

ORIGINAL ARTICLE

Fast itch relief in an experimental model for methylprednisolone aceponate topical corticosteroid activity, based on allergic contact eczema to nickel sulphate

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Abstract

Background Topical corticosteroids (TC) consistently show effectiveness against itch, a paradigmatic symptom, in various eczemas. Rapid itch relief is a therapeutic goal. The early response of itch to TC has not been adequately studied.

Objectives To assess the effect on itch of a TC, methylprednisolone aceponate 0.1% ointment (MPA), in induced eczema in volunteers sensitized to nickel sulphate.

Methods Sixteen volunteers with a late positive patch-test reaction to nickel sulphate entered the study. Eczema was treated once daily with ¼ fingertip unit of MPA for 5 days. Pruritus intensity was assessed with a 10 cm visual analogue scale (VAS). Mean time to itch relief (T_R) defined as the time to reach a 30% decrease in the highest VAS value recorded was assessed, as well as $T_{R\text{-baseline}}$, colorimetry and planimetric morphometry of the reaction.

Results Mean T_R was 1.0 days [standard deviation (SD) = 1.1] and mean $T_{R\text{-baseline}}$ was 1.6 days (SD = 1.4). Five volunteers reached 100% decrease from itch baseline-VAS in 2.0 ± 1.2 days, whereas a 75% decrease was obtained in 1.7 ± 1.6 days by 16 volunteers. A clinical improvement of patch-test reaction was apparent at day 11, although erythema was still present.

Conclusion We present a valid model to assess the efficacy and speed of action of TC treatment to alleviate pruritus and the signs of eczema. The fast effect of MPA against pruritus supports the appropriateness of treating allergic contact eczema with TC.

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Conflicts of interest

A.M. Giménez-Arnau has been an Advisor for Uriach Pharma, Novartis, Genentech, Basilea, Almirall, Unilever, has received Grants supported by Uriach Pharma, Novartis, Bayer-Intendis, and has carried out Educational Activities sponsored by Uriach Pharma, Novartis, Basilea, Almirall, Bayer-Intendis, Menarini, GSK and Merck. No other authors have any conflict of interest.

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Introduction

Allergic contact eczema (ACE) is an inflammatory cutaneous response to exposure to topical allergens. This response is mediated by an immunologic mechanism of delayed hypersensitivity (type IV reaction, according to the classification by Gell and Coombs).^{1,2} The sensitization phase requires a variable period of exposure, but once a subject has become sensitized to an

allergen, subsequent dermatitis is triggered during the elicitation phase.

In a meta-analysis of different studies from Europe and North America covering over 12 years (1996–2007), the median prevalence of ACE to at least one allergen in the general population was 21.2% (range 12.5–40.6%). The most prevalent ACE trigger was nickel (median 8.6%, range 0.7–27.8%).³

The epicutaneous test (patch test) is used as gold standard provocation test for ACE diagnosis.^{4,5} The most characteristic elemental lesions are those associated with the acute phase of eczema, involving papules and vesicles; the presence of pruritus is the main symptom associated with this condition.⁶ Pruritus has a chronic, persistent and refractory behaviour, and may be resistant to treatment. Dawn *et al.*⁷ reported that over 98% of patients with atopic dermatitis (AD) pointed out the disturbing and unpleasant character of itch, with a negative impact on quality of life (QoL).^{8–10} Weisshaar *et al.*¹¹ found a negative correlation between QoL and pruritus intensity [graded by visual analogue scale (VAS)] in AD. The VAS is found to be the best option for the subjective evaluation of itch by patients.^{12,13}

Around 83% of patients with AD suffer from itch. Twenty-eight percent experience itch daily, mostly appearing in the evening (52.8%) and at night (38.2%).⁶ Yosipovitch *et al.*¹⁴ showed that almost the entire population of patients with AD felt itch at least once every 2 weeks. The conjunction of all these reasons configures eczema-related itch relief as one of the main therapeutic goals.

Despite pruritus being a guide symptom of ACE, few studies exist about its impact in the QoL of these patients. Ayala *et al.*¹⁵ developed a 20-item questionnaire to explore the QoL of patients with contact eczema, and found itch as one of three aspects strongly associated with a poor QoL.

