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Analytical Assessment of TNF-Antagonist Early Effects on Psoriasis: *In Vivo* Real-time Reflectance Confocal Microscopy and Skin Capacitance Mapping

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Abstract

Objective: Treatment options for moderate to severe skin psoriasis have considerably progressed over the past decades with the widespread use of targeted biologicals including Tumor Necrosis Factor antagonists (TNFa). Objective and reliable analytical assessments of the disease course and the treatment efficacy are eagerly awaited.

Methods: To disclose initial therapeutic effects of the adalimumab TNFa in a group of 13 psoriatic patients. The analytical observations relied on two *in vivo* real-time non-invasive methods, namely Reflectance Confocal Microscopy (RCM) and skin capacitance mapping (SCM). The L^* colorimetric assessment of pictures was used for analytical assessments.

Results: At initiation and after a 6-week adalimumab treatment, the comparative values of both RCM and SCM disclosed significant improvements ($p<0.01$) in the quantitative parameters of the skin inflammatory condition in most of the 13 patients. The SCM gray level values appeared more sensitive than RCM parameters.

Conclusion: Clinicians could possibly take advantage from SCM and RCM for disclosing early signs of efficacy of any TNFa treatment for psoriatic lesions. It is expected that any failure or any decline in therapeutic efficacy would be disclosed quite early. These objective methods could be used for comparing with objectivity novel biologicals in clinical trials.

Keywords: Biological; Confocal microscopy; Skin capacitance Mapping; Psoriasis; Tumor necrosis factor antagonist

Introduction

Psoriasis is a common skin inflammatory disease further responsible for a series of comorbidities leading to the definition of a systemic psoriatic syndrome [1,2]. Its prevalence reaches about 2-4% of most world populations. The disease is far from being trivial as it is commonly involved in physical and psychological morbidity. The initial manifestations of skin psoriasis usually develop during adolescence and young adulthood. The onset often follows some triggering events such as a streptococcal throat infection. Following the initial skin lesions, the disease commonly tends to spread to various sites over the body [3]. By contrast, in a more restricted group of patients, lesions first develop later in life, typically pointing in the sixth and seventh decades. The various patterns of psoriatic syndrome progress with unpredictable alternances of exacerbations and remissions of the autoimmune pathobiology initiated and mediated by T-cells [1,4-6]. Psoriasis is fostered by peculiar activation of TH1 lymphocytes and CD123+ plasmacytoid dendritic cells releasing various pro-inflammatory cytokines [6-8]. Such a complex process probably correlates positively with the severity of both inflammation and the combined hyperplasia of the epidermis and upper dermal microvasculature [9].

In recent decades, progress in the knowledge on immunopathology has improved the understanding of psoriasis pathogenesis [1-4,8-12]. It fostered the development of new treatment options based on rational developmental designs. As a result, a series of critical important topical and systemic treatments are presently available for daily clinical practice in psoriatic patients. Inflammatory cytokines, particularly tumor necrosis factor (TNF) are targeted. Other treatment options are frequently introduced into the market, and they globally exhibit a favourable balance between efficacy and toxicity. In general, the quest for getting a healthy-looking skin has become nowadays an important issue in many psoriatic patients.

A range of methods are currently available for assessing treatment efficacy of skin psoriasis. They include among others the clinical presentation of the lesions, the psoriasis area severity index (PASI) and the quality of life index [13]. However, none of these scales accurately determines the global severity of the disease or the early signs of the growth/regression activity of selected individual lesions. Histo-pathological examination allows objective assessment of the effectiveness of treatment modalities at the epidermal, dermal and vascular levels [9]. However, such examination is invasive, time consuming, and costly. In addition, the histo-pathological

examinations are restricted to the status of a given tissue at the specific time of sampling. Thus, it is confined to a snapshot sight of the disease.

