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Randomized, Within-Patient, Clinical Trial Comparing Fluorine-Synthetic Fiber Socks with Standard Cotton Socks in Improving Plantar Pustulosis

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Key Words
Within-patient randomized trial · Plantar pustulosis · Textile · Fluorine-synthetic fiber

Abstract
Background/Aims: Rubbing the skin may influence the persistence of pustulosis over time. The aim of this study was to assess the impact of a new fabric made with fluorine-synthetic fiber in improving plantar pustulosis. ***Methods:*** A total of 17 patients were randomized to receive on one side a sock made of fluorine-synthetic fiber and on the other a sock made of cotton fabric for 4 weeks. The main outcome was the percentage reduction of lesional area at week 4. ***Results:*** The median lesion reduction at week 4 was 42.6% in the fluorine-synthetic fiber arm and 2.7% in the cotton arm ($p = 0.148$). Among secondary outcomes, the overall reduction over time in the treated areas was significantly in favor of the fluorine-synthetic fiber arm ($p = 0.045$) as well as the perception of the disease by the patient ($p = 0.025$). ***Conclusion:*** Despite the fact that the primary outcome was not reached, there was a tangible reduction in the extension of the treated areas and in the perception of the disease by the patient.

Introduction

Plantar pustulosis is a disabling skin condition presenting sterile, yellow pustules on a background of erythema and scaling affecting the palms and/or soles [1]. Palmoplantar pustulosis is frequently associated with classic psoriasis vulgaris, but it is now believed that it may not be a form of psoriasis [2, 3].

Since pustulosis patches frequently occur in correspondence with the areas subject to pressure or friction [4], they may be disabling interfering with walking and other physical activities. Topical or systemic treatment can only temporarily control symptoms, and relapses are commonly observed after treatment withdrawal [5]. Rubbing the skin and prolonged mechanical stress may influence the persistence of lesions over time [6]. In principle, fabrics with smooth surfaces which decrease friction may represent effective tools to relieve signs and symptoms, and to improve the quality of life of those suffering from psoriasis [7, 8].

A new fabric made with a special fluorine-synthetic fiber has been proposed for this task [8]. It presents inter-

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esting characteristics that make it suitable for creating garments for patients with psoriasis: excellent flow properties and low surface friction, nonstick capability, complete biocompatibility and chemical inertness. The fabric is hydro- and oleorepellent, breathable and fresh, smooth and slippery with a coefficient of friction close to zero. We evaluated the effectiveness and safety of socks made of fluorine-synthetic fiber in a randomized trial of patients with plantar pustulosis.

Materials and Methods

Patients

Patients were recruited from 3 Dermatologic Departments in Italy: the Department of Dermatology of the General Hospital of Prato, the Department of Dermatology of the University of Tor Vergata in Rome, and the Department of Dermatology of the San Raffaele Hospital in Milan. Eligible were patients of both genders, aged 18–65 years, with plantar pustular lesions and a diagnosis of chronic palmoplantar pustulosis, present for at least 1 year, involving at least 5% of the plantar surface area, symmetrically distributed, with a difference in extension between the right and left sides equal to or less than 10%. Patients with plantar hyperkeratotic lesions were excluded from the study, as were patients who had received any systemic treatment for psoriasis, ultraviolet B phototherapy or psoralen plus ultraviolet A therapy during the 3 months before inclusion in the study. Patients were still allowed to use topical therapy with corticosteroids or vitamin D derivatives. The study was approved by the medical ethics committee at each participating center.

Study Design

Eligible patients who had given their written informed consent received a kit containing 10 pairs of invisible socks. One sock of each pair was made with strands of a special high-quality polytetrafluoroethylene, called Profilen®, produced by the Austrian company Lenzing (trade name of the fabric Tepso®), and the other one with normal cotton fabric. Dressing sides were uniformly randomized on a 1:1 basis. Centralized telephone randomization procedures were adopted, and both investigators and outcomes assessor were blinded to the randomization rule. Both socks were tailor-made by the study sponsor in order to be as similar as possible regarding color, model and texture of fabric. The dressing side was clearly reported with a label sewn externally. The patients were instructed to wear socks every day for 4 weeks after initiation of the study and to change each pair every 3 days or so without wearing those already used, even after washing. Outcome measures were taken at baseline and every week until the end of the study (4 weeks).