The use of topical corticosteroids (TC) for itch relief has been studied in some clinical trials on eczema, including AD and contact dermatitis.^{16–20} Most patients treated with TC showed symptom relief in 2–3 days. Thomas *et al.*¹⁷ compared two potent and mild TC in an AD trial. They found no significant differences between them in the median number of scratch-free days (potent: 117.5; mild: 118.0), although scratch free days seems not to be a valid measure for itch severity evaluation.

Methylprednisolone aceponate (MPA) provides a quick, reliable and highly effective treatment of eczema, with an efficacy comparable to that of most reference TC (Ruzicka *et al.*¹⁹). In one of the studies, MPA reduced the rate of severe itch from 57% to 1%, and that of moderate itch from 31% to 5.5% in patients with AD. A study from Bieber *et al.*²⁰ in severe AD comparing MPA to tacrolimus 0.03% reported that intensity of itch declined substantially from baseline to end of treatment, especially by MPA at day 7. Finally, Szczepanowska J *et al.*²¹ showed how concomitant usage of emollients significantly improves pruritus during corticosteroid treatment.

Despite numerous studies confirming the efficacy of TC in pruritus improvement,²² studies evaluating how fast itch improves to disappear when ACE is present are lacking. Only a pilot study of the efficacy and start of action of hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% lotion in patients suffering from itch²³ reported a significant reduction for itch following one treatment day, suggesting an early onset of action.

Itch is a very irritating symptom, it being an unmet need to know how fast it can be controlled by an active treatment. The

aim of this study was specifically to assess the mean time to itch relief, under TC treatment. TCs are widely used and show an optimal safety profile. We expect to increase our knowledge about how TC alleviates this disabling paradigmatic symptom of ACE. In addition, we further characterize the evolution of different aspects of experimentally induced eczema. Although there are studies about the benefits of TC in eczema, very few studies have been carried out in ACE. Indirectly, our study may support the use of TC as a quick way to improve the QoL of patients.

Materials and methods

Study design and population

This is a phase I, single blind, interventional study. Sixteen of 18 screened volunteers with a history of nickel sensitivity (mean age 39.8 years, range 18–75) fulfilled the initial inclusion criteria confirmed by a patch test and were enrolled (all women). Volunteers were evaluated in the Department of Dermatology at the Hospital del Mar, Barcelona. History of volunteers involved eczema ($n = 3$), urticaria ($n = 3$), hypersensitivity ($n = 2$) and drug reactions ($n = 2$). Volunteers having active skin or systemic disorders producing itch, an active cutaneous disorder in the upper back affecting the evaluation of the topical application of the allergen, or a psychiatric disease interfering in the itch evaluation were not included. Subjects under any treatment conceivably producing itch or altering the experimental pruritus sensation were also not included. The study protocol conformed to the Declaration of Helsinki and applicable European ethical regulations and was approved by the local ethical committee of scientific research (CEIC-Hospital del Mar). Before any study procedure, volunteers were informed about the study aims and gave their written consent to participate. The study was registered as a trial at the Spanish Agency of drugs, and has EudraCT Number 2011-005284-25.

Methods

Patch testing for eczema and itch development

A transdermal patch test (Finn Chambers®; SmartPractice, Phoenix, AZ, USA) with 5% nickel sulphate in petrolatum (Trolab-Almirall®; Hermal Trolab-Almirall, Barcelona, Spain) was applied on Day 0 in the upper back of volunteers for eczema development. After removal of the patch on Day 2 (48 h of patch application) pruritus VAS measures were obtained. Patch-test reactions were evaluated on Day 7 (Figs 1, S1), and involved the clinical evaluation of pruritus by VAS and of the eczema intensity by planimetric morphology.

A positive patch-test reaction (at day 7) (Figs 1, S1), and thus the inclusion of a volunteer in the study for the initiation of the active treatment, required a pruritus VAS evaluation of ≥ 3 cm and an intensity of eczema graded ++ or +++ according to International Contact Dermatitis Research Group (ICDRG) criteria.

