Post marketing surveillance on safety and effectiveness of ANGIPARS in treatment of diabetic foot ulcers

[1]Ebrahimi M., [1]Bakhshayeshi S., [1]Heshmat R., [1]Shahbazi S., [1]Aala M., [1]Peimani M., [1]Khushechin G., [1]Mohajeri Tehrani M.R., [2]Shojaeefard A., [3]Kamali K., [1]Azimaraghi O., [*1]Larijani B.

[1]Endocrinology and Metabolism Research Center (EMRC), Tehran University of Medical Sciences, [2]Department of Surgery, Shariati Hospital, Tehran University of Medical Sciences, [3]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background and the purpose of the study: One of the most important complications of diabetes is foot ulcers with a life time risk of 15% among diabetics. The main objectives of this study was to evaluate adverse drug reactions(ADR) of oral and topical application of ANGIPARS, a novel compound applied in treatment of diabetic foot ulcers and also its effect on wound surface area, Ankle Brachial Index(ABI), Toe Brachial Index(TBI) and wound temperature .
Material and Methods: A total number of 75 diabetic patients who were over 50 years (56.7± 9.7 years) and had foot ulcers without any signs of osteomyelitis were enrolled in this study. A basal wound surface area, ABI, TBI and wound temperature was measured and routine hematological and biochemistry tests were performed. Six weeks and 6 months after simultaneous application of oral and topical forms of ANGIPARS, mentioned parameters were evaluated again and analysis was carried out using standard methods.
Results and Conclusion: The mean surface area of the ulcers were 6.05 ± 11.1 cm^2 at the baseline and 2.4±6.9 cm^2 after six weeks of therapy showing a considerable decrease. A significant rise in ABI and TBI ($p<0.05$) was observed after 6 weeks of treatment. The results also demonstrated a significant fall in erythrocyte sedimentation rate (ESR) for 45 days after drug administration but no significant changes in the other laboratory tests were observed at this time. No significant side effects or toxicity was reported by the participants during the course of the study.
This study showed the immense effect and safety of ANGIPARS on treatment of diabetic foot ulcers.

Keywords: Post marketing surveillance, safety, effectiveness, ANGIPARS

INTRODUCTION

Diabetes mellitus with rising incidence worldwide has become a dilemma for health systems around the world (1, 2). One of the most important complications of diabetes is diabetic foot ulcer which is caused by a number of disorders such as neuropathy, peripheral vascular disease, trauma and infection. An estimated 15% of the patients with diabetes will experience a foot ulcer during their life time and 14% -24% of people with a foot ulcer require the ultimate treatment, amputation, and the recurrence rates of diabetic foot ulcer is high. It is clearly explicable the burden that diabetes mellitus has on the healthcare costs and therefore immense effort is needed to prevent and treat diabetic foot ulcers (3-5). Several recently clinical studies have offered a variety of novel topical and systemic treatments for the management of diabetic foot ulcers. The effect of platelet-derived growth factor, adenosine receptor agonists, topical ketanserin, hyperbaric oxygen therapy, skin grafts, laser therapy, iloprost and prostaglandin E1 on diabetic foot ulcers have all been studied (6, 7). One of the most recently proposed treatments for diabetic foot ulcers is the oral and topical application of ANGIPARS, a novel herbal compound (8) .The main objectives of this phase IV trial was to assess the possible side effects and complications that ANGIPARS may cause throughout the course of therapy and also to evaluate its effect on wound surface area, Ankle Brachial Index (ABI), Toe Brachial Index (TBI) and wound temperature in diabetic foot ulcers.

Methods

Study Design

In phase IV trial (after the release of the drug into the market) with the aim of evaluating safety and effectiveness of ANGIPARS, a total number of 75 subjects were selected from the patients who were referred to Shariati Hospital Diabetes Clinic over a

Correspondence: emrc@sina.tums.ac.ir

period of 7 month (April –November 2008) based on non probability consecutive sampling.

Inclusion and Exclusion Criteria

Adults of either sex who were previously diagnosed with type 1 or 2 Diabetes mellitus and were older than 18 years, with at least one diabetic foot ulcer with the minimum size of 1cm^2 which had not healed for at least two weeks, patients also mentally intact to be able to sign a written form of consent and attend the diabetes clinic every two weeks for the follow up visits participated in the study. The ulcers might have been caused by different mechanisms.

The exclusion criteria consisted of the patients who had a grade III or higher diabetic foot ulcer based on Wagner classification, evidence of systemic or local infection such as more than 3 cm width of erythema around the edge of the wound or visible purulent drainage, bone exposure in the wound, heart failure(function class III or higher), signs of severe or chronic ischemia of the lower extremities or pulselessness on physical examination, chronic alcohol or drug abuse, medical history of immunosuppressive drugs, a previously diagnosed hematological, renal, hepatic or endocrinal disorder apart from diabetes which affected the wound healing, past medical history of acute/chronic autoimmune disease. Patients who were not compliant with the inclusion criteria or had one of the exclusion criteria were not allowed to participate in the study.