Outcome Measures

Photographs under visible light were taken in standard conditions by using the same machine at the same distance (30 cm), uniform room illumination, neutral background and adhesive metric references of known extension in order to get the real scale of acquired photographs (fig. 1). The primary outcome measure was the percentage reduction from baseline of lesion areas evaluated at week 4. Area extension and reduction were evaluated by software specifically developed using MATLAB (MathWorks, Natick, Mass., USA) and this was conducted by an investigator who was unaware of treatment assignments. Secondary outcome measures included the physician evaluation of lesion severity by the Physician Global Assessment on a 6-point scale, patient evaluation of the pathological condition and estimation of disease impact on daily life activities on each treated side by using an anchored horizontal 100-mm visual analog scale. In addition, at the end of the study, global satisfaction was assessed by asking patients to mark which side had, in their opinion, the best outcome. This was evaluated on a modified visual analog scale having treated sides as extremities and with no side difference corresponding to the center of the scale. Positive scores were calculated for the side assigned to the fluorine-synthetic fiber and negative scores for the one assigned to cotton, resulting in a scale ranging from –100 to 100. All secondary outcomes, except for global satisfaction, were evaluated as differences between final and initial scores and as overall changes considering all the evaluations performed.

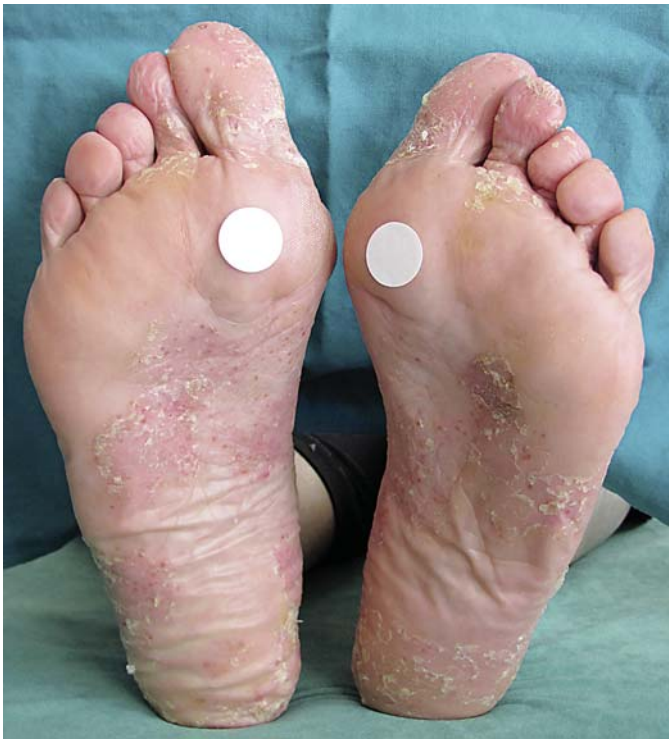

Fig. 1. Baseline characteristics of pustular lesions considered in the study. On the upper side of each foot, the metric patch used for image analysis is visible.

Side Effects

We evaluated any potential side effect and adverse event associated with the use of clothing. In particular, we considered erythema, irritant reactions and allergic dermatitis, needing temporary or permanent treatment discontinuation. These were evaluated at each treatment session.

