

**EFFICACIA E TOLLERABILITA' DI UNA CREMA DERMOCOSMETICA A BASE DI
AR-GG27[®] * (Sorbityl furfural palmitate) NEL TRATTAMENTO DI FORME LIEVI
MODERATE DI DERMATITE ATOPICA DELL'ETA' PEDIATRICA ASSOCIATA A
PITIRIASI ALBA**

Studio Clinico in doppio cieco, controllato versus placebo

**Efficacy and tolerability of a cream containing AR-GG27[®] * (Sorbityl furfural palmitate) in
the treatment of mild/moderate childhood atopic dermatitis associated with pityriasis alba
Double-blind, placebo-controlled clinical trial**

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Summary.

Background

Pityriasis alba (PA) is a skin disorder characterized by finely scaly, hypopigmented patches, typical of childhood, that also represents an atopic dermatitis (AD) minor sign according to Hanifin and Rajka criteria. It may be isolated or associated with AD representing, sometimes an atypical manifestation of AD during the long term follow-up of the disease.

Aim

To evaluate of the efficacy and tolerability of AR-GG27[®] (sorbityl furfural palmitate) cream in the treatment of childhood mild or moderate atopic dermatitis (AD) associated with pityriasis alba (PA).

Methods

The trial is a single center, double-blind, randomized, placebo-controlled study.

The study included patients of both sexes, aged between 2 months and 15 years, suffering from mild and moderate AD always associated with PA. Xerosis was present in all patients. The treatment with topical steroids or topical calcineurin inhibitors (TIMs) had to be suspended for at least 15 days. Any systemic therapy and phototherapy or sun exposure were withdrawn at least 30 days before. Emollients were stopped at least 7 days before. During the trial, no other local or systemic treatments were allowed, as well as sun exposure. Patients affected by AD with viral, bacterial or fungal overinfection or patients with diabetes mellitus, severe systemic diseases or intolerance to one or more components of the product were excluded.

The primary endpoint was the evaluation of the average change in the IGA (Investigator Global Assessment) after 15 and 30 days of treatment. The second endpoint was the evaluation of severity of 3 different clinical signs: erythema, excoriation desquamation, using a subjective 5-point scale. Changes in pruritus severity was also considered during the entire period of treatment, through the use of a Visual Analogue Scale (VAS). A $p < 0,05$, two tailed was considered as statistically significant.

Results

After 15 and 30 days there was a statistically significant difference in the group treated with AR-GG27[®], compared to the placebo (respectively, $p = 0.0007$ and $p = 0.005$)

After 15 days of treatment, itching was clearly reduced in AR-GG27[®] treated group compared with the placebo, both in the study population ($p = 0.01$) and in patients where the symptom was present from the beginning ($p = 0.05$).

Conclusion

AR-GG27[®] showed a beneficial action associated with high compliance and tolerability in dermatological skin conditions characterized by inflammation and tissue oxidative stress in children, as PA with mild and moderate AD.

Keywords: AR-GG27[®]; pityriasis alba, atopic dermatitis, eczema,

RIASSUNTO

Introduzione

La pitiriasi alba (PA) è una malattia della pelle caratterizzata da macchie finemente desquamanti ipopigmentate, tipica dell'infanzia, che rappresenta un segno minore di dermatite atopica (DA), in accordo ai criteri Hanifin e Rajka. Può essere isolata o associata ad DA, che rappresentando, una manifestazione atipica di DA durante il lungo periodo di follow-up della malattia.

Lo scopo di questo studio clinico era di valutare l'efficacia e la tollerabilità di AR-GG27[®] (furalglucitolo palmitato) in crema dermocosmetica nel trattamento della dermatite atopica (DA) dell'età pediatrica di grado lieve o moderato associata a pitiriasi alba (PA).

Metodi

Lo studio monocentrico, è stato condotto in doppio cieco, randomizzato e controllato *versus* placebo.