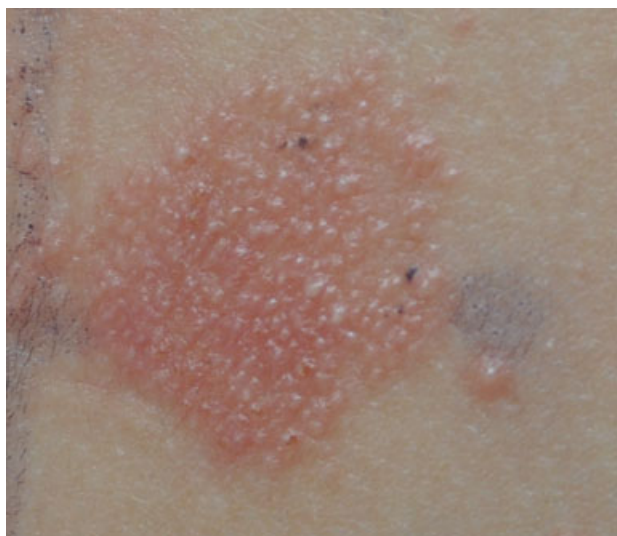


Figure 1 Positive patch-test reaction in a volunteer at day 7.

Active treatment

Visible eczema in the positive nickel patch test was treated once daily with an active treatment consisting of $\frac{1}{4}$ fingertip unit intended dosis (UID) (approximately 125 mg) of MPA 0.1% ointment provided in a blinded tube. Volunteers with positive patch reaction received one MPA ointment application per day, for at least 5 consecutive days (days 7, 9 and 11, the investigator applied the ointment at the hospital; days 8 and 10, the volunteers were helped by a third person at home). The volunteers were blinded regarding the active ingredient applied. From day 11 onwards, the investigator could decide to continue the treatment application until day 15. At day 15, a final control visit was carried out. During the study all topical treatments except for the active study treatment were forbidden.

Measurements

For the assessment of different aspects of the experimental eczema and itch, three main parameters were collected: subjective intensity of pruritus by volunteers (VAS measurements), colorimetry and planimetric morphometry of the eczema. Itch intensity was measured using a VAS, in an unmarked 10-centimetre horizontal line format.^{24,25} The volunteers were asked to indicate a point along the line representing their perception of itch, considering the left-hand extreme of the line as 'no itch' (0) and 'worst itch imaginable' (10) at the right-hand extreme, in agreement with the International Forum for the Study of Itch (IFSI) consensus terminology.²⁶ Specific time points for VAS itch evaluation were as follows: once every 24 h in days 2–7 (before active treatment); day 7 (after active treatment application), an evaluation every 2 h during the first 24 h (except for 6 h at night); day 8, every 4 h

(except for 8 h at night); day 9, every 6 h; days 10 and 11, every 12 h. This provided a total of six pretreatment itch-VAS measurements and a total of 23 time points for posttreatment itch-VAS measurement, compared to the usual 1 or 2 basal and 3 or 4 post-treatment assessment time points, thus providing a VAS vs. time curve much richer in detail.

To ensure compliance and the correct VAS assessment by volunteers, at the specified times, they received a mobile phone message to remind them to carry out the assessment of the itch felt at that moment; they also had to obtain the VAS score and send this measurement to a central data station via mobile phone. To avoid recall bias, each VAS in the volunteers' diary was covered, once used, by an opaque adhesive label. Several parameters of the VAS vs. time curve (time to reach maximum VAS from the start of treatment, area under the curve (AUC), $dVAS/dT$), were calculated. Itch relief, T_R , from the start of treatment with MPA 0.1% ointment was defined as the time needed to reach a 30% VAS decrease vs. the maximum VAS score registered. Baseline-VAS was defined as the VAS at day 7 assessed immediately before the first MPA application. $T_{R\text{-baseline}}$ was defined as the time needed to reach a 30% VAS decrease vs. the baseline-VAS score registered.

At days 7, 9 and 11, colorimetry of the eczema intensity [a* parameter (redness or erythema)] by patch test was evaluated with the Mexameter MX 18 (Courage-Khazaka Electronic, Köln, Germany). Eczema intensity by planimetry and morphometry (ICDRG scale) were also evaluated. In cases of absence of eczema remission and of the continuation of active treatment until day 15, the eczema intensity evaluation (maximum diameter of the positive patch test) was also performed.

Visual analogue scale scores and planimetric measurements at day 7 were used as main criteria for patch test positive reaction and posterior inclusion of volunteers for active treatment (Fig. 2).

