DERMATOLOGY PRACTICAL & CONCEPTUAL
www.derm101.com

Dermoscopic hemorrhagic dots: an early predictor of response of psoriasis to biologic agents

Aimilios Lallas[1], Giuseppe Argenziano[2], Iris Zalaudek[3], Zoe Apalla[1], Marco Ardigo[4], Patricia Chellini[5], Natalia Cordeiro[5], Mariana Guimaraes[5], Athanassios Kyrgidis[6], Elizabeth Lazaridou[1], Caterina Longo[6], Elvira Moscarella[6], Ilias Papadimitriou[1], Giovanni Pellacani[7], Elena Sotiriou[1], Efstratios Vakirlis[1], Dimitrios Ioannides[1]

1 First Department of Dermatology, Aristotle University, Thessaloniki, Greece
2 Department of Dermatology, Second University, Naples, Italy
3 Non-melanoma Skin Cancer Unit, Department of Dermatology, Medical University, Graz, Austria
4 Clinical Dermatology Department, IFO-San Gallicano Dermatological Institute, Rome, Italy
5 Instituto de Dermatologia Professor Rubem David Azulay—Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, Brazil
6 Skin Cancer Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
7 Department of Dermatology, University of Modena, Modena, Italy

Key words: dermoscopy, psoriasis

Citation: Lallas A, Argenziano G, Zalaudek I, Apalla Z, Ardigo M, Chellini P, Cordeiro N, Guimaraes M, Kyrgidis A, Lazaridou E, Longo C, Moscarella E, Papadimitriou I, Pellacani G, Sotiriou E, Vakirlis E, Ionnides D. Dermoscopic hemorrhagic dots: an early predictor of response of psoriasis to biologic agents. Dermatol Pract Concept 2016;6(4):2. DOI: 10.5826/dpc.0604a02

Received: June 30, 2016; **Accepted:** July 18, 2016; **Published:** October 31, 2016

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

Corresponding author: Aimilios Lallas, MD, MSc, PhD, First Department of Dermatology, Aristotle University, Thessaloniki, Greece. Tel.: +302313308882; Fax: +302310277979. Email: emlallas@gmail.com

ABSTRACT

Background: Biologic agents are routinely used in the treatment of severe psoriasis. The evaluation of treatment response is mainly based on the physician's global clinical assessment.

Objective: To investigate whether dermoscopy might enhance the assessment of response of psoriasis to treatment with biologic agents.

Methods: Patients with severe psoriasis scheduled to receive a biologic agent were enrolled in the study. A target lesion from each patient was clinically and dermoscopically documented at baseline and after one, two and six months. The clinical response was evaluated by the recruiting clinicians at all visits, while dermoscopic images were evaluated by two independent investigators, blinded to the clinical information. Chi Square test was used for cross-tabulation comparisons, while odds ratios, 95% confidence intervals and p values were calculated using univariate logistic regression.

Results: Overall, there was a significant correlation between clinical response and vessel distribution at all time points: a regular vessel distribution correlated with no response, a clustered distribution with partial response, and the dermoscopic absence of vessels with complete response. The presence of dermoscopic hemorrhagic dots was a potent predictor of favorable clinical response at the subsequent visit at all time points. Among lesions initially clinically responding and later recurring, 87.5% displayed dermoscopic dotted vessels despite the macroscopic remission.

Conclusion: Dermoscopy might be a useful additional tool for evaluating the response of psoriatic patients to biologic agents. Hemorrhagic dots represent an early predictor of clinical response, while the persistence or reappearance of dotted vessels might predict clinical persistence or recurrence, respectively.

Introduction

The induction of biologic agents targeting immunologic alterations of psoriasis significantly changed the management of the disease. With gathering evidence and experience on their safety and efficacy, these agents acquired an important role in the management of psoriatic patients, and their use expanded worldwide [1]. The assessment of response to treatment with biologics is mainly based on the calculation of the PASI score, which is almost universally used in studies and clinical trials [2]. In daily practice, the application of PASI score is restricted by its complexity, and the routine evaluation of treatment is typically based on the physician's global assessment and the patient's perspective, which is typically quantified with the DLQI form [2,3].

Dermoscopy represents an easily applicable clinical diagnostic method of well-documented value for the diagnosis of skin tumors [4]. In addition, dermoscopy has been shown to be a valuable tool for monitoring response of skin cancer to topical treatment, especially after the application of non-surgical modalities [5]. This is because it allows the visualization of alterations occurring in sub-macroscopical structures as a result of the applied treatment.

