Acta Derm Venereol 2015; 95: 432–438

INVESTIGATIVE REPORT

Psoriasis and Skin Pain: Instrumental and Biological Evaluations

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The prevalence of skin pain and the molecular mechanisms responsible for pain in psoriasis remain unclear. This study assessed skin pain in 163 patients (98 males, 65 females, range 18–81 years) with plaque psoriasis, evaluating: the subjective/objective features of this symptom compared with clinical severity of the disease; and the role of interleukin (IL)-33, (involved in both psoriasis and pain pathogenesis), in psoriasis-related pain. Clinical measures used were a questionnaire, plaque Physician Global Assessment (PGA) index, pressure algometry to measure pain threshold and tactile/thermal sensitivity test. IL-33 gene expression was examined *in vivo* (*n*=12) in patients skin and through an *ex vivo* model of nociception using sodium dodecyl sulphate. Of the psoriatic patients 43.6% reported skin pain during the previous week; itchy, unpleasant, aching, sensitive, hot/burning, tender and cramping were the most reported qualities. Patients' pain threshold decreased with increasing PGA index and pain intensity. Sensitivity to touch/heat was reduced in lesional skin, compared with unaffected psoriatic skin. IL-33 expression was increased in lesional skin of patients reporting pain and in the *ex vivo* system. In conclusion, symptoms of skin pain should be taken into account in the management of psoriasis. *Key words: psoriasis; skin pain; pressure algometer; interleukin-33.*

Accepted Sep 1, 2014; Epub ahead of print Sep 2, 2014

Acta Derm Venereol 2015; 95: 432–438.

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Psoriasis is a chronic inflammatory skin disease; it is the most prevalent autoimmune disease in Italy, affecting approximately 2.1% of the population (1). Although rarely fatal, a high proportion of psoriatic patients report severe skin discomfort, sleep disturbance, psychological distress and reduced quality of life (QoL) due to their psoriasis (2–6). Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (7). Skin pain is reported by up to 42% of patients with psoriasis (2, 8, 9). Psoriatic patients with bodily pain have been shown to report a negative impact on QoL comparable to those of patients with heart disease and diabetes (10–17). In particular, pain is reported by female, older patients, or by those with less education, chronic co-morbidities, more severe or longer duration psoriasis (10–12, 14, 16).

Psoriasis Area and Severity Index (PASI) only partly explains changes in skin pain intensity; hence, skin pain intensity cannot be explained merely by erythema, induration, desquamation and affected body surface area (18). For example, patients experience less severe psoriasis and pain in warm, sunny climates (19). Further studies show that pain perception is influenced by psychological distress (e.g. anxiety, depression, anger), withdrawal from social settings and work, negative beliefs about symptoms or disease, and poor coping strategies (10, 20, 21).

Little is known about the mechanisms of cutaneous pain in psoriatic patients. Interleukin (IL)-33, a recently identified member of the IL-1 family, is considered to be an endogenous "alarmin" released by necrotic cells in response to tissue injury or damage. However, this release was thought to be too passive for the wide range of activities of IL-33. It has also been reported as a pain mediator in immunized mice (22) and contributes to inflammatory pain triggered by a variety of phlogistic agents (23, 24). Since we have previously identified a pro-inflammatory role of IL-33 in psoriasis (25), we focused on this cytokine as a good candidate for investigation of its potential involvement in psoriatic nociception.

The aim of the study was to characterize the subjective and objective features of skin pain in patients with psoriasis and to explore its underlying pathophysiological mechanisms.

MATERIALS AND METHODS

Sample and setting

The clinical section was designed as a case-control study. The protocol was approved by the ethics committee of the University of Naples Federico II. After obtaining written informed consent, adult patients (> 18 years of age), with plaque psoriasis attending the Psoriasis Care Center of the Outpatient Clinic of the Section of Dermatology, University of Naples Federico II, between July 2012 and October 2013 were enrolled. Exclusion criteria were psoriatic arthritis, other skin or internal disorders that might cause pain, cognitive difficulty preventing questionnaire completion, or psychiatric diseases that could alter

 doi: 10.2340/00015555-1965
 ISSN 0001-5555

the subjective perception of pain. Patients did not receive any systemic or topical treatment for psoriasis for at least one month before the study onset.