Statistical analysis

Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all the statistical and descriptive analyses. Quantitative data were presented as mean $\pm$ standard deviation (SD), whereas qualitative data were presented as number (*N*) and percentage (%). The VAS curve vs. time has been calculated considering the following parameters: time to reach maximum VAS from the start of treatment, AUC and $dVAS/dT$. Different Kaplan–Meier Curves have been calculated for different times to reach given percentages of itch VAS decrease, including Itch relief, defined as 30% decrease in maximum and baseline itch VAS value. McNemar–Bowker's test of symmetry for the ICDRG scores was used for the comparison of the distribution of eczema intensity grades at different time points. An analysis of variance (ANOVA) was calculated for the colorimetry data. Significance (*P*) values with a threshold of 0.05 were considered.

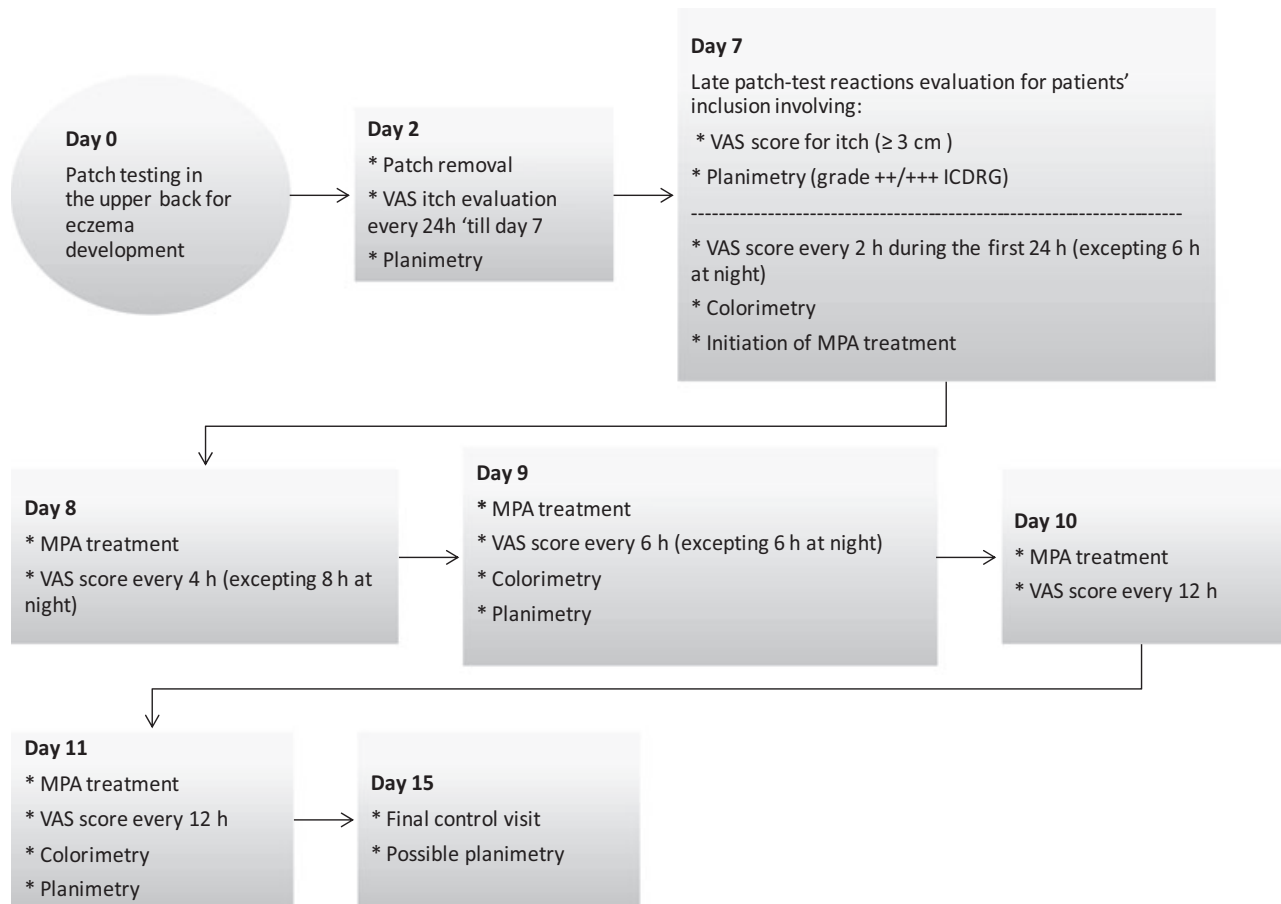


Figure 2 Schedule of visits and procedures during the study.