More recently, the application of dermoscopy expanded also to the field of inflammatory and infectious skin diseases [6-9]. There is mounting evidence that dermoscopy enhances the differential diagnosis between psoriasis and other inflammatory dermatoses, such as dermatitis, lichen planus and pityriasis rosea [6]. Furthermore, it has been assumed that dermoscopy might also be useful for monitoring the response of psoriasis to systemic drugs by providing early signs of response to treatment and by revealing residual disease or recurrence before it becomes clinically evident [8]. Undoubtedly, such beneficial results of dermoscopy would be clinically relevant, providing clinicians early information on disease activity, thereby helping them to optimize patient treatment management. However, this hypothesis has not been tested up to date.

The aim of this study was to investigate whether dermoscopic criteria observed in psoriatic lesions of patients under treatment with biologics could improve the assessment of the response to the applied treatment.

Methods

This was a prospective multicentric study conducted in three dermatology centers in Greece and Italy. Patients with severe psoriasis scheduled to receive a biologic agent were enrolled in the study. During the time period of the study, which was between September 2013 and June 2015, the four available biologic agents were adalimumab, etanercept, infliximab and ustekinumab. Involved clinicians were free to administer the agent of their choice based on standard clinical procedures, with the choice of drug not being at all influenced by the present study.

A target lesion located on the trunk or the extremities was selected from each patient to be documented and monitored. The target lesion could be of any size and lack significant hyperkeratosis. In case all the psoriatic lesions were highly hyperkeratotic, a keratolytic cream, without steroid, was applied one week prior to the enrollment. Exclusion criteria were: the previous application of topical treatment, with the exception of the keratolytic cream mentioned above, on the selected lesion or the administration of any systemic agent within the previous three months of enrollment.

A clinical and dermoscopic image was captured from the target lesion at baseline visit (T0). Follow up visits were scheduled after one month (T1), two months (T2) and six months (T3). During all the follow up visits, a clinical and dermoscopic image of the target lesion was captured. All dermoscopic images were captured with polarized light using Dermlite Photo System (3Gen, San Juan Capistrano, CA, USA). Minimal pressure was applied in order to preserve vessel morphology and to facilitate their visualization.

The clinical response of the target lesion was evaluated by the recruiting clinicians in all follow up visits (T1, T2, T3) as: not responding, partially responding or completely remitted, always as compared to the baseline visit. This means that there was the possibility for a lesion to be evaluated as completely responding at a certain time point and partially (or not at all) responding at a later point (recurrence).

The dermoscopic images were evaluated by two independent investigators, blinded to clinical information. In case of disagreement, a third investigator was involved. The dermoscopic variables were selected on the basis of available literature on dermoscopy of psoriasis and our initial observation that hemorrhagic dots represent a common finding in psoriatic lesions under treatment with biologic agents [6, 10-12]. An example highlighting the difference between hemorrhagic dots and the typical red dots of psoriasis is shown in Figure 1 and several additional examples of hemorrhagic dots in Figure 2.

During the follow-up visits, the distribution of red dot vessels was assessed as regular (i.e., equally covering all the surface of the lesion), clustered (i.e., grouped arrangement of dotted vessels in some areas of the lesion, while other areas displayed no vessels), or minimal, when only a few (<10) red dots could be seen either isolated or scattered on the lesion surface. White scales are also known as a frequent dermoscopic finding in psoriasis. However, the presence of this criterion was not assessed in our study, since the included lesions were intentionally selected to exhibit minimal scaling, allowing the best possible visualization of the underlying vessels.