A total of 257 adult patients with psoriasis were screened. A total of 72 patients were excluded for the following reasons: erythrodermic psoriasis ($n = 2$), pustular psoriasis ($n = 4$), psoriatic arthritis ($n = 22$), concomitant skin diseases ($n = 19$), ongoing treatment ($n = 17$), psychiatric diseases, including depression ($n = 5$), and cognitive impairment ($n = 3$). Of a total of 185 eligible patients, 163 agreed to participate. A total of 287 healthy controls with matching demographic characteristics were recruited.

Study procedures

Following clinical assessment, patients were screened for skin pain with a questionnaire, and then investigated with digital algometry and sensitivity tests. The role of IL-33 in pain was assessed through *in vivo* and *ex vivo* laboratory procedures.

Instruments

Psoriasis severity. An overall clinical examination of psoriasis was performed and determined as PASI (26). Moreover, for each patient who reported pain, the Physician Global Assessment (PGA) index (26) was used only to assess target plaques localized on the scalp, lumbosacral region and palmar area. Specifically, each psoriatic plaque chosen for the subsequent instrumental evaluation was graded (from 0: "no evidence" to 5: "severe") for induration, erythema and scaling. The sum of the 3 scales was divided by 3, to obtain a final target lesion PGA score.

Qualities of skin pain. Psoriatic patients indicated, using a yes/no format, if they had experienced skin pain over the past week. In case of a positive response, they completed the so-called Pain Qualities Assessment Scale (PQAS) (27), comprising 20 queries (including a question about pain intensity), to evaluate how much of each different pain quality and type, the patient may have felt, on average, over the last week. The questionnaire also assessed the presence of "itchy pain"; with this reference, it was assumed that PQAS questionnaires for patients who did not report any pain quality except for the "itchy" quality were considered positive for itch and were not included in the pain analysis. On the other hand, PQAS of patients who reported an itchy sensation together with other pain qualities were considered positive for itchy pain.

Moreover, one of the queries asked for an estimate of the severity of deep and surface pain; in order to help patient to distinguish between "surface" and "deep" pain, we explained that the former is generally highly localized, hot and burning, whereas the latter is usually dull and may be felt as if it comes from deep inside the body. Since, as specified above, subjects presenting other diseases different from psoriasis that possibly caused the pain were excluded, patients did not need to differentiate skin pain from other pain types.

Patients answered each of 20 pain (quality and spatial) descriptor domains expressing a score on a numerical rating scale (NRS) ranging from 0 ("absence of pain" or "absence of the sensation") to 10 ("the worst pain imaginable" or "the most [descriptor] pain sensation imaginable"). According to pain intensity, NRS limits for mild, moderate and severe pain were 1–3, 4–7 and 8–10. The PQAS also included a query for assessing the temporal pattern of pain (intermittent, variable or stable). A time of 30 min was reserved for each patient for the compilation of PQAS.

The questionnaire had been properly adapted for Italian patients using the Linguistic Validation Method (28), with the help of a previous work by Negri et al. (29), about the validation of the Italian version of a "neuropathic pain scale", which shares many features with PQAS. In particular, PQAS underwent a translatability review to discover and assess any potential concept or wording issues that might arise during translation and adaptation for Italian psoriatic patients. The questionnaire was then translated from English to Italian through a collaboration between English and Italian certified mother-tongue translators. The translation was then reviewed by a dermatologist (C.P.), who verified that references to medical conditions and pain features were expressed using understandable terms for Italian patients. Moreover, the translated and reviewed questionnaire was actively tested in a sample of 15 psoriatic patients attending our outpatients clinic, through cognitive debriefing interviews, ensuring that items were culturally and contextually acceptable to the Italian population.

Experimental algometry and sensitivity tests. A pressure digital algometer (FPK, Wagner Instruments, Greenwich, CT, USA) was adopted. Scalp, lumbosacral and palmar regions were chosen to measure subjects' pain, because of their different sensory connections to the brain, as represented in Penfield's sensitive homunculus (30). For each body region examined, the instrument was applied on: (*i*) the psoriatic plaque (lesional skin), (*ii*) the perilesional skin, and (*iii*) the unaffected skin (non-lesional) at a distance of 10 cm from the evaluated plaque.

