 ± 3.0	
K (mEq/l)	4.1 ± 0.3	4.0 ± 0.2	4.2 ± 0.1	4.2 ± 0.2	4.2 ± 0.2	4.2 ± 0.2	4.3 ± 0.4	4.3 ± 0.3	4.2 ± 0.2	-	4.4 ± 0.4	
(mg/dl)	3.4 ± 0.3	3.9 ± 0.3	3.9 ± 0.4	3.7 ± 0.3	3.8 ± 0.4	3.9 ± 0.3	4.2 ± 0.5	4.2 ± 0.4	3.9 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	
a (mg/dl)	9.3 ± 0.3	9.5 ± 0.3	9.4 ± 0.3	9.4 ± 0.3	9.3 ± 0.4	9.4 ± 0.3	9.5 ± 0.3	9.4 ± 0.3	9.4 ± 0.3	9.5 ± 0.5	9.3 ± 0.6	
Mg (mEq/l)	2.2 ± 0.2	2.3 ± 0.	2.0 ± 0.2	2.0 ± 0.1	2.0 ± 0.02	2.0 ± 0.1	2.0 ± 0.2	2.0 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.1	
UN (mg/dl)	12.1 ± 2.4	13.4 ± 4.0	13.4 ± 3.2	12.5 ± 3.5	11.9 ± 2.1	13.8 ± 5.0	13.1 ± 3.7	10.8 ± 3.0	12.3 ± 3.0	14.6 ± 11.6	12.1 ± 3.6	
r (mg/dl)	0.8 ± 0.09	0.8 ± 0.07	0.8 ± 0.09	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.08	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	

oxaloacetic transaminase SGPT, Serum glutamic pyruvic transaminase, AIP, alkaline phosphatase, Total Pr, total serum protein, Alb, serum albumin, Na, serum sodium, K, potassium, P, phosphorous, Ca, calcium, Mg, magnesium, BUN, blood urea nitrogen, and Cr, creatinin.

Discussion

Our results showed that ANGIPARS™ is safe and could significantly reduce skin thickness and finger to palm distance as well as helping with the process of healing pitting ulcers in patients with scleroderma.

It also improves mouth opening by increasing the size of the open-mouth area. The safety of the drug was confirmed by serial measurements of a wide spectrum of laboratory parameters. We did not see any serious side effect that would have resulted in discontinuation of the treatment during the study period. In this study, we performed a phase 2 clinical trial. Phase 2 trials include studies that evaluate the effectiveness of a drug for a particular indication, or indications, in patients with a disease or condition under study. This is done to determine the common short-term side effects and risks²⁵. We managed to recruit and retain 11 patients in this study. Although we were 3 short of our target sample size, because treatment effect was greater than 20% of ANGIPARS™²⁴, our study demonstrated the therapeutic effect.

Angiogenesis has been described as a possible mechanism for ANGIPARS™ and has been successfully demonstrated in previous studies on diabetic foot ulcers and pressure ulcers [19, 20, 22, 23]. The present study revealed that ANGIPARS™ is effective in the treatment of pitting ulcers. As ischemia plays an important role in development of ulcers in scleroderma, we believe that this finding provides further evidence for the angiogenesis effect of the ANGIPARS™ and confirms the results of previous studies [19, 20, 22, 23].

Several medications such as Methotrexate [26, 27], Bosentan [7, 12, 28] and some herbal medications (including Chinese herbs [29], evening primrose oil [30] and avocado/soybean extract [31]) have been used for the treatment of the skin manifestations of scleroderma. However, the results obtained from these studies are mixed. Korn et al. evaluated the effect of Bosentan on digital ulcers in 122 patients with scleroderma [7]. The results showed that Bosentan is effective in the treatment of skin ulcers in scleroderma. With regard to the efficacy and safety of Bosentan, the same results were achieved by other researchers [12]. Methotrexate has also been used for the treatment of

digital ulcers in scleroderma, however, controversy exists surrounding the efficacy of Methotrexate. Pope and colleagues evaluated the effect of Methotrexate on 71 patients with early diffuse SSc in a randomized controlled trial [26] and did not find a considerable improvement in skin condition with this drug. In contrast, Kroft and associates [27], in a recent study, assessed the efficacy of Methotrexate on 58 patients and concluded that Methotrexate is effective in the treatment of various sclerotic skin diseases.

Evening primrose oil contains a high concentration of gamma-linolenic acid, a precursor for prostaglandin E1 [30], and it may therefore be effective in the treatment of vascular abnormalities, including the skin manifestations of scleroderma. However, there has not been a consensus regarding its possible therapeutic effects in the treatment of Raynaud's phenomenon in other studies [32, 33].

Another herbal medication that has been used successfully for the management of the skin manifestations of scleroderma is avocado/soybean extract³¹. However, penicillin use before the initiation of the treatment has made the interpretation of the results difficult. There are some reports that say infection may play a role in the pathogenesis of ulcers in SSc and it is not clear whether the improvement of the ulcers relates to the penicillin or the avocado/soybean extract [30].

In spite of the introduction of these treatments, prostaglandin analogue infusion is still considered to be the gold standard treatment for refractory digital ulcers in scleroderma. However, the results have been heterogeneous and administration of the drug has been associated with many adverse effects that result in hospitalization [10]. Bosentan has also been suggested as the line of treatment in refractory ulcers second to the standard treatments [10]. Our study shows that ANGIPARS™ could be added to the current list of treatments. However, the efficacy of the drug must be tested in a further large, randomized controlled trial before its routine clinical application.

ANGIPARS™ is effective in reducing skin thickness in scleroderma measured by the modified Rodnan score. A higher Rodnan score has been described as a risk factor for the development of digital ulcers in scleroderma [34], this led us to believe that it could be the mechanism that ANGIPARS™ helps with the healing of pitting or digital ulcers.

Skin thickness in scleroderma is the result of an increase in collagen, intercellular matrix formation in the dermis, and edema - likely developed by both

microvascular injury and inflammation. Because of the accumulation of collagen and fluid, the skin becomes thickened, making it impossible to pinch it into a normal skin fold [35]. ANGIPARS™ reduces the skin thickness, although its exact mechanism of action is not yet fully known. There is evidence to suggest that ANGIPARS™ acts directly on endothelial cells and plays an important role in angiogenic activity [23] as well as acting indirectly through its immunomodulatory effect [36-38]. Improvement in finger to palm distance and open-mouth area are two other manifestations of reduction in skin thickness by ANGIPARS™.

In conclusion, our study shows that ANGIPARS™ is safe and could significantly reduce the thickness of skin. Its therapeutic effects however, should be further examined in larger placebo controlled trials.

Conflict of interests

Authors have no conflict of interests.

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