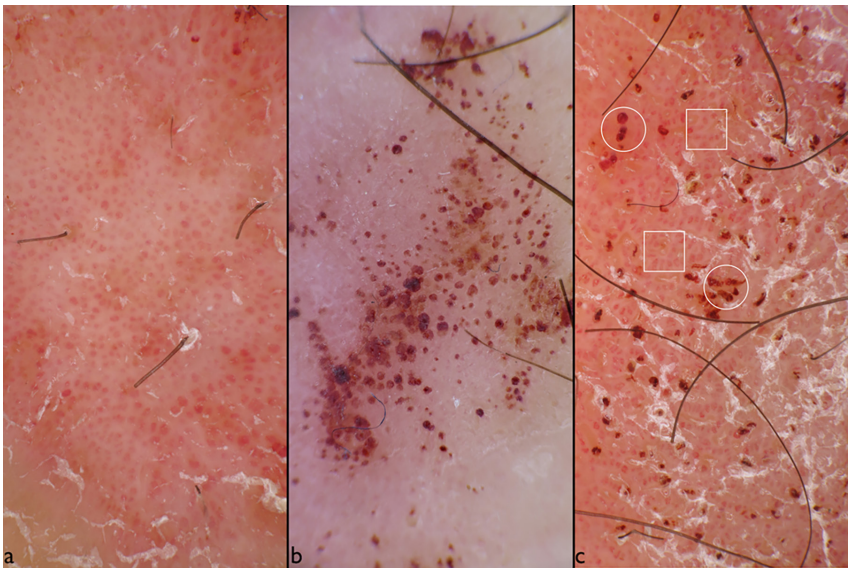

Figure 1. The difference between red dots and hemorrhagic dots. (a) The red dots (dotted vessels) of psoriasis before treatment. (b) Hemorrhagic dots in a psoriatic plaque under treatment. (c) Red dots (squares) and hemorrhagic dots (circles) in psoriatic lesion under treatment. [Copyright: ©2016 Lallas et al.]

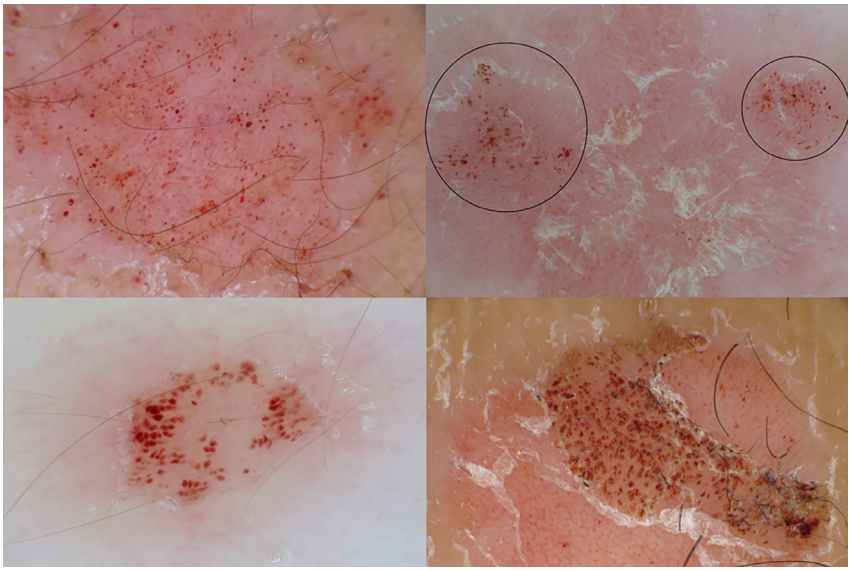

Figure 2. Examples of hemorrhagic dots. Their presence was strongly associated with a subsequent clinical response to treatment. [Copyright: ©2016 Lallas et al.]

Statistical analysis

The patients' sex, drug administered, lesion location, clinical response (no response, patial response or complete response), vessel distribution (regular, clustered, minimal or none) and the presence of the purpuric dots were the variables used. Absolute and relative frequencies for all variables were obtained. Non-parametric Pearson's Chi Square test was used for cross-tabulation comparisons. We used Spearman's rho coefficient to flag significant correlations, which were subsequently quantified. Odds ratios (OR), 95% confidence intervals (CI), and P values were calculated using univariate logistic regression with categorical coding. Alpha level was set at 0.05. Statistical analyses were performed using the IBM SPSS 23.0 package (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY, IBM Corp).

Results

Overall, 92 individuals were enrolled at baseline. Of them, nine patients were lost at follow-up before completing the designed study period, while in eight patients the treatment was terminated or changed because of adverse events. Of 75 finally included patients, 34 were men (45.3%) and 41 women (54.7%). Mean age at baseline was 48.7 years and did not differ significantly between genders. Of 75 target lesions, 45 were located on the trunk (60.0%) and 30 on an extremity (40.0%). The administered drugs were adalimumab in 31 patients (41.3%), etanercept in 20 patients (26.7%), infliximab in 11 patients (14.7%) and ustekinumab in 14 patients (17.3%).