La popolazione in studio, di entrambi i sessi e con età compresa tra 2 mesi e 15 anni, era affetta da (PA) sempre associata a DA di grado lieve moderato. La xerosi era presente in tutti i pazienti. Ogni trattamento con steroidi topici o immunomodulatori doveva essere sospeso da almeno 15 giorni, così come qualsiasi altra terapia generale. Erano esclusi i pazienti affetti da DA in fase attiva e/o con sovrainfezione virale, batterica o micotica, oppure i soggetti affetti da diabete mellito, da altre malattie sistemiche gravi o con intolleranza verso uno o più componenti del prodotto.

L'obiettivo primario dello studio era la variazione del punteggio totale IGA dopo 15 e 30 giorni di trattamento. Il secondo obiettivo è stata la valutazione della gravità di 3 diversi segni clinici: eritema, desquamazione escoriazioni nella zona di PA, con una soggettiva scala a 5 punti. Cambiamenti nella gravità prurito erano anche considerati durante l'intero periodo di trattamento, attraverso l'uso di una scala analogica visiva (VAS). Un valore di $p < 0,05$, è stato considerato statisticamente significativo.

Risultati

Dopo 15 e 30 giorni di trattamento era presente una differenza statisticamente significativa a favore del gruppo trattato con AR-GG27[®], rispetto al placebo (rispettivamente, $p = 0.0007$ and $p = 0.005$)

Inoltre, dopo 15 giorni trattamento, il prurito risultava migliorato in modo statisticamente significativo in favore di AR-GG27[®] rispetto al Placebo sia nella popolazione in studio ($p = 0.01$) sia nella casistica in cui il sintomo era presente al basale ($p = 0.05$).

Conclusioni AR-GG27[®] risulta efficace, ben tollerato e con un' elevata compliance, in quadri dermatologici caratterizzati da infiammazione e stress ossidativo, come la dermatite atopica associata a PA.

Parole chiave: AR-GG27[®]; pitiriasis alba, dermatite atopica, eczema.

INTRODUCTION

We present a randomized, double-blind, vehicle-controlled clinical study that evaluated the efficacy and safety of Dermolichtena cream*. This product was tested, in comparison to vehicle, in paediatric patients with mild/moderate atopic dermatitis (AD) always associated with pityriasis alba (PA).

The first in vitro experiments for the new AR-GG27[®] molecule demonstrated its antioxidant and lenitive actions. Modelling studies showed that the AR-GG27[®] molecule had high affinity for the biological membrane, an easy membrane permeation and a stable anchorage of its palmitic portion, highly lipophilic¹⁻².

This supported the hypothesis of a positive effect of AR-GG27[®] molecule (contained in Dermolichtena[®] cream) on the control of AD and other inflammatory skin diseases.

Pityriasis alba (PA) is an inflammatory self-limited dermatosis, typical of childhood, that also represents an atopic dermatitis (AD) minor sign according to Hanifin and Rajka criteria³. In the inflammatory phase, PA is characterized by finely scaly, pale, pink or red in color, round or oval patches, ranging from 0.5 cm to a few centimeters in diameter with well defined borders, even if sometimes, they may be irregular⁴⁻⁵. These lesions evolve into the characteristic hypopigmented patches. Typically, PA occurs in individuals with skin type III and IV, but can also be observed in fair-skinned patients. The most frequently involved area is the face (50-60% of cases); patches, however, can be observed on the neck, arms and shoulders⁶⁻⁷ and, more rarely, on the trunk. An extensive form has been recently described and named Extensive Pityriasis Alba (EPA)⁸. PA may be isolated or associated with AD representing, sometimes, an atypical manifestation of AD during the long term follow-up of the disease. In fact, in children affected by AD, we can observe periods where the disease is characterized mainly by patches of inflammatory PA. In these cases, PA shows extensive and symmetric no well-defined limits⁹. In this subgroup of patients, PA is often associated with itching.

PA is a frequent reason for dermatologic consultations, especially for its chronic course, its tendency to seasonal relapses mainly after the summer, and, finally, for its aesthetic impact. Recently, the incorrect hydration of the skin has been considered the key risk for the PA¹⁰⁻¹¹. The improper use of moisturizers, associated with the habit of frequent baths using drying soaps result into poor skin hydration and inadequate melanogenesis. Education, the use of emollients and mild detergents may prevent its onset. To our knowledge, a specific topical therapy for PA does not exist yet.

