

HIGH-FREQUENCY ULTRASONOGRAPHIC ANALYSIS IN THE EVALUATION OF THERAPEUTIC RESPONSE IN PATIENTS WITH *PSORIASIS VULGARIS*

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HIGH-FREQUENCY ULTRASONOGRAPHIC ANALYSIS IN THE EVALUATION OF THERAPEUTIC RESPONSE IN PATIENTS WITH *PSORIASIS VULGARIS* (Abstract): Plaque psoriasis is a chronic, immune-mediated disease which represents a global health problem. The main objective of the study was to determine the monitoring performance of non-invasive tests of high frequency ultrasonography (HFUS) in psoriasis vulgaris. **Materials and methods:** In a prospective interventional analytic study, we aimed to assess whether the first chronologically obtained change in psoriasis plaque assessment in monitored patients was a decrease in psoriasis plaque thickness and subepidermal hypoechoic band as compared to baseline values. The study was carried over a period of 8 weeks and included 50 patients diagnosed with psoriasis vulgaris in the Dermatology Clinic of the “Sf. Spiridon” County Clinical Emergency Hospital, Iasi. We assessed the evolution under topical (calcipotriol/betamethasone 50 micrograms/0.5mg/g gel or fluticasone propionate 0.05% cream in combination with lipolotion urea 10%) combined with systemic (Etanercept) in severe forms of disease. Target lesions of psoriasis vulgaris were analyzed by clinical examination and by HFUS. **Results:** The results showed that the first change obtained chronologically was the decrease in psoriasis plaque thickness and subepidermal hypoechoic band in the target plaque as compared to baseline values (i.e. at week 4 compared to week 0). After comparing the mean values of psoriasis plaque tegument thickness and hypoechoic subepidermal band thickness, we found that they decrease significantly both in week 4 compared to week 0 and in week 8 compared to week 4. **Conclusions.** HFUS examination allows an objective and reproducible measurement of skin thickness and is a useful technique for a non-invasive assessment of treatment efficacy in psoriasis. **Keywords:** HIGH FREQUENCY ULTRASONOGRAPHY (HFUS), PSORIASIS VULGARIS, TOPICAL THERAPY, SUBEPIDERMAL LOW ECHOGENIC BAND (SLEB), MONITORING.

INTRODUCTION

Skin ultrasonography is a non-ionizing imaging method useful in the in vivo study

of skin lesions using ultrasound as a vector for imaging. Miller and Alexander reported that A-mode (Amplitude) sonography is an

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effective method of determining skin thickness (1). Subsequently, in 1987, the introduction of 20-Megahertz (MHz) B-mode (Brightness) ultrasound scanning systems with axial and lateral resolution of 200 μm and 75-80 μm respectively made two-dimensional (2D) imaging possible (2). Psoriasis is a chronic immune-mediated inflammatory disease characterized by an excessive hyperproliferation of keratinocytes with extracutaneous manifestations, that affects about 1-3% of the world's population (3, 4).

The inflammatory pathology represented by psoriasis vulgaris is much more than just a skin condition and is a global health problem, with over 125 million individuals affected by this multisystemic inflammatory condition (5). Worldwide, the prevalence of psoriasis has increased from 758 cases per 100,000 population in 1990 to 812 per 100,000 population in 2017. In Europe and the U.S. 21-55% of patients have a moderate to severe form of the disease (6, 7, 8).

The examination of psoriasis plaque lesions with HFUS may indicate the following: hyperechogenic band representing the epidermis with hyperkeratosis and parakeratosis; echogenic or hypoechogenic band corresponding to the elongation of the dermal papillae as one of the most common features, hyperechogenic band given by the reticular dermis and subcutaneous hypoechogenic layer. The subepidermal hypoechogenic band is due to edema and inflammatory infiltrate in the papillary dermis. Furthermore, the overall thickness of the integument in psoriatic plaques is increased and its reduction during therapy can be objectively demonstrated (9, 10). High frequency ultrasonography (HFUS) is a proper method for psoriasis assessment without causing subjective differences in clinical scoring systems such as PASI (Pso-

riasis Area Severity Index), TLS (Target Lesions Score) or DLQI (Dermatology Life Quality Index) (11,12).