The aim of the present study was to explore early clinical signs of the effect of a 6-week treatment using a TNF antagonist (TNFa). Adalimumab (Humira®, Abbott) was the selected biological agent for treating evolving plaque type psoriasis. The *in vivo* non-invasive methods were reflectance confocal microscopy (RCM) [14-19], and skin capacitance mapping (SCM) [20-23].

Patients and Methods

The present observational study was approved by the Ethic Committee of the University Hospital of Liège. It was performed in accordance with the Declaration of Helsinki. Non-invasive observations were performed in 13 patients (7 women and 6 men) suffering from progressive moderate plaque type psoriasis. Their average age was 43 years (range: 32-47). They were followed up in a routine adalimumab therapeutic procedure in outpatient clinics. At entry in the treatment phase, the patients were informed about the aims and procedures of RCM and SCM image captures. Two untreated patients were involved as controls for the technical procedures. The present internal-controlled analytical non-invasive observations were conducted with the understanding and consent of the volunteers.

Psoriatic lesions corresponded to enlarging plaques unresponsive to previous systemic treatments. The patients were out of topical and systemic treatments for at least one month prior entering the observational study phase. Patients who were immuno-compromised or taking drugs at risk of psoriasis exacerbation (lithium, beta-adrenergic blocker agents, anti-malarials) were not included in the study protocol.

Small plaque psoriasis located on the arms was selected for RCM and SCM evaluations. Any change in the structure of the stratum corneum (SC) is indeed frequently associated with alterations of both its barrier function and water holding capacity. The selected lesions were not covered by a thick hyperkeratosis. A control area of apparently normal skin was considered at least 4 cm from the lesional site. At entry in the observational phase (T0) and 6 weeks after initiating the adalimumab treatment (T6), the PASI score was calculated, and both RCM and SCM were recorded.

In vivo RCM imaging used the Viva scope 1500® (Mavig Gmbh, Munich, Germany). Examinations were performed at a wavelength of 785 nm. SCM was obtained using the Moisture Map MM-100 prototype (CK Technology, Visé, Belgium). Exploratory data analysis was performed using the two-sided paired Student t test. A p value lower than 0.05 was considered statistically significant.

In vivo real-time reflectance confocal microscopy

RCM is a non-invasive, high-resolution method providing *in vivo* imaging of the skin [14-19]. RCM provides real-time recordings of cell shapes and overall structure of superficial tissues down to a depth of about 200 µm. The images are captured in horizontal planes. The observed skin tissues are not subjected to chemical fixation and staining. Thus, their native structures remain intact. Furthermore, RCM allows repeat observations of the same location. Therefore, the findings shed light on any dynamic aspect including tissue growth, lesion progression, and response to treatment. One of the emerging and intriguing applications of RCM is the *in vivo* evaluation of disease progression. RCM findings in psoriasis focus on diagnostic criteria of the skin conditions and on assessments of the dynamics of inflammatory processes under or out of therapy [24-29]. Thus, the RCM advantage appears obvious in the assessment of the dynamics of treatment responses [29].

In the present study, the RCM criteria for psoriasis corresponded to previous RCM studies for assessing the treatment response in psoriasis [24-26]. Five contiguous fields were scrutinized in each patient. We looked for well-established psoriasis RCM characteristics including the number of para-keratotic cells and spongiotic foci, the proportion of regular/irregular honeycomb-like aspects in the SC, the density in inflammatory cells, and the proportion in edge/non-edge dermal papillae [29]. More precisely, spongiosis shows wider intercellular spaces that appear with increased brightness. The honeycomb pattern presents as grill-like clearly demarcated keratinocyte outlines in the upper part of the stratum spinosum. Inflammatory cells appear as round on polygonal moderately refractile small cells. Edge dermal papillae appear as dark structures surrounded by a bright contour corresponding to a single layer of basal cells. By contrast, the non-edge dermal papillae lack the bright contour. Swelling of the dermal papillae already visible at the upper level of the living epidermis, is a sign of papillomatosis combined with the presence of dilated and tortuous vessels [25]. Previous studies have revealed a high correlation between RCM findings and histo-pathological features of plaque psoriasis [24-26]. In the present study, quantitative analytical assessments were performed using a tristimulus color analysis of RCM images. The CIE L^* parameter was measured by the Visi-Chroma VC-100 (Biophotonics, Lessines, Belgium).