The pressure stimulus was increased until the subject said "stop", at the minimum pressure that induced pain. The algometer reading at that time was recorded as pain threshold, expressed as kilogram-force (kgf; 1 kgf = 10 Newtons (N)). In addition, the sensitivity to tactile and thermal stimuli was assessed in lesional, perilesional and non-lesional psoriatic skin, by applying a gauze dry or soaked with cold (20°C) or warm (40°C) water (31).

Similarly, the pain threshold and sensitivity to tactile and heat stimulus were measured in the control study group.

Biological investigation

In vivo. Twelve subjects (6 males and 6 females) were selected from the group of 163 psoriatic patients, according to the following criteria: (*i*) PASI <10, (*ii*) PGA of the lumbosacral region plaques ranging from 3 to 5, and (*iii*) absence of pain (NRS: 0) or severe pain (NRS: 8–10) at PQAS.

Patients underwent skin punch biopsy (3 mm diameter) in a lesional plaque and in an unaffected site localized at distance. Skin biopsies (3 mm) of 3 healthy subjects with no evidence of inflammatory diseases, who were undergoing plastic surgery, were used as controls. Each skin biopsy was processed for quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) in order to investigate IL-33 gene expression at the skin level. We firstly compared IL-33 mRNA expression in lesional and non-lesional skin of psoriatic patients (without discriminating the presence/absence of pain) with that of healthy controls. Then, we compared IL-33 mRNA expression in psoriatic skin from patients reporting severe pain (NRS: 8–10) and patients without pain (NRS: 0) at PQAS.

Ex vivo skin organ culture. Skin biopsies from 3 healthy subjects undergoing plastic surgery were cultured as follows: a hole was punched in a transwell filter (pore size 1 μm; Beckton Dickinson Labware, Franklin Lakes, NJ, USA). Each biopsy was inserted into the hole, and the filter containing the biopsy was placed in a 12-well culture plate (Beckton Dickinson Labware) containing 1 ml Dulbecco's modified Eagle's medium (DMEM, Gibco, Grand Island, NY, USA) containing 10% FBS (Gibco), 2 mM L-glutamine (Gibco) and antibiotics (100 IU/ml penicillin G, 100 μg/ml streptomycin, Gibco) with the epidermis facing upwards at the liquid-air interface and the dermis suspended in the culture medium. IQ chamber filter

paper discs (Chemotechnique Diagnostics, Vellinge, Sweden), impregnated with Sodium Dodecyl Sulphate (SDS, 25 µl) at non-cytotoxic concentrations (2 and 4 mM) (Sigma Chemical Co., St Louis, MO, USA) or vehicle (water) only, were applied topically to the uppermost surface of cultured skin for 72 h. The biopsies were incubated at 37°C in a humidified atmosphere containing 5% CO_2.

RNA extraction, cDNA synthesis and qRT-PCR. Skin biopsy specimens from psoriatic and healthy subjects were snap-frozen in liquid nitrogen and stored at –70°C before RNA extraction. Total mRNA was isolated using the RNAasy Mini Kit (Qiagen, Doncaster, Australia) according to the manufacturer's instructions. cDNA was prepared using Transcriptor High-fidelity cDNA Synthesis Kit (Roche, Indianapolis, IN, USA). qRT-PCR (LightCycler, Roche, Indianapolis, IN, USA) was performed to confirm differences in the expression level of IL-33. Amplification of the expected size fragment was confirmed by gel electrophoresis and melting curve analyses. Relative mRNA expression levels were calculated with the delta-delta Ct method (32) and normalized to housekeeping 18S ribosomal mRNA expression.

Statistical analysis

All statistical analyses were performed using GraphPad Prism 4.0 (GraphPad Software Inc, La Jolla, CA). Student's *t*-test or Mann-Whitney *U* test were used to calculate statistical differences. Comparison of biopsies from lesional vs. non-lesional psoriatic skin was performed with Wilcoxon matched pairs test. Values of $p < 0.05$ were considered significant.