MATERIALS AND METHODS

The main objective of the present study was to determine the monitoring performance of non-invasive test of HFUS in psoriasis vulgaris. In a prospective interventional analytic study justified by the need to improve monitoring modalities for plaque psoriasis vulgaris, our goal was to determine whether the first chronologically obtained change in psoriasis plaque assessment in monitored patients was a decrease in psoriasis plaque thickness and subepidermal hypoechogenic band as compared to baseline values. Thus, the current research aims to evaluate the contribution of imaging techniques such as HFUS in the algorithm of diagnosis and monitoring of psoriasis plaques, starting from the hypothesis that this technique may provide the possibility of establishing prognostic factors in the therapeutic management of psoriasis vulgaris.

The prospective study was carried over a period of 8 weeks (January-February 2020) and included patients diagnosed with psoriasis vulgaris in the Dermatology Clinic of the "Sf. Spiridon" Emergency Hospital, Iasi. The study was conducted on a group of 50 patients with psoriasis vulgaris composed mainly of men (78%) from urban areas (54%). The average age of the patients was $48,12 \pm 14,11$ years, with variations between 18 and 75 years. The parameters analyzed in the group of patients with psoriasis vulgaris were disease-related data (sex, rural/urban area), disease severity scores (PASI, DLQI) and Target Lesions Score/ TLS in weeks 0, 4, 8. Calculation of PASI scores was performed by the same examiner in weeks 0, 4, 8 with values between 0 and 72 and DLQI scores were

obtained in weeks 0 and 12 by the method of the questionnaire completed by the patient, with values between 0 and 30.

Clinical evaluation of erythematous-squamous lesions was performed by calculating a score called TLS which assesses erythema, scales and the presence of infiltration by assigning the following values: 0 - no, 1 - weak, 2 - moderate, 3 - severe. The TLS score has a maximum value of 8 and a minimum of 0 (when psoriasis plaque resolution is complete) and was clinically determined at weeks 0, 4, 8. Skin lesions with a score of 3 for scales were excluded to avoid interference with hyperkeratosis. The evaluation of the TLS therapeutic response was performed with the distribution of the therapeutic response in full resolution, major improvement, minor improvement or no response/non-responder. Others studied factors were the ultrasonographic diagnosis of the psoriasis target plaque. They were performed at weeks 0, 4 and 8 defined by the following parameters: thickness (mm) of the plaque analyzed in weeks 0, 4, 8; thickness (mm) of the hypoechogenic band in weeks 0, 4, 8; thickness (mm) of normal adjacent integument in weeks 0, 4, 8; thickness (mm) of hypoechogenic band normal integument adjacent to psoriasis plaque analyzed in weeks 0, 4 and 8.

We compared the evolution under topical and/or systemic treatment of patients with plaque psoriasis vulgaris both by classical means (clinical examination) and by non-invasive imaging techniques (HFUS). Inclusion criteria were patients clinically diagnosed and histopathologically confirmed with psoriasis vulgaris; age older than 18 years; presence of accessible lesions with cutaneous localization that can be examined using ultrasonography probe. The criteria considered for imaging selection of erythematous-squamous lesions (target lesion) required that the skin lesion

examined had an active character, with onset less than 6 months; the lesion was visible and well defined. Using exclusion criteria we eliminated patients on immunosuppressive therapy other than Etanercept, on systemic corticosteroids or lithium-containing, beta-blocking medicines during the study, or 1 month prior to examination, or on other topical therapies other than those administered during study assessments; patients on current phototherapy or 6 weeks prior to study; patients with neuropsychiatric pathology; patients with the presence of tuberculosis infection, severe comorbidities, diabetes, diseases of autoimmune character, exogenous or endogenous eczema such as atopic dermatitis; patients with marked photoaging (with history of chronic sun exposure) or sun exposure within the last 6 weeks or during the study; patients with contraindications for topical treatment with calcipotriol/betamethasone gel or fluticasone propionate combinations: bacterial, viral or mycotic infections, with skin atrophy or allergic contact dermatitis due to corticosteroids or formulation constituents; pregnant or lactating patients; smoking patients.