Treatment Protocols

After patients were selected to enroll in the study, all participants were fully informed of the nature of the study and provided a written informed consent.

During the primary assessment a detailed past medical history was taken which stressed on duration since the first time diagnosis of diabetes mellitus, previous ulcers, treatments used and allergies to drugs. A comprehensive thorough physical examination of the lower extremities and the ulcers was carried out by trained physicians and photographs of the wounds were taken and the exact surface area of the wound was measured. Baseline laboratory tests were carried out for a complete blood count, erythrocyte sedimentation rate, fasting blood sugar, lipid profile, liver and renal function tests plus serum phosphorus, calcium, sodium, potassium and amylase. Also a baseline wound surface area (the greatest length multiple by greatest width measured in centimeters), ABI and TBI using Doppler sonography was determined. In addition temperature in the surface and margin of the ulcer, dorsum of the foot and similar point in the other foot was measured by dermatemp.

All patients were administered 100mg of ANGIPARS capsules orally twice a day plus topical 3% gel for 45 days during which they were visited biweekly and evaluated for possible side effects. Patients also during the course of the study received conventional treatments such as wound debridement, antibiotic therapy and pressure off-loading. Assessment of changes in the ulcer size and likely adverse drug reactions were documented by physicians in every visit. After 45 days of therapy and also 6 months after the start of the study all laboratory parameters plus wound surface area, ABI, TBI and wound temperature were checked again.

Statistical analyses

Statistical analyses of the results were performed using SPSS for windows, release 11.5 (SPSS .Inc) and data are presented as means±standard deviations (SD). Paired t- test was used for comparison between pre- and post-treatment results and P-values<0.05 were considered statistically significant. Adjustment for type one error (α) was carried out by Dunett's Post Hoc test where baseline data was selected as the reference group.

RESULTS

Basic characteristics

A total number of 110 participants were chosen but only 75 patients met the eligibility criteria for this study (28% female and 72% male).The mean age of the participants was 56.77± 9.7 years.

Safety results

During 6 months after beginning of the study, the patients were evaluated for Adverse Drug Reactions (ADR) by monitoring laboratory parameters and through physical examinations but no clinical significant side effects were observed. There were just 6 patients who reported mild gastrointestinal complications such as nausea at the beginning of the drug consumption but all patients tolerated the treatment.

Laboratory parameters

In the laboratory parameters, shown in Table 1, 45 days after drug administration, no significant laboratory changes were observed with exception of falling of ESR. Six months after follow up, a statistically significant increase in serum creatinine, serum calcium and PT was observed. Red blood cell(RBC) count, total billirubin (Bil T), amylase and ESR levels also decreased significantly. Other clinically meaningful alterations in the other hematology and chemistry parameters were not observed.

Assessment of the wound

Mean ulcer surface area measured on the first visit of the patients before initiation of the treatment was 6.05±11.1cm^2 which improved to 2.4±6.8cm^2 after 6 weeks of simultaneous oral and topical ANGIPARS therapy with the mean improvement ratio of 68.7±37.6 percent(P value=0.000). The ulcer surface area was measured for the third time 6 months after beginning of the study and results showed that the

Table 1. Mean of the clinical laboratory parameters measured at baseline, 1.5 and 6 month after oral and topical ANGIPARS therapy (n=75).

Variable	Pre-Treatment	After 1.5 month	P value	After 6 month	P value
WBC(x10³)	7.8±2.4	7.6±2.2	0.388	7.9±1.9	0.458
Hgb	12.4±1.7	12.5±1.6	0.612	12.4±1.7	0.775
Platelet(x10³)	235.1±78.2	226.2±75.8	0.230	235.80. ±82.1	0.724
RBC	4.5±0.6	4.6±0.6	0.227	4.3±0.6	0.016
Triglyceride	154.5±82.3	151.3±84.8	0.659	163.5±87.8	0.069
Cholesterol	163.9±84.4	159.2±33.2	0.325	168.9±44.4	0.491
Creatinine	1.1±0.2	1.1±0.4	0.217	1.3±0.5	0.000
SGPT	23.1±18.6	25.2±22.5	0.553	15.3±10.1	0.090
SGOT	23.2±13.2	23.7±10.9	0.801	21.2±15.8	0.603
Billirubin (T)	0.7±0.3	0.7±0.3	0.843	0.5±0.2	0.000
Billirubin(D)	0.1±0.0	0.1±0.0	0.404	0.1±0.0	0.214
PT	12.6±0.8	12.7±0.8	0.207	13.0±0.2	0.004
PTT	32.4±4.3	32.0±3.9	0.415	32.0±4.1	0.317
Calcium	9.3±0.6	9.3±0.5	0.824	9.6±0.5	0.005
Phosphorus	4.0±0.6	4.1±0.6	0.100	4.0±0.4	0.457
Sodium	139±3.0	140.1±2.8	0.089	139.8±1.9	0.331
Potassium	4.4±0.5	4.4±0.5	0.953	4.5±0.4	0.778
Amylase	101.8±76.6	93.2±79.4	0.264	51.8± 24.1	0.000
ESR	46.2±29.4	30.7±19.4	0.000	26.7±21.0	0.000