RESULTS

Demographic and clinical characteristics

The psoriatic patients comprised 98 (60.1%) men and 65 (39.9%) women, mean age 48.3 (range 18–81) years. The mean PASI score was 7.1 ± 4.8, and the mean plaque PGA score was 2.8 (range 0.6–5). There were 287 healthy controls (165 (57.4%) males and 122 (42.6%) females; mean age 51.8 (range 18–85)).

Symptom qualities

A total of 71 (43.6%) patients with psoriasis reported skin pain during the previous week, with a mean intensity score (NRS) of 7.1 (Table I). The most frequently reported pain qualities were: itchy (95.8%), unpleasant (94.4%), aching (83.3%), sensitive (77.5%), hot/burning (73.2%), tender (66.2%) and cramping (60.6%). The severity scores for these qualities ranged from 3 to 7.5 (Table II).

Responses of patients with psoriasis to PQAS were analysed focusing on pain intensity vs. itchy pain scores. Twenty percent of patients reported an identical score (on the 0–10 NRS) for both items, 45% reported a similar score (i.e. difference less than or equal to 2), whereas 35% of patients reported totally different scores. With reference to the latter category of patients, 28.6% experienced pain, but did not describe it as "itchy pain".

Table I. *Prevalence and intensity of skin pain in 163 patients affected with psoriasis*

Response	*n* (%)	Pain intensity[a] Score 0–10 Mean ± SD
Yes	71 (43.6)	7.1 ± 3.2
No	92 (56.4)	Not applicable
Total	163	Not applicable

[a] Patients indicated, using a yes/no format, if they had experienced skin pain over the past week. In case of a positive response, they also specified pain intensity. SD: standard deviation.

Estimation of the severity of deep vs. surface pain showed that the latter was reported more frequently (45.1% vs. 90.1%) with a mean score of 5.4 (Table II). Concerning the intensity of clinical pain over time, 3 patterns were recognized: 49.3% of patients described variable pain (a constant background pain, the intensity of which varied from time to time), 36.6% of patients experienced intermittent pain (they sometimes felt pain, but had pain-free moments), whereas only 14.1% of interviewed subjects reported stable pain (Table II).

Moreover, patients reporting severe pain in the questionnaire had a higher PASI score than patients with no pain (7.2 ± 3.3 vs. 3.0 ± 1.7, data not shown).

Algometry and sensitivity tests

Pressure algometry was used to measure the pain threshold of patients with psoriasis who reported pain on the PQAS (Fig. 1). In the scalp and palmar regions of

Table II. *Results of Pain Qualities Assessment Scale (PQAS) questionnaire in 71 psoriatic patients with pain*

Pain characteristics	*n* (%)	Score 0–10 Mean ± SD
Sharp	25 (35.2)	2.4 ± 3.6
Hot/burning	52 (73.2)	5.0 ± 3.6
Dull	1 (1.4)	0.1 ± 0.8
Cold	11 (15.5)	0.9 ± 3.4
Tender	47 (66.2)	4.8 ± 2.8
Sensitive	55 (77.5)	5.4 ± 3.4
Itchy	68 (95.8)	7.5 ± 2.8
Shooting	17 (23.9)	1.5 ± 3.0
Numb	24 (33.8)	2.3 ± 3.5
Electric	24 (33.8)	1.9 ± 3.1
Tingling	21 (29.6)	3.8 ± 3.5
Cramping/tight	43 (60.6)	3.0 ± 3.5
Radiating	33 (46.5)	3.1 ± 3.7
Throbbing	34 (47.9)	1.4 ± 3.0
Aching	62 (87.3)	6.6 ± 3.4
Heavy	25 (35.2)	2.3 ± 3.4
Unpleasant	67 (94.4)	7.4 ± 2.8
Deep	32 (45.1)	2.5 ± 3.3
Surface	64 (90.1)	5.4 ± 2.8
Time qualities		
Intermittent	26 (36.6)	Not applicable
Variable	35 (49.3)	Not applicable
Stable	10 (14.1)	Not applicable

Patients expressed how much of each different pain quality and type they may have felt, on average, over the past week. SD: standard deviation.

patients with a plaque PGA score ranging from 3 to 5, a lower pain threshold was registered in lesional and perilesional skin, compared with the same body areas in healthy controls. In the palmar region, moreover, a lower pain threshold was found in patients with a plaque PGA score ranging from 2 to 3, but exclusively in lesional skin. In all examined body areas, the unaffected skin of psoriatic patients seemed to present a slightly reduced pain threshold compared with the control population, albeit not statistically significant.

