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ORIGINAL ARTICLE

Randomized, controlled, double-blind clinical study evaluating the safety and efficacy of MD2011001 cream in mild-to-moderate atopic dermatitis of the face and neck in children, adolescents and adults

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Abstract

Introduction: This mono-center randomized, controlled, double-blind study evaluates the safety and efficacy of MD2011001 cream versus placebo, in mild-to-moderate atopic dermatitis (AD). MD2011001 is a nonsteroidal topical cream containing vitamin E, epigallocatechin gallate and grape seed procyanidins.

Methods: Patients with AD (corresponding to an IGA score of 2 or 3), involving the face, the perioral/periorcular area and/or the neck, were enrolled. Patients were randomized 1:1 ratio to receive MD2011001 or placebo before the start of the study (D0), then evaluated after 7 days, and after 28 days. The study was approved by the Local Independent Ethics Committee and conducted according to the Declaration of Helsinki and local regulations. The statistical tests used were the Wilcoxon test and the Mann–Whitney U-test.

Results: Forty-four patients (29F and 15M) were enrolled. The IGA values showed a statistically significant reduction during the treatment period obtaining a favorable safety profile and local tolerance for both the products. The reduction in the surface area affected by AD was significantly faster with MD2011001.

Discussion: This study focuses on very sensitive areas known to be particularly susceptible to local complications.

Conclusions: These results suggest the usefulness of an emollient treatment for mild/moderate AD.

Keywords

Atopic dermatitis, nonsteroidal topical cream, antioxidant properties

History

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Introduction

Atopic dermatitis (AD) is an inflammatory skin disease with a chronic relapsing course and a significant impact on the quality of life of patients and their families. AD is characterized by acute, subacute or chronic eczematous lesions, associated with intense itching and/or burning, which predominantly affect the face, the neck, the retroauricular folds and limb flexures. In adults, the involvement of the hands and periorificial sites is common. AD seems to be the consequence of the interaction between environmental triggers and a genetic predisposition, leading to an abnormal immune response and a defective epidermal barrier (1).

The therapeutic management is based on preventive measures, limiting the exposure to potential triggers, and on the use of emollients and different drugs (2,3). The most common treatments include topical corticosteroids and topical calcineurin

inhibitors. Emollients have a key role in the control of skin xerosis and in promoting the restoration of the skin barrier. The regular use of emollients as a “background therapy” can decrease the risk of flares in the long term, thus exerting a “drug-sparing” activity (4,5).

MD2011001 is a nonsteroidal topical cream containing vitamin E, epigallocatechin gallate (EGCG), which is the most abundant catechin in green tea, and grape seed procyanidins, all antioxidant and emollient ingredients thoroughly tested and widely employed in cosmetics. Patch testing previously demonstrated the good safety profile of MD2011001, disclosing the absence of any irritating and sensitizing potential.

The aim of this double-blind, controlled study was to evaluate the safety and efficacy of the medical device MD2011001 in mild-to-moderate AD localized on the face and/or neck in children, adolescents and adults. Attention was also given to the application of the product on sensitive areas, such as the perioral region, the neck and the eyelids and periorcular area.

Materials and methods

Patients

The study population consisted of 44 patients with mild-to-moderate AD, with a cephalic distribution and a particular

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involvement of the areas around the mouth and/or the eyelids/periorcular area and/or the neck. Patients of both sexes aged 6 years or more, affected with AD, diagnosed according to Hanifin and Rajka's criteria (6), were enrolled. The evaluation of AD severity was made using the Investigator's Global Assessment (IGA), based on a six-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). Participants had to present with AD lesions on the face and/or neck with a mild-to-moderate severity, corresponding to an IGA score of 2 (mild disease with mild erythema and mild papulation/infiltration) or 3 (moderate disease with moderate erythema and moderate papulation/infiltration). The patients or their parents/legal representatives were required to sign the informed consent before entering the study. An adequate contraceptive method was recommended in women of childbearing age. Moreover, an appropriate washout period prior to the start of the study treatment was necessary as follows: 1 week and 2 weeks for emollients and topical medications, respectively (for the face and neck), 1 week for oral antihistamines and systemic antibiotics, 1 month for systemic corticosteroids, other systemic immunomodulators and UV radiations, including sunlight.