No clinical response of the target lesion after one month of treatment was seen in 29 patients (38.7%), partial response in 34 (45.3%) and complete response in 12 patients (16%). After two months of treatment, the clinical response of the target lesion was assessed as absent in 16 patients (21.3%), partial in 31 patients (41.3%) and complete in 28 patients (37.3%). Finally, after six months of treatment, 11 target lesions (14.7%) were assessed as not responding, 23 (30.7%) as having responded partially and 41 (54.7%) as having remitted completely. During the study, clinical recurrence was detected in 8 target lesions, meaning that these plaques were assessed as completely responding at a time point and partially or not responding at a later point.

At baseline visit, all included lesions dermoscopically exhibited red dots distributed regularly and densely all over the surface of the lesion, while purpuric dots were present only in one case. The results of the dermoscopic analysis at all follow up visits are shown in Table 1.

Results of the clinical and dermoscopic analysis at follow-up visits

Overall, there was a significant correlation between clinical response and vessel distribution at each time point

Table 1. Results of the clinical and dermoscopic analysis at follow-up visits. [Copyright: ©2016 Lallas et al.]

Dermoscopic criteria	T1 (1 month)	T2 (2 months)	T3 (6 months)
Clinical response			
None	29 (38.7%)	16 (21.3%)	11 (14.7%)
Partial	34 (45.3%)	31 (41.3%)	23 (30.7%)
Complete	12 (16.0%)	28 (37.3%)	41 (54.7%)
Vessel distribution			
Regular	31 (41.3%)	14 (18.7%)	16 (21.3%)
Clustered	21 (28.0%)	19 (25.3%)	14 (18.7%)
Minimal	15 (20.0%)	22 (29.3%)	17 (22.7%)
None	8 (10.7%)	20 (26.7%)	28 (37.3%)
Purpuric dots	42 (56.0%)	31 (41.3%)	5 (6.7%)

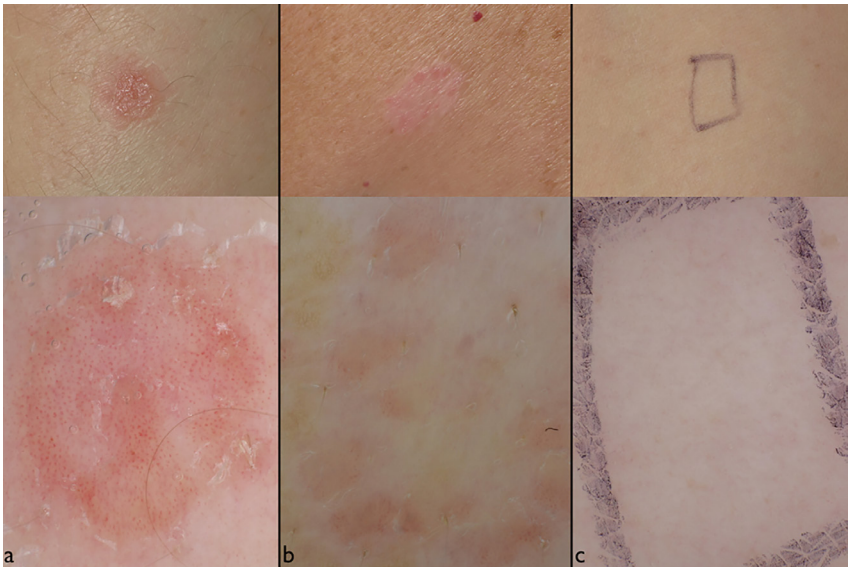

Figure 3. At follow-up visits: (a) Dermoscopy of lesions clinically assessed as non-responding usually revealed a regular distribution of red dots. (b) A strong association was found between partial clinical response and a clustered vessel arrangement in dermoscopy. (c) A complete clinical response was typically associated with a complete dermoscopic disappearance of vessels. [Copyright: ©2016 Lallas et al.]

(Figure 3). In detail, at all time points, a regular vessel distribution correlated with no response, a clustered distribution with partial response, and the dermoscopic absence of vessels with complete response (T1: Spearman's rho = -0.755, p<0.001; T2: rho=-0.677, p<0.001; T3: rho=-0.746, p<0.001).