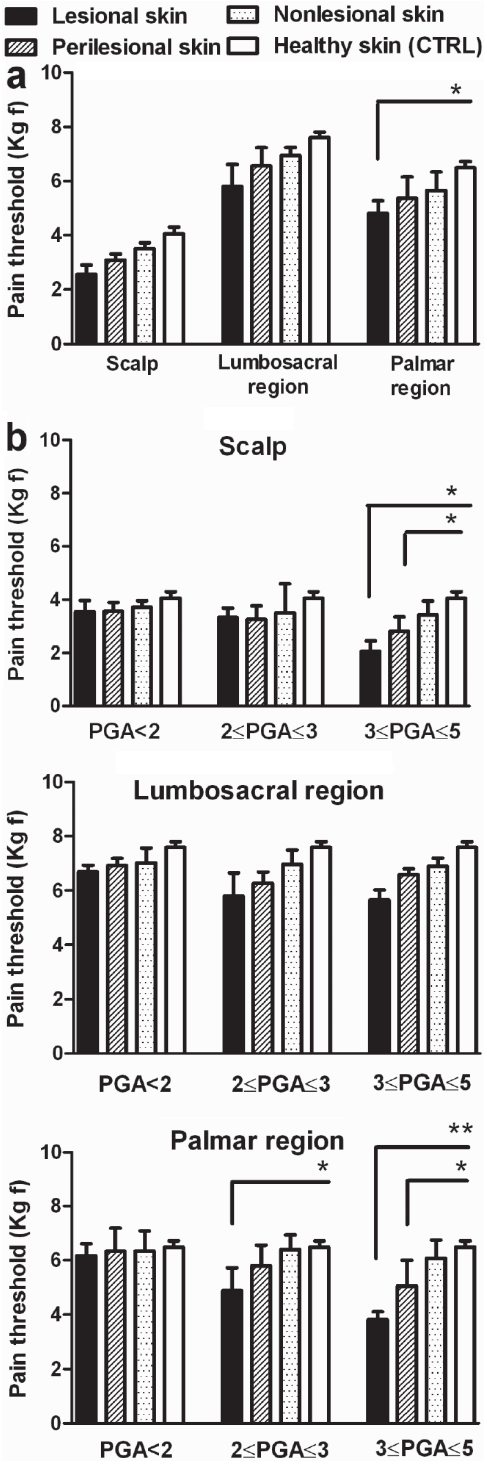

Fig. 1. Evaluation of pain threshold in psoriatic patients compared with healthy controls (CTRL). (a) Pain threshold assessed at scalp, lumbosacral and palmar regions. (b) Analysis of the data shown in panel (a), grouped according to the physician global assessment (PGA) score attributed to the examined plaques. Data are shown as mean ± standard deviation. (1 kgf = 10 N, *$p < 0.05$, **$p < 0.01$).

Having obtained these data, we correlated the patients' pain threshold, measured at the described body regions, with the PQAS score attributed to pain intensity. As showed in Fig. 2, the patients' pain threshold decreased progressively with increase in pain intensity; however, only patients with a pain intensity score ranging from 8 to 10 showed a statistically significant reduction in pain threshold, compared with healthy controls.

Skin sensitivity to mild and superficial stimuli, such as the sense of touch and heat, was reduced in lesional skin compared with non-lesional skin of the same patient, with a more pronounced alteration in tactile sensitivity. In perilesional skin, a lower sensitivity was found only to tactile stimulus. All these alterations were detected in each examined body region, when the plaque PGA score ranged from 3 to 5. Tactile sensitivity was more impaired with increasing lesional infiltration and desquamation rate (data not shown).