Results

The main demographic and clinical data of volunteers screened are summarized in Table 1. No adverse events were reported. Seven of 18 volunteers showed concomitant disorders at screening, hypertension being the most common condition. Ten of 18 subjects were under medical treatment; contraceptive hormonal treatment and beta-blockers were the most common (3 and 2 cases respectively). Physical examination of the skin of the upper back where the patch was to be placed showed no abnormalities in any of the volunteers at inclusion.

Itch VAS measurements throughout the study showed mean daily measurements of 5.7, 4.2, 2.4 and 1.3 mm, at days 2 (patch removal), 7 (first treatment application), 9 and 11 respectively.

Using the VAS curve, the AUC was calculated. The AUC per day observed was of mean 35.0 ± 20.4 . The slope of the dVAS/dT curve was of mean -1.1 ± 0.5 : itch-VAS assessment decreased approximately by 10 mm/day (Fig. 3).

The analysis of the primary study endpoint, the mean T_R for highest VAS pruritus assessed from the start of treatment with MPA 0.1% ointment, in patients reaching the 30% VAS decrease ($N = 15$), showed a mean time $\pm$ SD of 1.0 days $\pm$ 1.1. The analysis of the $T_{R\text{-baseline}}$ ($N = 16$), showed a mean time $\pm$ SD of 1.6 days $\pm$ 1.4. The Kaplan–Meier curve estimation of the $T_{R\text{-baseline}}$ in the whole sample ($N = 16$) is represented in Fig. 4.

A 100% decrease in the baseline-VAS measurements was found in five volunteers, whereas 75% decrease was obtained by the 16 volunteers. A 50% and 75% decrease in the itch baseline-VAS measurements was reached in 1.7 ± 1.6 days and a 100% decrease was obtained in 2.0 ± 1.2 days.

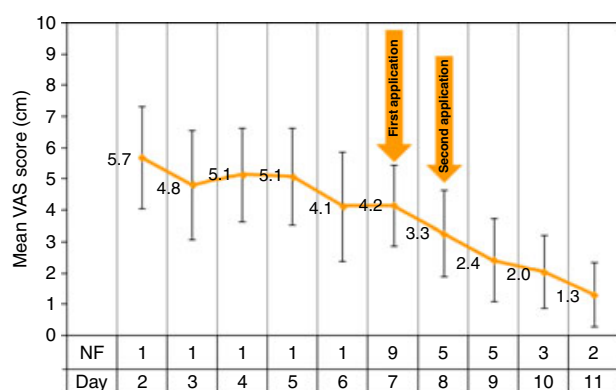
The decrease in the itch VAS during the study from the maximum itch measurement observed at day 2 (patch removal), of 5.7 mm, is accompanied by an increase in eczema intensity on day 7, at the start of treatment. Figure 5 shows both the eczema intensity by colorimetry and morphometry evaluation (days 7, 9 and 11). Eczematous erythema (by colorimetry) did not experience improvement across the study. The redness or erythema

Table 1 Demographic and clinical data of the screened volunteers

Variable	N = 18
Age (years, mean $\pm$ SD)	39.8 $\pm$ 14.1
Body Mass Index (kg/m ² , mean $\pm$ SD)	23.8 $\pm$ 5.4
Abnormalities in physical examination related to skin (n) ^a	
Eczema	1
Poikiloderma	1
Medical History ^a	
Eczema	3
Urticaria/chronic urticaria	3
Hypersensitivity	2
Adverse drug reactions	2
Arrhythmia	1
Thyroid cancer	1
Cholecystectomy	1
Ulcerative colitis	1
Depression	1
Hypertension	1
Lung neoplasia	1
Cardiac assist device	1