For the study we used a high frequency ultrasound scanner (Dermascan C Cortex Technology Denmark[®]) with a 20 MHz transducer, 12.1 mm wavelength, with a 13 mm focus (maximum 15 mm penetrability), with 1580 m/s velocity, 0.06 mm axial resolution/0.3 mm lateral resolution, mode A of examination. 19 patients enrolled in the study received topical treatment (calcipotriol/betamethasone 50 micrograms/0.5mg/g gel in combination with lipolotion urea 10% 1 application/day) or fluticasone propionate 0.05% cream in combination 2 applications/day and emulsion urea 10% 1 application/day combined with systemic treatment (Etanercept) previously initiated in severe forms of disease (31 patients).

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We chose this way of dividing the topical therapy, according to the severity of the disease from a clinical point of view, quantified by PASI and DLQI score.

Patients without biological systemic therapy received topical treatment with combination of vitamin D3 analogues and dermatocorticoids (calcipotriol with betamethasone propionate gel) for their synergistic effect and obtaining a better therapeutic effect quantified by severity scores. These topical therapies (topical dermatocorticoids fluticasone propionate, combinations of dermatocorticoids with calcipotriol vitamin D3 analogues with betamethasone dipropionate) and emollient (10% urea emulsion) have been applied as recommended in current psoriasis vulgaris treatment guidelines by the American Dermatology Association as well as that of the Romanian Society of Dermatology. The research was carried out in accordance with the Declaration of Helsinki 1964 and subsequent amendments and was

approved by the Ethics Committee of the “Grigore T. Popa” University of Medicine and Pharmacy Iasi and by the Ethics Committee of the “Sf. Spiridon” County Clinical Emergency Hospital, Iasi. Volunteers were informed about how the research would be carried out and gave their written consent by signing the informed consent form before the start of the study. The statistical data processing was performed using STATISTICA var. 7.0 software and Microsoft Excel.

RESULTS

In the current study, psoriasis plaque thickness values ranged in week zero between 1.70 mm and 3.77 mm, in week four between 1.34 mm and 3.56 mm, and in week eight between 1.11 mm and 3.31 mm (tab. I). The clinical and ultrasound analysis of target psoriasis plaques showed that thickness decreased continuously from one assessment in week 0 to the next in week 4 and 8.

TABLE I.
Medium skin thickness of psoriasis plaque

Variables	N	Mean	Minimum	Maximum	SD
Skin thickness plaque psoriasis (mm) in Week 0	50	2.71	1.70	3.77	0.56
Skin thickness plaque psoriasis (mm) in Week 4	50	2.50	1.34	3.56	0.57
Skin thickness plaque psoriasis (mm) in Week 8	50	2.21	1.11	3.31	0.55
N, participants number; SD, Standard Deviation					

Comparison of the mean skin thickness of the psoriasis plaque between weeks 0, 4 and 8 using the t test for repeated measurements showed that the mean thickness decreased continuously from one assessment to another:

- compared to week 0, the mean skin thickness of the psoriasis plaque decreased significantly by 0.21 mm on average in week 4, from 2.71 mm to 2.5 mm ($t=9.82$, $p<0.0000001$);
- compared to week 4, the mean skin

thickness of the psoriasis plaque decreased significantly by 0.29 mm on average in week 8, from 2.5 mm to 2.21 mm ($t=7.32$, $p<0.0000001$).

The analysis of target psoriasis plaques continued in the present prospective study with the comparison of mean hypochoic subepidermal band psoriasis plaque thickness at weeks zero, four and eight. Comparison of the mean thickness of the hypochoic subepidermal band between weeks 0, 4 and 8 using the t test for repeat-

ed measurements showed that the mean thickness decreased continuously from one assessment to another:

- compared to week 0, the average thickness of the hypoechoic subepidermal band decreased significantly by 0.23 mm on average in week 4, from 0.60 mm to 0.37 mm ($t = 10.39$, $p < 0.0000001$);

- compared to week 4, the average thickness of the hypoechoic subepidermal band decreased significantly by 0.24 mm on average in week 8, from 0.37 mm to 0.13 mm ($t = 6.21$, $p < 0.0000001$) (tab. II).