IL-33 expression analysis

The group of 12 patients selected for *in vivo* biological investigation comprised 6 males and 6 females, with a mean PASI score of 5.3 ± 2.6 and a mean plaque PGA of 3.6 (range 3–5). With reference to pain intensity reported at PQAS, 6 (3 males and 3 females) had no pain and 6 (3 males and 3 females) had severe pain. We found a statistically significant higher IL-33 gene expression in lesional as well as non-lesional skin of psoriatic patients (without discriminating the presence/absence of pain), compared with that of healthy controls (Fig. 3a). When we divided psoriatic patients on the basis of the presence or absence of pain at PQAS, we observed a higher IL-33 expression in subjects who reported severe pain at questionnaire (Fig. 3b). Moreover, through the use of *ex vivo* skin organ cultures treated with SDS, at 4 mM, we found significantly increased IL-33 gene expression in comparison with control cultures treated with vehicle alone (Fig. 3c).

DISCUSSION

Patient-reported cutaneous symptoms associated with psoriasis are often underestimated and have been poorly investigated (33), despite physicians rising awareness of the need to pay attention to symptoms such as itching, pain and discomfort.

We found a high prevalence (43.6%) of skin pain among the patients, with a notable mean intensity score

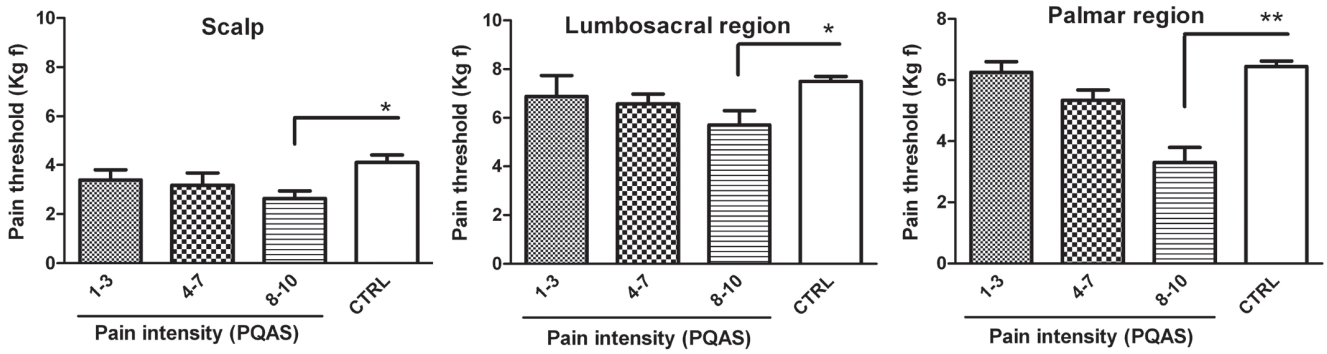

Fig. 2. Comparison of pain threshold and pain intensity reported in the Pain Qualities Assessment Scale (PQAS) questionnaire. Data are shown as mean ± standard deviation. (1 kgf =10 N; *$p<0.05$; **$p<0.01$).

(7.1, 0–10 NRS). The most frequently reported pain qualities were: itchy, unpleasant, aching, sensitive, hot/burning, tender and cramping. This reproduces the results reported by Ljosaa et al. (2), who found the features: itchy, unpleasant, sensitive, hot/burning and tender to be most frequent. In particular, we found that 68 out of 71 patients reported itchy pain at PQAS. In this group, we found patients with pain who also reported an itchy pain sensation, in addition to patients with pain without an itchy component. This might suggest that itch and pain are different sensory modalities, but also that they sometimes coexist as itchy pain in psoriatic patients. Interestingly, although cutaneous pain is mainly considered superficial, we found that 45.1% of patients also reported deep pain, confirming a previous report (2). The PQAS items help physicians to distinguish between superficial pain, which is mainly neuropathic/dysesthetic, and deep pain, which is mainly somatic/nociceptive, although deep and surface pain sometimes co-exist. This is essential because the pathogenetic mechanisms of pain, and the subsequent therapy, sometimes differ, even in the presence of the same aetiology.