Real-time skin capacitance mapping

SCM records some specific electrometric properties of the skin that are influenced by the SC texture and micro-relief, its water and electrolyte contents, and by sweat production. The capacitance method is rooted on water permittivity, which is higher than for most bio-molecular compounds [20-22]. In the present study, the SkinChip® device and the Moisture Map MM100 prototype were used. A total of 92160 micro-capacitors were dispersed every 50 µm on a 18×12.8 mm sensor probe. The device was closely applied to the skin surface for a maximum of 5 s in order to avoid any interference with both the water flux and content inside the SC. Real time measurements were acquired and displayed on a computer screen where the capacitance values were transformed into a range of 256 gray levels to form a non-optical image. In psoriatic plaques, a great variety of skin surface patterns of hydration and topography is expected [22]. The darker pixels represent hydrated high capacitance spots. Clear pixels represent dry spots of the skin as well as depressions and lines in the SC micro-relief, impeding the contact between the probe and the skin.

The typical SCM aspect of psoriasis lesions corresponds to a patchwork of darker and lighter spots. In each volunteer, the relative area (%) of the darker spots was averaged for 5 continuous fields. Results were expressed as means and standard deviations (SD) for the relative area under consideration. The mean areas at T0 and T6 were compared by the Student's t-test. Results were considered to be significant at the 5% critical level ($p<0.05$). All calculations were performed using SAS (version 8.2 for Windows) and S-PLUS (version 6.1) statistical packages.

TNFa and skin psoriasis

TNF plays a central role among the various cytokines present in excess in psoriatic lesions. TNF is produced by a wide range of immune and non-immune cells. It exerts broad inflammatory effects, up regulating both innate and adaptive immunity. It activates a range of cells, including keratinocytes and dermal dendrocytes. TNF triggers the production of IL-1, IL-6, IL-8 and NF-κB, initiating a cascade of inflammatory events.

Adalimumab is a monoclonal antibody to TNF that has proven its activity on recalcitrant psoriasis including some of its comorbidities [1,12,30-34]. It is composed of human heavy- and light chain variable regions that confer specificity to human TNF, as well as human IgG1 heavy-chain and kappa light-chain sequences. The drug binds specifically to TNF and neutralizes its biological function by blocking its interaction with the p55 and p75 cell surface TNF receptors [1]. In addition, adalimumab modulates biological responses induced or regulated by TNF. After adalimumab treatment, levels of acute-phase reactants of inflammation such as the C-reactive protein, and serum cytokines rapidly fade out.

In clinical settings, adalimumab is self-administered subcutaneously. The recommended dosing regimen for moderate-to-severe psoriasis encompasses one 80 mg injection at initiation of treatment, followed by 40 mg every other week for maintenance treatment, beginning 1 week after the induction dose.

Results

The mean PASI score remained globally unmodified between baseline and T6. At T6, the PASI score was decreased ($p<0.05$) in 8 of the 13 patients. It was increased in 2 patients, and remained unmodified in 3 patients. One case of adalimumab-associated adverse effect occurred. It corresponded to a paradoxical new onset of cutaneous psoriasis observed in one woman. It consisted in palmar lesions evoking a troublesome palmar pustulosis.

At the SCM examination, most examined psoriatic lesions exhibited an overall whitish aspect in reticular and cobbled patterns indicating low conductance. The whiter areas were not sharply circumscribed, and they merged with foci of moderately higher capacitance. In some instances, the low capacitance areas were contiguous to a contrasting, sharply circumscribed, high capacitance area. The latter aspect often corresponded clinically to a more erythematous area. At T0, the relative area of individual high capacitance values showed a wide distribution around the means of the gray values (22.1 ± 8.4%). At T6, the capacitance values were more steeply distributed around the mean (8.2 ± 3.1%).