Table 1. Baseline characteristics of randomized patients

		Median	Range	p value
Gender				
Male	4 (23.5)			
Female	13 (76.5)			
Age, years		57 (19.5)	27–65	
Weight, kg		68.5 (16.5)	48–92	
Height, cm		164 (18.5)	155–190	
BMI, kg/m^2		25.6 (5.4)	17.6–34.5	
Sock size (European)		37 (4.2)	35–44	
Alcohol consumption				
Occasional/nondrinkers	12 (70.6)			
Regular drinkers	5 (29.4)			
Smoking habits				
Nonsmokers	4 (23.5)			
Smokers	12 (70.6)			
Ex-smokers	1 (5.9)			
Age at onset, years		51 (27)	20–64	
Disease duration, years		3 (8)	1–21	
Lesion area, cm^2				
Fluorine-synthetic fiber		14 (40.2)	2.0–67.1	0.723
Cotton		23.5 (26)	2.9–68.2	
PGA				
Fluorine-synthetic fiber		3 (0)	2–5	1
Cotton		3 (0.2)	2–5	
Pathological condition perception (VAS)				
Fluorine-synthetic fiber		100 (42.5)	10–100	0.504
Cotton		73 (40)	10–100	
Estimation of disease impact on daily life (VAS)				
Fluorine-synthetic fiber		90 (39)	10–100	0.991
Cotton		83 (38.7)	10–100	

For continuous variables, values are expressed as medians with interquartile ranges in parentheses, otherwise as numbers with percentages in parentheses; p values are calculated from the Wilcoxon signed-rank test. PGA = Physician Global Assessment; VAS = visual analog scale.

Statistical Analysis

Data were presented as medians with ranges and/or interquartile ranges, or numbers with percentages. Baseline lesion characteristics and reduction from baseline of primary and secondary outcomes evaluated at week 4 were compared between groups by using the Wilcoxon signed-rank test. Patient global satisfaction at the end of the study was compared by the Wilcoxon signed-rank test in order to assess significance of one of the study arms (positive or negative scores) against the null hypothesis of no effect based on the side treated (zero score). Time-dependent variations in primary and secondary outcomes were evaluated by Friedman's test for repeated measures with Page's test for trend in time variations. An intention-to-treat approach was adopted in the primary analysis. In this analysis, patients lost to follow-up were recovered by the last observation carried forward technique. Intention-to-treat analysis was then complemented by per-protocol analyses, which considered only those patients who completed the study period. When designing this trial, we calculated that 20 patients would be needed for the study to have an 80% statistical power to detect a supposed difference of 25% in the mean reduction rate of lesion areas to be compared, also assuming standard deviations of 20 and 30% in cotton and fluorine-synthetic fiber arms, respectively. No interim analyses were performed. Two-sided p values <0.05 were considered to indicate statistical significance in all tests.

Results

Between March 2010 and June 2012, 21 patients were screened, 17 of whom (13 women and 4 men, median age 57 years) underwent randomization. Reasons for exclusion were age greater than 65 years (n = 1), little chance of compliance (n = 2) and hyperkeratotic lesion type (n = 1). The trial was halted prematurely due to the low prevalence of the disease and the difficulty in recruiting pa-

Table 2. Median change rates from baseline of primary and secondary outcomes at 4 weeks

	Median		p value
	fluorine-synthetic fiber	cotton	
Per-protocol			
Lesion area, cm^2	54.0 (73.2)	4.3 (71.0)	0.273
PGA	33.3 (42.5)	25.0 (42.5)	1
Pathological condition perception (VAS)	50.0 (59.5)	11.1 (42.0)	0.121
Estimation of disease impact on daily life (VAS)	45.0 (72.2)	5.0 (41.7)	0.416
Global satisfaction (VAS)	100 (67.5)		0.074
Intention-to-treat			
Lesion area, cm^2	42.6 (68.3)	2.7 (56.5)	0.148
PGA	0.0 (35.0)	0.0 (35.0)	1
Pathological condition perception (VAS)	29.2 (60.0)	0.0 (40.0)	0.080
Estimation of disease impact on daily life (VAS)	12.5 (60.0)	0.0 (37.5)	0.416
Global satisfaction (VAS)	20 (100)		0.074

For all variables except global satisfaction, values are expressed as medians of change rates with interquartile ranges in parentheses; p values are calculated from the Wilcoxon signed-rank test. PGA = Physician Global Assessment; VAS = visual analog scale. Global satisfaction is expressed as median of a modified VAS scale having treated sides as extremities and with no side corresponding to the center. Positive scores were calculated for the side assigned to fluorine-synthetic fiber and negative scores for the one assigned to cotton, resulting in a scale ranging from –100 to 100.