To our knowledge, this is the first study that objectively measured cutaneous pain threshold in patients with psoriasis. For this, a pressure algometer was used, which has already proven to be a valid method of measuring localized pain in muscle, joints, tendons, ligaments and bones (34, 35). Among patients who reported pain at PQAS, we found that the pain threshold progressively decreased, proceeding from healthy to lesional skin. Moreover, the pain threshold decreased with the increase in PGA, achieving statistical significance in the scalp and palmar regions compared with the lumbosacral region. This finding is not surprising, because the palm and scalp are more richly innervated with nociceptors than the lumbosacral region. Furthermore, palmo-plantar, inverse, and genital psoriasis are more prone to pressure and friction, which are stimuli that activate pain-sensitive nerve fibres (i.e. nociceptors) (18). The slightly reduced pain threshold in unaffected skin of patients compared to controls is of interest, although not statistically significant. The same result was found in all the examined regions and could be explained by the persistent, chronic inflammation extending to clinically

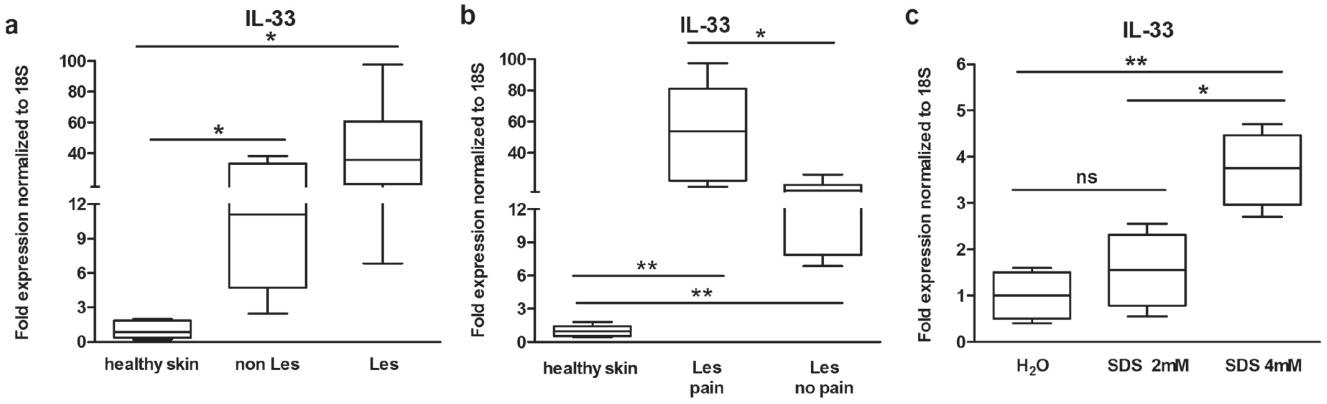

Fig. 3. Relative expression levels of interleukin (IL)-33 in psoriatic patients and in *ex vivo* skin organ culture. (a) IL-33 mRNA expression in skin biopsy samples from the psoriatic plaque (lesional, lumbosacral region) and from uninvolved skin (non-lesional) of psoriatic patients, compared with skin from healthy donors used as control. (b) IL-33 mRNA expression in lesional psoriatic skin of patients subdivided on the basis of the presence of severe pain (NRS: 8–10) or the absence of pain (NRS: 0) at Pain Qualities Assessment Scale (PQAS) and in skin from healthy donors. (c) IL-33 mRNA expression in *ex vivo* organ culture of healthy skin treated with the vehicle (water) or with 2 and 4 mM Sodium Dodecyl Sulphate (SDS), respectively. All values were normalized to the housekeeping gene 18S and presented as relative-fold increase with respect to untreated skin from healthy donors. Data are shown as boxes, with the top and bottom representing the 25th and 75th percentiles, respectively. The line in the box represents the median, and whiskers represent min and max. Statistical comparisons were performed using Wilcoxon matched pairs test. Les: lesional; ns: not statistically significant; *$p<0.05$; **$p<0.01$.

unaffected skin areas. We assessed patients' pain threshold, also taking into account the possible influence of psychological factors on pain perception, in order to objectively evaluate the clinical utility of the PQAS. This assessment was made comparing patients' pain threshold, measured objectively using algometry, with the questionnaire score attributed to experienced pain intensity. Patients with a pain intensity score ranging from 8 to 10 showed a statistically significant reduction in pain threshold, compared with healthy controls. Such results imply that physicians should take anamnesis of cutaneous pain into consideration. Indeed, the reported symptoms, especially when particularly severe, correlate with a lower objective pain threshold, probably due to a long-lasting inflammatory process, characterizing psoriasis physiopathology.