The main exclusion criteria were as follows: severe or moderate/severe AD, the presence of other skin disorders, including infections, in the affected AD areas, the use of systemic drugs or other procedures that might influence AD activity and/or study assessments, the presence of any medical condition that could interfere with the study participation and/or predispose to the use of forbidden drugs. Pregnant or breastfeeding women were excluded, as well as those patients with known hypersensitivity to the ingredients contained in the study products.

Study design and treatments

This was a single-center, double-blind, randomized, controlled study carried out in the Dermatology Unit of the University of Bologna, Italy. The protocol and study procedures were approved by the Local Independent Ethics Committee and conducted according to the Declaration of Helsinki and local regulations. The placebo (vehicle) was an optimal soothing cream containing the same ingredients as the MD2011001 cream, with the exclusion of vitamin E, EGCG and grape seed procyanidins, which were present only in the active product. Unfortunately, the two study products had different color and smell because of the dissimilar composition, and this could have impaired the double-blind design of the study. Therefore, the products under investigation were packaged and labeled in a completely anonymous way by the study promoter, so that both participants and study staff members were blinded to the study cream assignment. Indeed, none of the study staff members could have access to the randomization list or to the nature of the tested product until the end of the study.

Patients were evaluated for primary and secondary endpoints at baseline, before the start of study treatment (D0), 7 days after D0 (D7) and 28 days after D0 (D28, end of the study).

At D0, the eligible patients were randomized following a 1:1 ratio to receive MD2011001 or placebo. It was advised to apply the study product twice daily on the affected AD areas of the face and/or neck for 4 consecutive weeks. At D0, all topical and systemic treatments had been stopped for an adequate period, as described in the eligibility criteria. However, during the study period, topical therapies could be applied on body areas affected by AD in accordance with clinical practice. In the event of a significant worsening of the AD of the face and/or neck and/or in the presence of other conditions requiring the use of prohibited therapies, the study participation had to be interrupted. The use of any topical medications on the face and neck areas as an add-on

therapy was not permitted from D0 to D7 and resulted in the withdrawal of the subject from the protocol. Instead, the use of the above-mentioned topical medications as rescue treatments was allowed at the investigator's discretion, only after completion of study procedures at D7 or beyond.

Study endpoints and assessments

All the study endpoints were determined in reference to the affected areas of the face and/or neck. The primary endpoint corresponded to the IGA value of the AD lesions on the face/neck at D28. The assessment was also dichotomized in terms of therapeutic success (IGA 0 or 1) or treatment failure (IGA $\geq$ 2).

The secondary endpoints were: IGA at D7, the change in the surface of the lesional area, and the variation in the severity of subjective symptoms (itching and/or burning) and clinical signs. In fact, at each visit, physicians recorded the extension of the affected areas of the face and the neck expressed as the percentage of the total corresponding area, while the severity of six individual signs (erythema, papules/edema, vesiculation/crusting, excoriation, lichenification/prurigo and xerosis) was evaluated using a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The same four-point scale was utilized by patients to report the severity of subjective symptoms. Apart from the cumulative evaluation of the cephalic region, the same assessments were individually performed for each of three particular target areas, represented by eyelids and the adjacent skin, the perioral region and the neck, respectively.

Moreover, at each visit, the patients and/or their parents/legal representatives were asked to give their overall opinion about the severity of their AD on the face and/or neck by means of the patient's global assessment (PGA), which is identical to the IGA scale of disease activity, ranging from 0 (clear) to 5 (very severe disease).

All therapies, including rescue treatments, and any adverse events were registered. Furthermore, at D7 and D28, the patients and/or parents/legal representatives completed a study-specific questionnaire about the tolerability of the treatment.