At the RCM examination, both the patterns and the relative areas of darker spots showed large intra-lesional variations. When pooling all data (5 sites) in the 23 patients before and after the 6-week adalimumab therapy, a global significant difference ($p<0.01$) was yielded in the mean relative areas of darker spots which were abated during the treatment phase (Figure 1a and b).

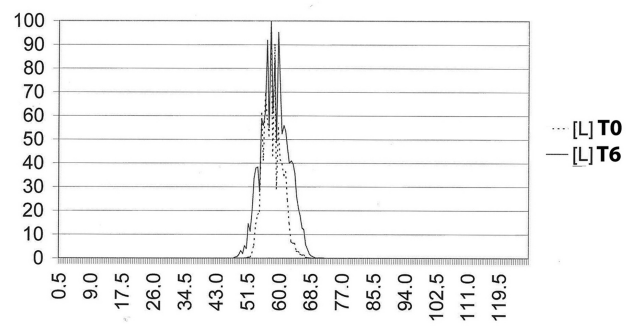

Figure 1a: L* colorimetry of pooled RCM pictures of a psoriatic plaque at inclusion (T0) and at completion of a 6-week period (T6). Untreated patient revealing the absence of changes in the L* value.

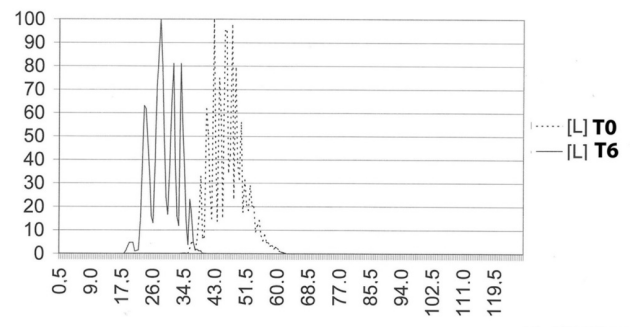

Figure 1b: L* colorimetry of pooled RCM pictures of a psoriatic plaque at inclusion (T0) and at completion of a 6-week period (T6). Adalimumab-treated patient showing a marked L* decrease over the 6-week treatment.

Compared to the normal control site, lesional skin at T0 and T6 showed obvious differences. The numbers of para-keratotic cells was significantly higher at T0, significantly reduced ($p<0.05$) at T6 and considerably lower ($p<0.001$) on normal skin. Similar trends were found with spongiosis. The ratio regular / irregular honeycomb sites were reduced ($p<0.05$) with the treatment duration. The number of intra-epidermal inflammatory cells followed the same trend in reduction over time in lesional skin. No significant difference was yielded in the ratio edge / non-edge dermal papillae. Only stochastic correlations were observed between each of the RCM parameters and the global PASI score.

Discussion

Both the clinic-pathological presentations of skin psoriasis vary according to a series of factors including the type and body location of the lesions. The PASI score is considered to be appropriate for evaluating the global severity of plaque-type psoriasis. However, in some instances, PASI only represents a gross evaluation, calling for more detailed information [22]. Indeed, the reliability of the visual grading method alone that is most commonly used in this scoring system is relatively poor. Important variations exist between the

estimates from clinicians, thus somewhat impeding the scoring reproducibility. Some objective and quantitative approaches have been developed to improve the validity of the PASI scoring system [35]. In addition, new assessment methods are welcome because the current and upcoming treatments offering new opportunities emphasize the need for objective and specific assessment of psoriasis evolution [22]. In the current study, no sharp correlation was established between the global PASI score and the analytical parameters of RCM and SCM.

A number of clinical trials on TNFa were performed with a special focus on plaque type psoriasis. Subjective clinical observations and close monitoring were made with limited sensitivity in the early efficacy assessment. In clinical practice, an optimal TNFa use is only guaranteed by the clinical experience of the consultant. The present study was an attempt at increasing the assessment sensitivity on the skin lesions. It remains that the impact of TNFa on psoriatic comorbidities is not explored by this way.