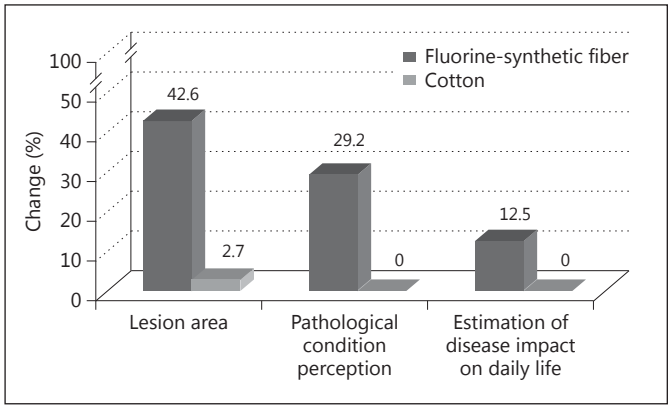

Fig. 2. Distribution of patient treated sides, according to median change rates from baseline of lesion area, pathological condition perception and estimation of disease impact on daily life at 4 weeks in the fluorine-synthetic fiber arm compared to the cotton arm.

tients. The baseline characteristics of randomized patients are shown in table 1. Three patients dropped out of the study for low compliance rate, one after baseline, one after the first week and one after the second week, while one patient withdrew from the study after the second week for worsening of pathological conditions. The two compared sides were homogeneous in terms of baseline lesion characteristics.

Effectiveness

The distribution of patient treated sides, according to percentage reduction from baseline of lesional areas, pathological condition perception and estimation of disease impact on daily life at week 4 is reported in figure 2. All outcome measures and their change from baseline at week 4 are reported in table 2. Assuming intention-to-treat analysis as reference, the median reduction rate in primary outcome was 42.6% in the fluorine-synthetic fiber arm and 2.7% in the cotton arm (p = 0.148). The median reduction rate for Physician Global Assessment was 0% in both arms (p = 1), for pathological condition perception it was 29.2% in the fluorine-synthetic fiber arm and 0% in the cotton arm (p = 0.080) and for estimation of disease impact on daily life it was 12.5% in the fluorine-synthetic fiber arm and 0% in the cotton arm (p = 0.416). Among secondary outcomes, patient global satisfaction at week 4 showed a median score of 20/100 towards the fluorine-synthetic fiber arm (p = 0.074). The overall changes over time of the assessed variables are shown in table 3. Arms were significantly different regarding the overall reduction of treated areas (p = 0.045) and pathological condition perception (p = 0.025). A significant shared trend was documented for all the assessed variables toward improvement with increasing time. The slope of change over time of median reduction rates of treated areas between study arms is illustrated in figure 3.

Table 3. Overall comparison over time of primary and secondary outcomes from baseline to 4 weeks

	p value	
	fluorine-synthetic fiber vs. cotton	trend over time
Per-protocol		
Lesion area	0.388	<0.001
PGA	0.140	<0.001
Pathological condition perception (VAS)	0.075	<0.001
Estimation of disease impact on daily life (VAS)	0.140	<0.001
Intention-to-treat		
Lesion area	0.045	<0.001
PGA	0.116	<0.001
Pathological condition perception (VAS)	0.025	<0.001
Estimation of disease impact on daily life (VAS)	0.385	<0.001

In the comparison of fluorine-synthetic fiber and cotton arms, p values were calculated from Friedman's test for repeated measures. Significance of trend toward improvement over time was computed by Page's test. PGA = Physician Global Assessment; VAS = visual analog scale.