Given that the first change obtained chronologically when assessing the target plaque of cutaneous psoriasis was the decrease in psoriasis plaque thickness and subepidermal hypoechoic band in the target plaque as compared to baseline values (i.e. at week 4 compared to week 0), after comparing the mean values of psoriasis plaque

tegument thickness and hypoechoic subepidermal band thickness, we found that they decrease significantly both in week 4 compared to week 0 and in week 8 compared to week 4. It was noted that the mean thickness of the hypoechoic subepidermal band of the adjacent normal integument did not change.

Comparison of mean scores of TLS between week 0, 4, and 8 using the T test for repeated measurements (repeated assessments over time) showed that the mean score decreased continuously from one assessment the high:

- compared to week 0, the average TLS score decreased significantly by 3.42 points on average in week 4, from 6.94 points to 3.52 points ($t = 21.82$, $p < 0.0000001$);

- compared to week 4, the mean TLS score decreased significantly by 2.96 points on average in week 8, from 3.52 points to 0.56 points ($t = 17.04$, $p < 0.0000001$).

TABLE II.
Comparison of the average thickness
of the hypoechoic subepidermal band in week 0, 4 and 8

Comparisons between	Mean 1	SD 1	Mean 2	SD2	N	Difference	SD of the difference	t	p
Week 0 with week 4	0.60	0.34	0.37↓	0.29	50	0.23	0.15	10.39	<0.0000001
Week 0 with week 8	0.60	0.34	0.13↓	0.24	50	0.47	0.35	9.48	<0.0000001
Week 4 with week 8	0.37	0.29	0.13↓	0.24	50	0.24	0.28	6.21	<0.0000001

N, number of participants; SD, Standard Deviation

In order to study the relationship between the clinical and ultrasonographic appearance of the psoriasis target plaque Pearson r correlation coefficients were calculated, being considered significant those coefficients that were at a significance threshold $p < 0.05$. The analysis of the correlations between the clinical and ultrasonographic appearance of the psoriasis target plate showed that:

- in the first week, no significant corre-

lations were found; from the fourth week, some small but statistically significant direct correlations were found, as follows:

- between the skin thickness of the psoriasis plaque from week four and TLS from week four ($r = 0.3970$, $p = 0.004$), between the skin thickness of the psoriasis plaque from week eight and TLS from week eight ($r = 0.3432$, $p = 0.015$); between the thickness of the hypoechoic subepidermal band at week eight and the TLS at week eight (r

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= 0.3475, $p = 0.013$).

The results revealed that the average PASI scores decreased significantly from one assessment to another, as follows:

- an average decrease of 5.66, from 23.62 in week 0, to 17.96 in week 4, ($t = 7.44$, $p < 0.0000001$);

- an average decrease of 4.96, from 17.96 in week 4, to 13 in week 8, ($t = 8.59$, $p < 0.0000001$);

- an average decrease of 4.3, from 13 in week 8, to 8.7 in week 12, ($t = 8.82$, $p < 0.0000001$).

Similarly, the average DLQI scores decreased significantly from one assessment to another, showing that:

- an average decrease of 10.48, from 23.08 in week 0, to 12.6 in week 8, ($t = 12.48$, $p < 0.0000001$);

- an average decrease of 2.54, from 12.6 in week 8, to 10.06 in week 12, ($t = 11.96$, $p < 0.0000001$).

Significant direct correlations were not obtained between skin thickness of psoriasis plaque or hypoechoic subepidermal band and PASI score.

DISCUSSION

HFUS of the integument or nail apparatus can be used in the evaluation of response to local and/or systemic treatment (13, 14, 15). In a pilot study of 30 patients with psoriasis vulgaris compared to 10 healthy volunteers who used topical clobetasol propionate 0.05% foam differently (one arm of patients with psoriasis vulgaris applied twice daily for 14 days, the second arm applied once daily for one month, and volunteers once daily for four weeks) Lacarrubba *et al.* reported reduced psoriasis plaque thickness when monitoring treatment response with 20 MHz HFUS (16).