We also found reduced skin sensitivity to mild and superficial stimuli, such as the sense of touch and heat, in all examined body regions, in patients with a plaque PGA score in the range 3–5. Such alteration may be attributed to histological features of psoriasis; indeed, hyperkeratosis, infiltration and desquamation make the skin less responsive to such stimuli, because of the greater interposed distance between the exogenous stimulus and skin nerve endings. However, the pressure exercised by the algometer effectively stimulated nociceptors, which were already overly stressed by inflammation, resulting in a painful sensation.

It is well known that psoriasis can cause tissue damage (i.e. sores, skin cracks) and that epidermal free sensitive nerve endings are activated by mechanical stimuli from damaged tissue, as well as by inflammatory mediators found in elevated levels in plaque lesions, e.g. prostagladins, tumour necrosis factor alpha (TNF-α) and IL-1β (18).

McMahon et al. (36) reported that a long-lasting inflammatory response from chronic psoriasis lesions may cause sensitization of the peripheral and central nervous system, which increases patients' pain experience. Our study is the first conducted on psoriatic patients, with the aim of deepening the understanding of cutaneous pain pathophysiology, focusing on IL-33. IL-33 mediates methylated bovine serum albumin-induced cutaneous and articular mechanical hyperalgesia in immunized mice via activation of the TNF-α, IL-1β, interferon-γ, endothelin-1 (ET-1), prostaglandin-E2 (PGE2) signalling cascade (22). Moreover, IL-33 signalling contributes to carrageenan-induced innate inflammatory pain, triggering the production of TNF-α, chemokine (C-X-C motif) ligand 1 (*CXCL1*), IL-1β, ET-1 and PGE2 (24). Magro et al. (23) demonstrated that IL-33 signalling is essential in overt pain-like behaviour triggered by a variety of phlogistic agents, including ethanoic acid, phenyl-*p*-benzoquinone (PBQ), formalin, and ovalbumin challenge in immunized mice. We firstly confirmed a higher IL-33 gene expression in lesional and non-lesional skin of psoriatic patients (with or without pain), compared with healthy controls. Such results might support the lower threshold of patients pain observed in their lesional as well as unaffected skin, compared with controls. When we subsequently examined IL-33 gene expression in lesional skin from the lumbosacral region of patients reporting severe pain at PQAS, we again found statistically significant greater IL-33 expression in psoriatic patients in comparison with patients without pain. At this point in our study, we decided to use *ex vivo* skin organ culture employing SDS as a model for studying inflammatory pain. Indeed, SDS, a well-known inducer of irritant contact dermatitis, determines the release or up-regulation of a variety of cytokines, among which many, including TNF-α, IL-1β, IL-6, IL-8, IL-10 and several chemokines, are involved in pain modulation (37). SDS was evaluated by Petersen et al. (37) for its effect on skin sensory functions, suggesting that SDS-induced inflammation may be a useful model for studying inflammatory pain mechanisms. Thus, we found increased IL-33 gene expression in organ cultures treated with SDS. These results support the role played by IL-33 in pain modulation and make its involvement in psoriatic pain physiopathology more plausible. However, further studies are needed to fully understand the multiple mechanisms responsible for induction/maintenance of pain in psoriasis, and to elucidate the impact of IL-33 on patients' cutaneous symptoms.

In conclusion, psoriasis-related skin pain may be a greater problem than previously estimated. Future studies on molecular mediators involved in psoriatic nociception are needed. Global examination of psoriatic patients, including evaluation of skin symptoms, may be crucial for clinical management, also in relation to the therapeutic choices, whose purpose is the amelioration of visible signs of the disease as well as the improvement in QoL. Indeed, severe cutaneous symptoms, which badly affect patients' QoL, may justify the use of systemic medication, including biological drugs, even in cases in which the disease is not extensive.

The authors declare no conflicts of interest.

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