Statistical analysis

Assuming a success rate of 80% in the active group and 26.3% in the placebo group (7), and considering a power of 90% and an alpha error of 0.05, a sample size of 16 patients per group (two-tailed test) was prescribed. However, presupposing a drop-out rate of about 25%, the size was increased to 22 subjects for each group (44 patients in total).

The considered population included all the randomized patients, who received at least one dose of the investigational product, were evaluated for the safety. The last observation carried forward ("LOCF") approach was used when the efficacy data were not available, including the early withdrawals caused by treatment failure. The statistical tests used were the Wilcoxon test to compare the differences between the different time points in each group and the Mann-Whitney U-test to compare the two groups. *p* values < 0.05 were considered statistically significant. The χ -square test was used to compare the probability of success (IGA 0 or 1) at D28.

Results

Patients

Forty-four patients (29 females and 15 males; 41 Caucasian), with a mean age of 22.6 years (range, 6–69 years) were randomized and entered the study. All patients had a mild-to-moderate AD (IGA 2 or 3) of the face and/or neck. The eligibility criteria were met in all cases but two (one in each group), for whom there was

an inadequate washout period prior to D0 (although this finding was revealed only after randomization). Moreover, other two patients (one in each group) were withdrawn because of the arbitrary “rescue” use of a topical corticosteroid between D0 and D7. In both cases, the IGA value increased from 3 at D0 to 4 at D7, and therefore, the study was stopped at D7. In addition, the analysis did not include another patient belonging to the placebo group because she never applied the product after randomization.

Therefore, the efficacy analysis was performed in 39 patients: 19 patients in the placebo group (12 females) with a mean age of 18.4 years (range, 6–60 years) and 20 patients in the MD2011001 group (14 females) with a mean age of 27 years (range, 6–69 years). Patients aged 18 years or older amounted to 53% and 65% in the placebo and MD2011001 groups, respectively.

Six patients withdrew at D7, one from the placebo group and five from the MD2011001 group, because of AD worsening or adverse events. In total, 33 patients regularly completed the study (18 in the placebo group and 15 in the MD2011001 group) and attended the final visit at D28.

The safety analysis involved 43 patients and excluded the only randomized patient who never applied the product.

Efficacy

Primary endpoint and IGA

The IGA scores were examined in terms of both the rate of therapeutic success (IGA 0 or 1) at D28 (primary endpoint) and the average values calculated during the study. At D28, the rate of patients achieving an IGA of 0 or 1 was 89% in the placebo group and 70% in the MD2011001 group. At D7, this rate was 79% and 70% after treatment with placebo and MD2011001, respectively. The difference in the probability of success between the two groups was not statistically significant at any time point.

The average values of IGA showed a statistically significant reduction during the treatment period as compared to the baseline in each group, without significant differences between the two treatment groups (Figure 1).

Secondary endpoints

A significant decrease in the lesional skin area in the face and neck was observed during the treatment period as compared to baseline, with the achievement of statistical significance at D28 versus D0 in both groups. Instead, at D7, the reduction of the surface area affected was statistically significant for the face in both groups and for the neck only in the MD2011001 group (Table 1).

Treatment with placebo and the MD2011001 cream resulted in a progressive improvement of skin inflammation, as demonstrated

by the change in the cumulative severity of signs and symptoms involving the total AD lesions on the face and neck (Table 1). Statistical significance was reached in most cases at D28, and for some components even at D7, without significant differences between the two groups. Similar clinical and statistical considerations could be applied also in respect to the severity of signs and symptoms in the single sensitive areas (data not shown). More specifically, in these target areas (cervical, perioral and periocular regions), all parameters showed a trend toward amelioration at D28 as compared to baseline, with a statistical significance consistently achieved for skin dryness, erythema and subjective symptoms. The PGA values constantly reproduced the same results obtained with the IGA scale at each determination.

Rescue therapy

Rescue therapy was required in four patients of the MD2011001 group at D7, when the patients withdrew from the study because of worsening of AD or superimposed impetigo, and in three placebo-treated patients group, between D7 and D28 for similar reasons. Rescue therapy consisted in topical steroids, or topical and/or systemic antibiotics, as needed.