Notably, 7 of 8 recurring lesions lacked a clinical-dermoscopic correlation, because at the visit when they were clinically assessed as completely responding, they displayed minimal or clustered vessels dermoscopically.

Several analyses were performed to investigate the possible correlation between the presence of hemorrhagic dots at one time point and the clinical response at following time points of the study. In particular, we investigated the association between the presence of hemorrhagic dots at T1 and clinical response at T2 and T3, as well as the presence of hemorrhagic dots at T2 and the clinical response at T3.

After multivariate regression, the presence of hemorrhagic dots at T1 posed 20-fold higher odds for partial response at T2 (OR=20.125, 95%CI: 3.73-108.62, p<0.001) and 10-fold higher odds for complete response at T2 (OR=20.818, 95%CI: 2.05-57.15, p=0.005). In addition, lesions displaying hemorrhagic dots at T1 had an 8-fold higher probability for partial response at T3 (OR=8.437, 95%CI: 1.46-48.85, p=0.017) and a 7-fold higher probability for complete response at T3 (OR=7.031, 95%CI: 1.34-36.82, p=0.021). Similarly, the presence of hemorrhagic dots at T2 was associated with a 11-fold higher probability for partial response at T3 (OR=10.91, 95%CI: 1.19-99.68, p=0.034) and an 8-fold higher probability for complete response at T3 (OR=8.636, 95%CI: 1.01-73.79, p=0.021).

Notably, due to limited sample size, we were not able to adequately quantify the latter associations within each subgroup of the four different drugs used. However, our descriptive results indicate that the predictive effect of hemorrhagic dots is not influenced by the administered drug.

Finally, no other parameter, including age, sex and location of the lesion, was significantly correlated with response at any time.

Discussion

Our results suggest that dermoscopy is useful in assessing and predicting treatment response of psoriatic lesions to treatment with biologic agents. Specifically, the appearance of dermoscopic hemorrhagic dots represents an early predictor of clinical response to treatment, while reappearance of dotted vessels correlate with disease recurrence (Figures 4 and 5).

Undoubtedly, the assessment of disease's response to treatment with biologic agents is based on the overall clinical examination. PASI score is the most commonly used tool for evaluating the disease severity and is almost universally used in studies and clinical trials [2]. However, PASI reduction has been shown to correlate poorly with the patient's perception of treatment success [3]. Effectively, in clinical practice, the evaluation of treatments and the decision for subsequent therapeutic plans are based on a more global assessment

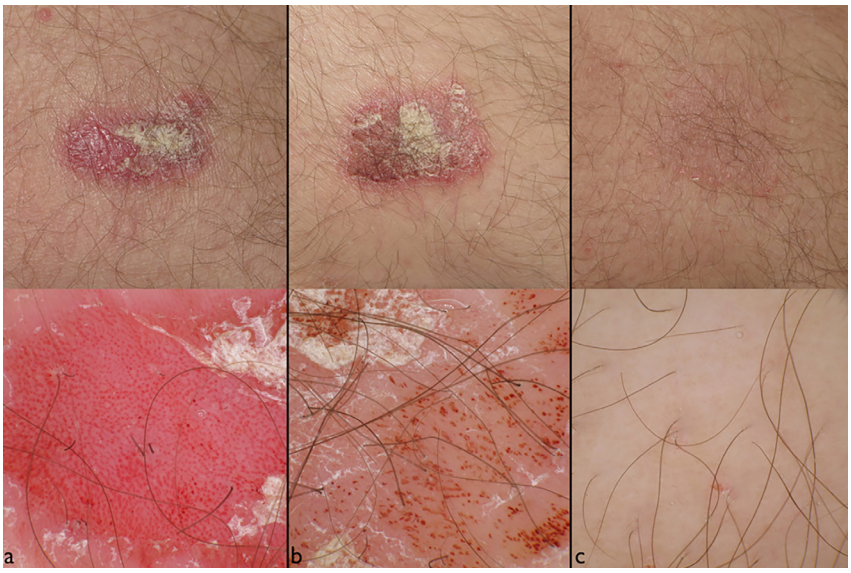

Figure 4. (a) A psoriatic lesion at baseline (T0). (b) No clinical response is observed after one month of treatment (T1). However, dermoscopy reveals numerous hemorrhagic dots. (c) One month later (T2), the lesion has clinically and dermoscopically remitted completely.