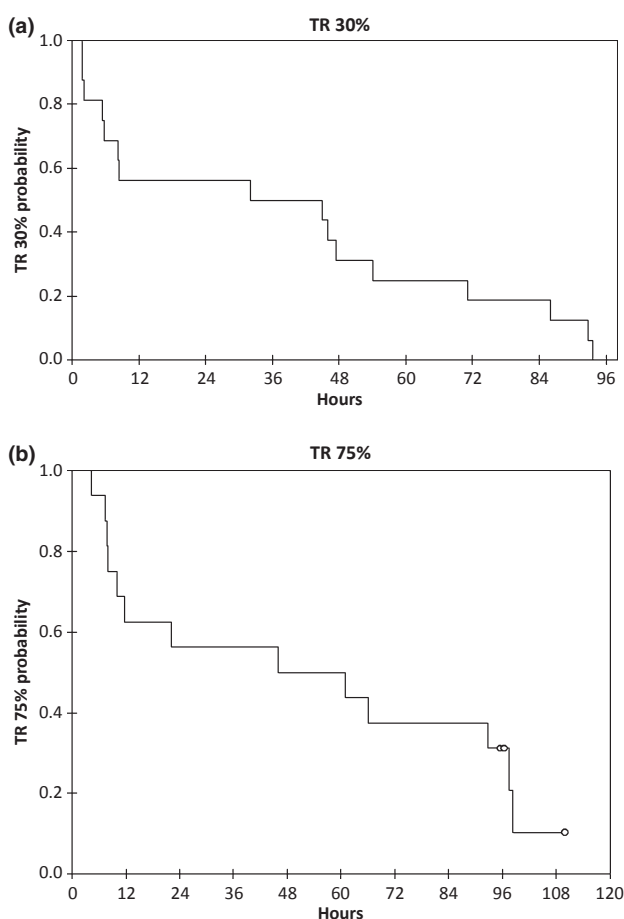
^aOne volunteer may show more than one antecedent.

SD, standard deviation.

**Figure 3** Itch evolution visual analogue scale (VAS measurement means) throughout the study. Mean daily itch VAS (in cm); mean score represents the point marked in a 10-centimetre of the itch intensity felt by volunteers; perpendicular lines represent the error bars. Abbreviations, NF, number of fulfilments.

evaluated by colorimeter (a* parameter) showed mean values of 419 ± 423 (day 7), 362 ± 374 (day 9) and 389 ± 399 (day 11) analysis of variance (ANOVA $P = 0.153$).

Mcnemar–Bowker's test for the differences in the ICDRG scores shows a significant change in the distribution of the categories for eczema intensity with time. At day 7, all volunteers had grade ++ or +++ of eczema intensity (10 and 6 volunteers respectively). The proportion of volunteers with grade ++ or

**Figure 4** Kaplan–Meier survival curve estimate. (a) $N = 16$. Assessment of the time to obtain a 30% reduction in the baseline itch visual analogue scale (VAS) score ($T_{R\text{baseline}}$ or time to itch relief) with methylprednisolone aceponate (MPA) 0.1% ointment. (b) Assessment of the time to obtain a 75% reduction in the baseline itch VAS measurement with MPA 0.1% ointment.

+++ eczema intensity at day 9 falls by about 25% vs. day 7 (7/16 volunteers with a moderate ++ reaction, vs. 11/16); in parallel, the proportion of volunteers with grade + intensity increases from none at day 7 to 9 volunteers at day 9 $P = 0.0003$. At day 11, we observe a significant reduction in grade++ eczema intensity (two volunteers) vs. day 9, and an increase in grade + (12 of 16 volunteers) ($P = 0.0018$) (Fig. 5). In general, 90% of volunteers improved patch testing signs (grades ++/+++ to + or doubtful in 4 days. All volunteers evaluated at day 15 (9 subjects) showed an eczema intensity of grade+.

Discussion

In this study, a treatment with 125 mg of MPA 0.1% ointment for five consecutive days in volunteers with ACE was found to be effective to alleviate pruritus, with an early onset of action, showing that itch-VAS assessment decreased approximately by

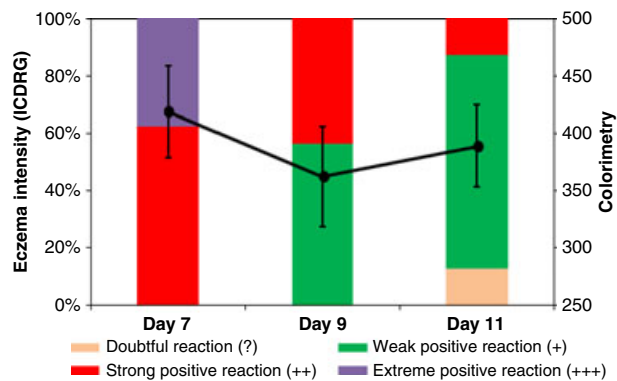


Figure 5 Eczema intensity by morphometry and colorimetry. Colour columns represent the intensity evaluation (%; left axis) of the eczema by International Contact Dermatitis Research Group (IC-DRG) for days 7, 9 and 11. The black line represents the colorimetry (a^*) values (means, right axis) for the same days.