Tolerability

Adverse events

Adverse events occurred in four patients of the placebo group (irritant contact dermatitis = 1, AD flare = 2, impetigo = 1) and in seven patients of the MD2011001 group (irritant contact dermatitis with AD flare = 1, AD worsening = 3, flu-like syndrome = 1, impetigo = 2). Their severity was usually mild or moderate, except in two cases (AD flare and impetigo in the periocular area, respectively), both associated with the use of MD2011001 and judged as severe but unrelated to the study treatment. Moreover, the correlation with the study treatment was considered probable in only two cases with an irritant contact dermatitis, one in each group, while it was regarded as uncertain in another two cases (AD worsening in a placebo-treated patient and impetiginization in one case of the MD2011001 group). No serious adverse events were observed.

Questionnaire

The assessment of the tolerability of the two products was also done using a study-specific questionnaire administered to patients at D7 and D28 (Table 2). The results revealed that approximately 90% of patients considered the tolerability of the study treatment good or excellent, and nearly half perceived the study products as better tolerated than topical preparations used in the past. Interestingly, significantly less patients in the MD2011001 group reported symptoms (defined as itching, burning or discomfort) at the site of the application of the study product as compared to those who applied the placebo cream (24% vs. 49% throughout the study period, $p = 0.034$).

Discussion

The results of this study suggest that, in most cases, the use of an emollient allows the control of symptoms and clinical manifestations in mild/moderate AD of the face and/or neck and, therefore, it can play a role as a drug-sparing strategy (4,5,7–10). Indeed, the application of an emollient (MD2011001 or placebo) led to a gradual improvement of skin xerosis and clinical signs and symptoms associated with inflammation, along with a progressive reduction in the extent of the affected area. These data were achieved after a treatment period of 4 weeks with statistically significant differences from baseline. A statistically significant

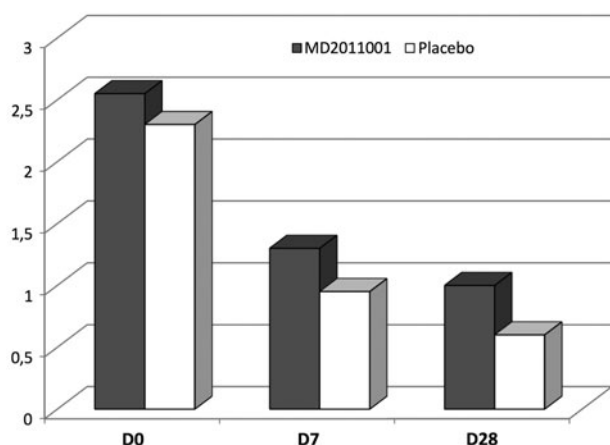


Figure 1. Average IGA scores during the treatment period.

Table 1. Surface area and severity of signs and symptoms in the lesional affected skin on the face and neck.

	MD2011001			Placebo		
	D0	D7	D28	D0	D7	D28
Surface area of affected skin ^a						
Face	22.7 (14.8)	9.1 (15.7) ^b	7.1 (15.8) ^b	19.7 (13.2)	6.7 (7.7) ^b	4.4 (8.2) ^b
Neck	14 (16.3)	5 (8.9) ^b	3.5 (8.1) ^b	10.1 (15.2)	5.8 (11.6)	0.3 (1.1) ^b
Severity of signs and symptoms ^c						
Erythema	1.45	0.85 ^b	0.7 ^b	1.3	0.6 ^b	0.4 ^b
Papules	0.65	0.4	0.2 ^b	0.4	0.1	0.05 ^b
Vesicles/crusts	0.4	0.5	0.3	0.3	0.1	0.05
Escoriation	1.1	0.55 ^b	0.4 ^b	0.7	0.2 ^b	0.05 ^b
Lichenification	1.7	0.75 ^b	0.6 ^b	1.5	0.5 ^b	0.2 ^b
Xerosis	1.8	0.7 ^b	0.4 ^b	1.8	0.7 ^b	0.4 ^b
Symptoms	1.55	0.7 ^b	0.4 ^b	1.05	0.3 ^b	0.2 ^b

^aResults presented as the mean percentage (in relation to the total area of the face and neck, respectively) and standard deviation.