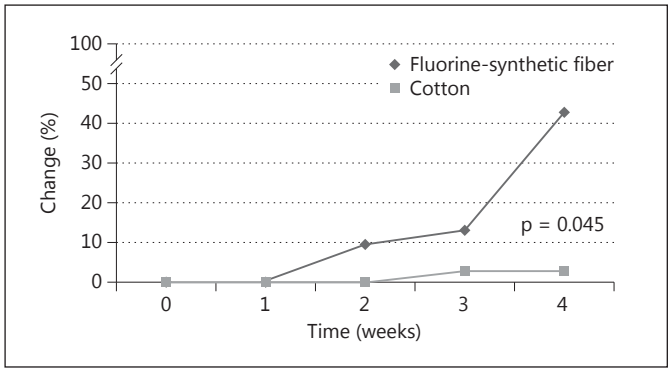

Fig. 3. Slope of change over time of median reduction rates of treated areas in the fluorine-synthetic fiber arm compared to the cotton arm.

Side Effects

No side effects or any other skin reactions were observed during the trial.

Discussion

We conducted a within-patient, randomized clinical trial to assess the advantages of a new fabric consisting of strands of high-quality polytetrafluoroethylene, in improving plantar pustulosis as compared with cotton fabrics. An effect of the textile on our primary outcome, namely reduction of lesional area, was found although it was not statistically significant. However, a significant difference between study arms was observed considering the overall changes over time. This was also supported by the pathological condition perception of the patient, although the patient may be satisfied by the softness of the synthetic fabric irrespective of its effect on the disease, and, in fact, no differences were observed in Physician Global Assessment. In a previous trial comparing fluorine-synthetic fiber socks with standard cotton socks in improving plantar psoriasis we failed to observe any clinical effect of textile on disease improvement [9]; we only found a significant satisfaction of the patient at the end of the study period (4 weeks) in the fluorine-synthetic fiber arm, which was partially confirmed in this clinical trial. Regarding the primary outcome measure, it is possible that the smaller number of patients (17/20 planned) and the loss of 23.5% of enrolled patients at the last follow-up (week 4) have significantly reduced the power of the study, regardless of the intention-to-treat analysis used to account for such losses. Despite the within-subject design of the study, that should have compensated for possible differences between study arms, the use of topical steroids in some patients (3/17) may be another source of 'bias'. Based on our results it is possible to calculate that, with this design, approximately 100 patients would be needed to show a significant effect of fluorine-synthetic fiber socks on the primary outcome. The adoption of a within-patient control design imposes restrictions (e.g. symmetrical lesions) and involves a high degree of collaboration from the patient. Contamination of treated areas is pos-

sible (i.e. patients putting the socks on the wrong feet), and relevant outcome measures such as patient quality of life are beyond the scope of this type of design. By necessity within-patient studies are conducted on a short-term basis [10]. The short time frame of our study may have influenced the outcome. It is expected that a nonpharmacological intervention like wearing specific fabrics could have a larger impact on a long-term run rather than a short-term one. In general, little interest has been paid to the relation between skin and textiles. Textiles, in particular clothing, interact with skin functions in a dynamic pattern [7, 8]. Mechanical properties like roughness of the fabric surface are responsible for nonspecific skin reactions. The microclimate in the skin/clothing system and especially the skin responses to moisture and heat play a critical role in skin irritation. Synthetic fabrics are textiles formed by strands of fibers made of small molecules (monomers) chemically joined into longer chains (polymers) by the process of polymerization. Due to the property of chemical elements or additions of other substances, synthetic fabrics can have different uses and qualities, some of which are not achievable with natural fibers. Regarding the dermatotoxicological effect of these materials, it was observed that some polymers and resins may cause dermatitis, although this was rarely, if ever, observed with fluorine-synthetic fibers such as polytetrafluoroethylene [11]. This material is characterized by a low friction coefficient and chemical inertness that made it suitable for reducing the impact of diseases like pustulosis.

Based on the encouraging results of this study and on the increasing trend observed in the reduction of the treated areas between the two study arms, we believe that it is important to continue to investigate the relationship between tissues and skin disorders, developing textile technologies that can improve the physical well-being in patients.

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