Data are means± standard deviation.

mean ulcer surface area had decreased to 1.1±3.5cm^2 with the mean improvement ratio of 82.3 ± 49.0 percent(P value=0.000). Mean ABI improved from 0.95±0.32 to 1.13±0.39 (P value=0.000) 6 weeks after therapy and the final ABI which was measured after 6 month was 1.06±0.32 (P value=0.050). Also TBI rose from 0.69±0.17 to 0.75±0.22 (P value=0.039) 6 weeks after therapy but TBI changes after 6 months was not significant. Dermal temperature at dorsum of foot and wound temperature of similar area in other foot had increased significantly after 6 weeks, but increase in the wound surface and its marginal temperature wasn't statistically significant.

DISCUSSION

Morbidity of the diabetic patients could be mainly due to chronic dermal ulcers and therefore pressure ulcers and delayed wound repair are a major concern in diabetic foot ulcers (9, 10). Not only foot ulcers have an effect on quality of life in diabetic patients but also could have a big impact on the health care costs (11). In the process of normal and pathological wound healing different biological markers are involved, therefore treatment of diabetic foot is often a complex clinical problem which requires new strategies to treat these costly clinical problems (12, 13).

Oxidative stress has been proposed as a common pathway to pathogenesis of complications in diabetes (14).Various antioxidants have been used in many studies of which some have not proved useful in wound healing. For example vitamin E, in supra- antioxidant doses have reported to be useful in normalizing oxidative stress and vascular dysfunctions, and consequently help the process of wound healing (15, 16). Natural antioxidants from plant materials have also been in the spot light to replace synthetic antioxidants (17, 18).

Angiogenesis is also considered to be one of the mechanisms responsible and helpful in the wound healing process (19, 20). ANGIPARS a novel herbal extract containing compounds such as coumarin and flavonoids has been studied in all steps of clinical trial and was recently presented as a novel treatment for diabetic foot ulcers, with a possible mechanism of angiogenesis (8).

In this study it was shown that while oral and

topical ANGIPARS have a significant therapeutic effect on the wound healing, they have no clinically or laboratory significant side effects. In a previously multicenteric clinical trial conducted to evaluate the wound healing effects of ANGIPARS, it was concluded that wound closure was significantly greater in patients treated with ANGIPARS compared to placebo group. (64% v 25% P=0.015) which was concordant with our results(21). A 50% decrease in wound surface area in 8 weeks trial of the drug was observed in another study (22). In a randomized clinical trial on 18 patients with pressure ulcers, topical ANGIPARS in comparison with conventional treatment was more effective (23). Other clinical trials which investigated the effect of ANGIPARS on wound healing also showed successful results (24, 25). In contrast to the previous studies, in the present study not only changes in wound surface area were significant but ABI changes were also prominent, which builds the evidence that ANGIPARS could be very effective in wound healing.

The only side effect reported in previous studies was phlebitis at the site of infusion with a daily dose of 13.5 ml (26). To study the possible toxicity of ANGIPARS 8 male and female dogs were administered 0.07 ml/kg of the body weight ANGIPARS once a day and chemistry and hematologic parameters of the animals were checked but no adverse effect was observed (27).Also in the study for evaluation of acute and sub chronic toxicity of ANGIPARS in rodent and in the other study which assessed the in vivo and in vitro genotoxicity, this drug was considered safe (28, 29).

In this study, among the laboratory parameters a significant decrease was found in ESR which might be due to the infection treatment. The changes in serum creatinine, calcium, billirubin (T), RBC and PT which were statistically significant: at the beginning, were in the range of Coefficient of Variation (CV) of these parameters and were not clinically significant. Secondly, these changes were not observed during treatment with ANGIPARS. No explicable reasons could be used to elucidate the statistically significant changes in Amylase. Further study is required to illuminate the possible role of ANGIPARS in these changes.

From the results of this study it may be concluded that not only ANGIPARS is an effective drug in the treatment of diabetic foot ulcers but also it is a very safe drug with no clinically significant side effects which can be recommended highly.

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