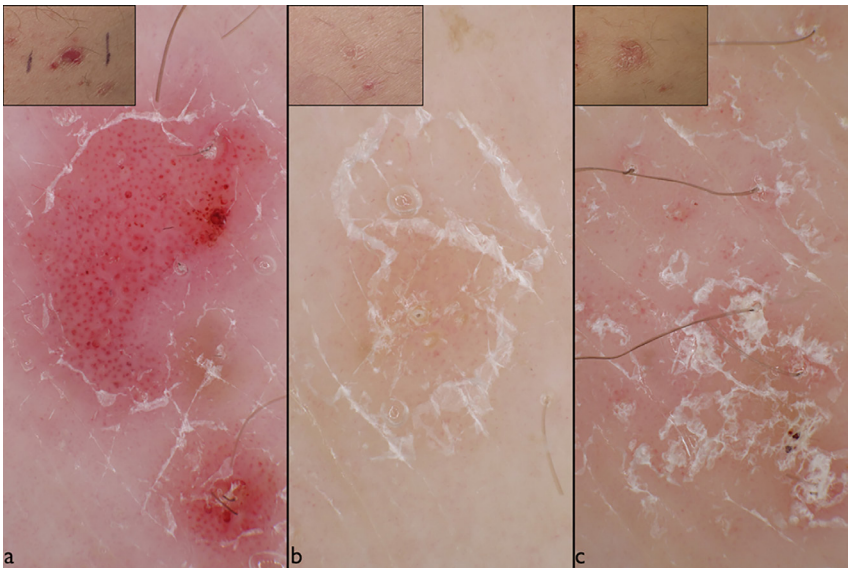

Figure 5. (a) A psoriatic lesion at baseline (T0). (b) After two months of treatment (T2), the lesion was clinically assessed as completely remitted. However, dermoscopy did not reveal the expected complete disappearance of vessels. (c) After four months (T3), the lesion had also recurred clinically. [Copyright: ©2016 Lallas et al.]

by the physicians in conjunction with the patient's perspectives and satisfaction.

The high efficacy of biologic agents significantly altered the perspectives of both clinicians and patients for therapeutic success. However, all biologic agents have been associated with treatment discontinuation in a considerable proportion of patients, with ineffectiveness and loss of efficacy being the commonest reasons [3,13-16]. Furthermore, the previous failure of a biologic agent was shown to represent a negative predictor of survival of the subsequent drug [3]. Considering the latter, as well as the limited range of biologic agents for severe psoriasis, developing and adopting strategies aiming to prolong the survival of these agents is considered one of the major goals for the near future. In this context, any reliable additional and early information on the disease activity and its response to treatment would be very useful for clinicians in optimizing therapeutic plans.

The dermoscopic pattern of psoriasis has been adequately investigated, with regularly distributed dotted vessels known to represent the dermoscopic hallmark of the disease [6,10]. Specifically, it has been demonstrated that all psoriatic plaques regularly display distributed dotted vessels, even when located on specific body sites such as the scalp, palms/soles and folds [10]. The universal presence of dotted vessels in psoriatic plaques has led to the suggestion that the absence of such a vascular pattern should exclude the diagnosis of psoriasis [9]. In addition, dermoscopy has been assessed as an accurate method to differentiate psoriasis from the erythematosquamous skin diseases, such as dermatitis, lichen planus and pityriasis rosea [6].

Although the latter data suggest that dermoscopy might be useful for recognizing clinically atypical psoriasis, this might not be clinically relevant for patients with moderate-to-severe disease, where the clinical diagnosis is usually straightforward, based on the typical morphology and distribution of skin lesions. However, our findings indicate that when these patients are treated with biologic agents, dermoscopy might provide useful information on the response to treatment and the disease activity. In detail, the appearance of hemorrhagic dots was shown to represent an early predictor of subsequent clinical response at all time points of our study. This finding might help clinicians to predict a favorable response to treatment even before clinical improvement appears or to expect a further improvement of lesions partially responding. This might reduce the risk of falsely assessing the drug as inefficacious in patients where clinical response appears later than the average time period.

Furthermore, our findings provide an initial indication that dermoscopy might enable an early detection of disease recurrence, since all recurring lesions in our study were characterized

by a lack of clinical-dermoscopic correlation. Specifically, although clinically assessed as completely responding, they dermoscopically displayed dotted vessels (minimal or in clusters). Indeed, at the subsequent visit they recurred also clinically. An early recognition of disease recurrence might be particularly relevant, since strategies to reinforce the drug efficacy do exist.