10 mm/day. Our finding supports ACE as a good experimental model to assess the efficacy of TC treatment to alleviate pruritus and the clinical signs of eczema, and confirms the appropriateness of TC to treat ACE. Our results are in agreement with recent studies reporting the role of TC in pruritus relief and the significant reduction in itch in 1 day.^{22,23} The inclusion of pramoxine in the formulation together with hydrocortisone probably increased the anti-itch efficacy; in our case, just MPA was the active principle.

Until now, there were no studies evaluating the initial response in the first days to MPA in ACE itch. We characterize the evolution of the time curve of VAS from the start of treatment and different aspects of the experimental eczema. Our results demonstrate a rapid relief of pruritus (VAS) during the study, going from 30% to 75% itch relief from the baseline-VAS in 1.6 to 1.7 days in all of volunteers. A complete pruritus relief is found to be present after a mean time of 2 days. These data give a more precise picture than the one derived from those studies reporting that most patients treated with corticosteroids show a reasonably rapid symptom relief in 2–3 days, and provide a benchmark for future studies on the benefits of therapy for patients. The rapid evolution of the VAS vs. time curve and of the clinical signs confirms the rapid efficacy of TC treatment in the course of acute ACE.

Colorimetry data did not show a significant reduction in the erythema in 4 days. Taking into account that clinical improvement usually involves, in this sequence, itch, the vesiculation and infiltration, and erythema as the last lesion to disappear in the area of induced eczema, we can confirm a delay between the early pruritus relief and clinical improvement of the induced eczema.

This result agrees with our VAS results showing the maximum pruritus measurements at day 2 (when patch was removed), fol-

lowed by the maximum eczema intensity at day 7 (when first treatment was applied and coinciding with a mild decrease in itch perception). This data highlights the subjective and multi-aetiological nature of the pruritus sensation.

The evaluation of eczema intensity by planimetry and morphometry showed a significant improvement of the IC-DRG grading with time, substantially improving patch testing signs from severe grades to more moderate or mild grades, in 4 days.

Pruritus is an aspect of potential QoL impairment. Considering previous studies about the negative impact that pruritus itch has in QoL of patients,^{7–11} and the lack of literature about the onset of action of a TC in itch relief in ACE, our study may contribute to highlight the future use of QoL measures in studies evaluating TC treatment effects in ACE.

Other than from environmental factors, genetics may play an important role in ACE pathogenesis^{27–29} (especially when due to hypersensitivity to nickel). Taking into account the incidence of different factors affecting the development of the disease, their evaluation and the specific responses to the treatment in a longitudinal design warrant special consideration for future studies. The role of these variables in the treatment response variability over time remains to be elucidated.

The objective of this study was to evaluate the kinetics of itch relief in an experimental model using TC on ACE to nickel sulphate. As it is an experimental approach this study does not reproduce what happens in normal clinical practice where many concomitant factors can be involved in the pruritus perception. In addition, if TC efficacy to treat pruritus should be evaluated again in the future, a double blind comparative randomized study vs. placebo would be desirable to maximize the level of evidence. In this sense, the absence of a placebo patient group constitutes a deserving limitation of the study, as we cannot discard some spontaneous pruritus improvement, i.e. after moisturizing the skin with the excipient of the TC applied in this study. Similarly, comparative randomized studies appear as a very interesting research line to capture differences between various contact eczemas or active treatments. Additional studies and increasing number of participants should also strengthen the power of the eventual findings.

In summary, this study demonstrates a fast onset of antipruritic action of the TC MPA in volunteers affected by ACE in a model that reasonably approximates a real clinical situation in various aspects. Based on our results, ACE can be flagged as a valid experimental model to assess the efficacy of TC treatment to pruritus relief.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Positive patch-test reaction in a volunteer at day 7.