^bDifference versus D0 within each group: $p < 0.05$; comparison between groups: $p > 0.05$.

^cResults presented as the mean values referred to the total face and neck area (severity score based on a four-point scale).

Table 2. Main results derived from the patients' assessment of tolerability of the study product.

	MD2011001	Placebo
Overall opinion about tolerability		
Excellent	32%	33%
Good	57%	57%
Discrete	3%	5%
Insufficient	8%	5%
Opinion about tolerability in comparison to products used in the past		
Better	49%	46%
Similar	43%	39%
Worst	8%	10%
Not applicable/not known	0	5%
Local symptoms reported at the site of application		
Total rate ^a	24%	49%

^aDifference between the two groups (total reported symptoms) $p = 0.034$.

reduction in the affected facial area was already observed after only 7 days of treatment in both groups, while it was obtained for the neck only in patients who applied the MD2011001 cream.

The protocol also focused on the particularly sensitive skin areas localized on the cephalic region (e.g. eyelids, the perioral area and the neck), highlighting the safe and effective use of the emollient products under investigation. There were, however, no statistically significant differences in the clinical outcome (primary endpoint and secondary endpoints) between the two studied groups.

In the small case series evaluated in this pilot study, therefore, the presence of vitamin E, EGCG and grape seed procyanidins in the MD2011001 cream did not seem to add any substantial benefit in the short-term treatment of mild-to-moderate AD of the face and neck compared to the vehicle cream without the aforementioned substances. Nevertheless, in the interpretation of the results, some clinical and statistical issues should be taken into account. First of all, certain aspects including the spontaneous fluctuation of AD activity and the use of a nonpharmacologic treatment in both arms, should be considered. Moreover, this study was interesting for the peculiarities of the examined areas (face and neck, and also the perioral area and eyelids), known to be particularly sensitive and susceptible to the risk of specific adverse events (e.g. irritation or impetiginization). Therefore, the treatment of these areas is perceived as a real challenge for clinicians, since most topical therapies provoke burning and skin irritation, making the management difficult.

The study population analyzed in this study was small in size and heterogeneous in terms of age with a greater tendency toward the enrollment of older patients in the MD2011001 group than in the placebo group. Even in the absence of substantial differences, comparing the two groups, we observed a slightly higher AD severity at baseline in the MD2011001 group than in the placebo group, especially in terms of IGA and extent of the lesional area.

The safety profile was generally favorable. Adverse events were generally of mild to moderate intensity and included worsening of AD or impetiginization, which are known to be a part of the natural evolution of AD. The tolerability of the treatment was judged as good or excellent by most of the patients, and more than 45% reported that the study treatment was better tolerated than other topical products used previously. Of note, a significantly lower proportion of patients complained of untoward symptoms (defined as itching, burning or discomfort) at the site of application of the MD2011001 cream compared to those who applied the placebo cream.

In conclusion, the data provided by this pilot randomized controlled trial confirmed the usefulness of an emollient treatment for AD, which proved to be effective in most cases of mild-to-moderate disease localized on the face and neck, even in particularly sensitive sites. Local tolerance of the MD2011001 cream was satisfactory. Moreover, the reduction in the surface area affected by AD was significantly faster with MD2011001 compared to the vehicle in the neck area, whereas no significant difference was observed between the two products in the face.

Overall, these results support the use of MD2011001 cream to improve the restoration and the integrity of the epidermal skin barrier and cutaneous inflammatory symptoms, thanks to the combined action of soothing ingredients, antioxidants and emollients.

Declaration of interest

Panin Srl, Rovigo, Italy, provided funds to this study.

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