In conclusion, our results provide an initial indication that dermoscopy might be useful for evaluating the response of psoriatic patients to biologic agents. Hemorrhagic dots represent an early predictor of subsequent clinical response, while the persistence or reappearance of dotted vessels might predict a subsequent clinical recurrence. This information might improve the assessment of disease activity and serve the goal of prolonging the survival of biologic agents.

References

1. Rustin MHA. Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. Br J Dermatol 2012;167 Suppl 3:3-11. PMID: 23082810. DOI: 10.1111/j.1365-2133.2012.11208.x.
2. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23 Suppl 2:1-70. PMID: 19712190. DOI: 10.1111/j.1468-3083.2009.03389.x.
3. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol 2015;172(1):244-52. PMID: 25132294. DOI: 10.1111/bjd.13343.
4. Zalaudek I, Lallas A, Moscarella E, Longo C, Soyer HP, Argenziano G. The dermatologist's stethoscope—traditional and new applications of dermoscopy. Dermatol Pract Concept 2013;3(2). PMID: 23785649. DOI: 10.5826/dpc.0302a11.
5. Apalla Z, Lallas A, Tzellos T, et al. Applicability of dermoscopy for evaluation of patients' response to nonablative therapies for the treatment of superficial basal cell carcinoma. Br J Dermatol 2014;170(4):809-15. PMID: 24283541. DOI: 10.1111/bjd.12749.
6. Lallas A, Kyrgidis A, Tzellos TG, et al. Accuracy of dermoscopic criteria for the diagnosis of psoriasis, dermatitis, lichen planus and pityriasis rosea. Br J Dermatol 2012;166(6):1198-1205. PMID: 22296226. DOI: 10.1111/j.1365-2133.2012.10868.x.
7. Lallas A, Argenziano G. Dermatoscope—the dermatologist's stethoscope. Indian J Dermatol Venereol Leprol 2014;80(6):493-4. PMID: 25382503. DOI:10.4103/0378-6323.144141.
8. Lallas A, Zalaudek I, Argenziano G, et al. Dermoscopy in general dermatology. Dermatol Clin 2013;31(4):679-94. PMID: 24075553. DOI: 10.1016/j.det.2013.06.008.
9. Lallas A, Giacomel J, Argenziano G, et al. Dermoscopy in general dermatology: practical tips for the clinician. Br J Dermatol 2014;170(3):514-26. PMID: 24266695. DOI: 10.1111/bjd.12685.
10. Lallas A, Apalla Z, Argenziano G, et al. Dermoscopic pattern of psoriatic lesions on specific body sites. Dermatology 2014;228(3):250-4. PMID: 24556706. DOI: 10.1159/000357914.
11. Lallas A, Apalla Z, Tzellos T, Lefaki I. Dermoscopy in clinically atypical psoriasis. J Dermatol Case Rep 2012;6(2):61-2. PMID: 22826724. DOI: 10.3315/jdcr.2012.1102.
12. Vazquez-Lopez F, Kreusch J, Marghoob AA. Dermoscopic semiology: further insights into vascular features by screening a large spectrum of nontumoral skin lesions. Br J Dermatol 2004;150(2):226-31. PMID: 14996092. DOI: 10.1111/j.1365-2133.2004.05753.x
13. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol 2011;164(5):1091-6. PMID: 21219290. DOI: 10.1111/j.1365-2133.2011.10213.x.
14. Menting SP, Sitaram AS, Bonnerjee-van der Stok HM, de Rie MA, Hooft L, Spuls PI. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. Br J Dermatol 2014;171(4):875-83. PMID: 24673245. DOI: 10.1111/bjd.13001.
15. Esposito M, Gisondi P, Cassano N, et al. Survival rate of antitumour necrosis factor-α treatments for psoriasis in routine dermatological practice: a multicentre observational study. Br J Dermatol. 2013;169(3):666-72. PMID: 23647206. DOI: 10.1111/bjd.12422.
16. van den Reek JMPA, van Lümig PPM, Driessen RJB, et al. Determinants of drug survival for etanercept in a long-term daily practice cohort of patients with psoriasis. Br J Dermatol 2014;170(2):415-24. PMID: 24117023. DOI: 10.1111/bjd.12648.