A previous study using non-optical SCM on untreated psoriasis plaques suggested some heterogeneity in the quality and physical properties of the SC in psoriatic lesions. Three main distinct gross levels of capacitance were revealed, each of them probably corresponding to structural and functional differences in the patho-biological stage of evolution of psoriasis [22]. A vast proportion of the whitish areas represented low capacitance structures in the SC. They probably corresponded to xerotic hyperkeratotic areas. These dryer areas formed different patterns of arrangement, merging with other fields showing a medium level capacitance. They were tentatively interpreted as para-keratotic foci admixed with neutrophils. Indeed these epidermal and inflammatory cells are likely more hydrated than the corneocytes cuffing the hyperkeratotic layer. In addition, psoriatic lesions showed other areas exhibiting a third level of much higher capacitance. These foci were sharply circumscribed and corresponded to erythematous parts of the lesions. These fields possibly fit with the site of superficial vascular hyperplasia and ectasia, and/or to more severe inflammation [22]. Whatever the case, the high capacitance probably results from serum leakage from the microvasculature, finally steeping the SC. This aspect suggests the presence of active pathogenic mechanisms in psoriasis. SCM was presently used for monitoring psoriatic lesions in a rapid and non-invasive way. The effects of adalimumab treatment on some physical characteristics are highlighted in that way. The method does not represent a diagnostic tool, but rather reveals some physio-pathological and functional features. TNF deposits are increased in the skin and various other tissues involved by the psoriasis syndrome. TNFa represent powerful and effective options for the treatment of moderate to severe plaque type psoriasis. In addition, these drugs are active for curbing some of the comorbidities, particularly arthropathies and Crohn's disease [1,2]. The effectiveness and safety of a set of TNFa strategies have been established in randomized controlled trials. Such data about biological therapies derive from randomized clinical trials and local registries. It remains that TNFa do not always fully control psoriasis activity. This is either due to non-responsiveness or loss of response in time. The present observations are in line with such events in the time-window defined at 6 weeks. The paradoxical range of psoriasis as observed in a single patient remains poorly understood [1,3,36,37] and should ideally be diagnosed early in its development to avoid burdening morbidity.

The present SCM findings confirm a previous report [22] contrasting 3-level capacitance of the SC in psoriatic lesions. The vast proportion of the whitish areas represented low capacitance structures in the SC probably corresponding to hyperkeratotic fields. These low hydration areas formed different patterns of arrangements, merging with other spots showing a medium level capacitance. These latter areas were tentatively interpreted as para-keratotic foci admixed with inflammatory cells which are presumably more hydrated than corneocytes. In addition, psoriatic lesions showed other areas exhibiting a third level of much higher capacitance. These foci were sharply circumscribed and apparently corresponded to an erythematous aspect of the lesions.

Overall, real-time RCM likely provides information for managing individual patients in the heterogeneous complexity of the psoriasis syndrome. However, it has some limitations in the diagnosis of the inflammatory skin conditions. It remains that a precise and reproducible identification of cellular types, the evaluation of nuclear changes and other subcellular structures are currently still difficult or even impossible [19]. Nevertheless, the effectiveness of RCM has been shown in the follow-up of some treatment responses [18,27-29,38,39].

The current study probably illustrates an anti-inflammatory effect of adalimumab in the majority of the treated patients at the issue of a 6-week treatment. Such findings call for further randomized controlled clinical trials with different TNFa in a substantial number of patients. By that way, objective comparisons between different therapeutic modalities could be performed. This might provide important insights into the real effectiveness of the treatments in a clearly defined time-window. In addition, the same methods could help detecting and monitoring the occurrence of some early adverse events.

Clearly the present non-invasive analytical methods have no specific diagnostic value. They only reveal some biological effects that are not restricted to psoriasis. From a clinical practice point of view, a preliminary careful diagnostic approach is warranted and expert dermatologist opinion required excluding other skin disorders mimicking clinical features of psoriasis.

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