This resulted in equal values of integument thickness to that of adjacent healthy

skin in all treated plaques, with no differences between the two psoriasis patient groups, and no sonographic variations in skin thickness were observed in the healthy group at the end of the study (16). In contrast to Lacarrubba's study, in the current study we evaluated the therapeutic response not only under topical treatment (Fluticasone Propionate 0.5g/g cream or Calcipotriol/Betamethasone dipropionate 50 micrograms/0.5 mg/g gel and 10% Urea Emulsion) but also systemic, with 31 patients also under biological therapy with Etanercept. Similarly, in the 20 MHz ultrasonographic examination using Dermascan C[®] the study published by Micali *et al.* showed that at the 15-day examination, psoriasis plaque values were reduced by 33.5% in Etanercept-treated patients, by 63.6% at 30 days, and by 79.3% at 60 days. In total, after 60 days of treatment, 23 of the 42 psoriasis plaques analyzed showed complete normalization (13).

Subepidermal hypoechoic band can also be found in other inflammatory conditions such as atopic dermatitis or contact dermatitis (17). As a result, patients with these pathologies were excluded. In addition to the Subepidermal Low Echogenic Band (SLEB), in psoriasis we may detect thickened entry echo and streaky which is perpendicular to the entry echo shadows caused probably by air bubbles trapped between the scales (18). HFUS of the normal skin shows a clear separation of the skin layers (19). Camerota *et al.* argue that entry eco is due to the difference in acoustic impedance between gel and skin (20). The average epidermal thickness in healthy individuals is 0.6 mm, being between 0.1-0.8 mm (21).

For inflammatory dermatoses like psoriasis vulgaris, eczema, atopic dermatitis as well as in mycosis fungoides, similarly to the skin elastosis SLEB may be easy to

identify (22, 23). Maria C *et al.* (24) compared the efficiency of 20 MHz skin ultrasonography but also 40 MHz conventional ultrasonography in the assessment of 16 plaques psoriasis in three consecutive patients. The measurement was made at baseline and after hydrocortisone acetate 1% ointment six-week application. In contrast with our study parameters (total psoriasis plaque thickness including epidermal and dermal thickness and hypoechogenic band), their parameters were represented by epidermal and dermal thicknesses for gray-scale ultrasonography. Their results indicated that epidermal thickness was significantly reduced with 20 MHz and 40 MHz sonography, while dermal thickness varied insignificantly with 20 MHz and 40 MHz sonography. Gutierrez *et al.* (25) have showed that dermal thickness has been found to be correlated with disease severity measured using PASI score and other scales assessing the severity or extent of disease (11). Similarly, Fernando Alfageme (26) indicated that in a multicenter study HFUS examination showed a reduction in plaque thickness and Doppler signal intensity in the dermis of patients treated with infliximab.

One limitation of the study is the lack of biological and hematological data such as inflammatory syndrome indicated by Erythrocyte sedimentation rate (ESR) or imagistic tests like joint x-rays which can facilitate the diagnosis of severe form of psoriasis ac-

companied by psoriatic arthritis.

CONCLUSIONS

HFUS examination allows an objective and reproducible measurement of skin thickness and is a useful technique for a non-invasive assessment of treatment efficacy in psoriasis. Psoriasis plaque thickness and subepidermal hypoechoic band thickness can be markers of progression and therapeutic efficacy. The efficacy indicators of therapy objectified by HFUS are decreases in epidermal and dermal thickness and disappearance of the hypoechoic band. In the current study, the first chronological change obtained in the assessment of the target plaque of cutaneous psoriasis was a decrease in the thickness of the psoriasis plaque and the subepidermal hypoechoic band in the target plaque as compared to baseline values (i.e. at week 4 versus week 0), and after comparing the mean values of psoriasis plaque integument thickness and hypoechoic subepidermal band thickness, we found that they decrease significantly both in week 4 as compared to week 0 and in week 8 as compared to week 4.

CONFLICT OF INTERESTS AND FUNDING

The authors declare that there is no conflict of interest and they received no specific funding regarding this scientific research.

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