METHODS

Study design

This is a single center, randomized, double-blind, placebo controlled study.

Eligible patients were randomized in 1:1 allocation to receive either AR-GG27[®] cream (Dermolichtena[®]; Giuliani SpA, Milan, Italy) or the placebo.

Dermolichtena cream* contained: Aqua, Peg-8 Beeswax, Caprylic/capric Triglyceride, Dicaprylyl Ether, Isostearyl isostearate, Diisopropyl Sebacate, Glycerin, Butyrospermum parkii butter, Zea mays, Calendula officinalis extract, Tapioca starch, Glycyrrhetic acid, Rhizobian gum, Sodium hyaluronate, Sorbityl furfural palmitate, Citric acid, Sodium Hydroxymethylglycinate, Betain, Inositol, Trehalose, Bisabolol, Phenoxyethanol, Allantoin, Diethylhexyl syringylidenemalonate, Carbomer, Beta-sitosterol, Pentaerythrityl tetra-di-t-butyl hydroxycinnamate, Dimethylmethoxy cromanol, Olea europea leaf extract, Rosmarinus officinalis extract, Tocotrienols.

Placebo contained: Aqua, Peg-8 Beeswax, Caprylic/capric Triglyceride, Isostearyl isostearate, Glycerin, Tapioca starch, Carbomer, Citric acid, Sodium Hydroxymethylglycinate, Phenoxyethanol.

Patients, caregivers, investigators and clinical staff were blinded to treatment. The AR-GG27[®] cream and placebo cream were identical in appearance, texture and odor.

The study obtained institutional ethical committee and parents or the legal guardians of children gave written informed consent and understand the procedures and implications of taking part in the study before enrollment.

Patient selection

Patients aged between 2 months and 15 years with normal dietary and social habits affected by PA located on the face and / or the limbs and / or the trunk. PA was always associated with clinical lesions of AD. AD had been previously diagnosed in all the patients on the basis of Hanifin and Rajka criteria. Xerosis was present, as well as pruritus.

Patients and parents' were required to meet the enrollment criteria and follow specific pre-study and concomitant therapy prescriptions.

Patients were excluded from the study if they had other skin diseases (except for a history of typical AD), co-existing viral infection, bacterial or fungal infections in the acute phase or if they were affected by diabetes mellitus, other severe systemic diseases or intolerance to one or more components of the product.

The treatment with topical steroids or TIMs had to be stopped for at least 15 days. Any general therapy and phototherapy or sun exposure was withdrawn at least 30 days before. Emollients were stopped at least 7 days before.

During the trial, no other local or systemic treatments were allowed, as well as sun exposure.

Treatment plan

Caregivers and patients were instructed (visit 0) to apply twice daily (~ 12 hours apart), 1 mg/cm² of Dermolichtena[®] or placebo cream on the affected and perilesional areas for a period of 30 days. Follow-up visits were performed after 15 days of treatment (visit 1) and 30 days (visit 2- end of treatment).

Primary and secondary efficacy outcome measure

The first endpoint was the average change on the Investigator's Global Assessment (IGA) between the 15th day of treatment and the baseline in the two groups. IGA score and a subjective 5-point scale were used for the evaluation of our enrolled patients because they showed a classic AD associated with PA.

The IGA was used to evaluate the overall disease severity of AD. The description of IGA score is presented in table I. The description of IGA clearly refers to inflammatory signs of AD (erythema,

excoriation, desquamation), so that the inclusion of PA and its assessment by mean of IGA continue to be unclear.

For evaluate the AR-GG27 effectiveness on PA, we considered the severity of 3 different clinical signs: erythema, excoriation, desquamation in areas of PA (table II), using a subjective 5-point scale (0= absent; 1=almost absent; 2=mild; 3=moderate; 4=severe). These 3 signs were evaluated in four different areas: head/neck, upper limbs, lower limbs and trunk. We did not considered skin hypopigmentation, because our study was short time observation, so for this parameter is needed a longer follow-up. Patients were enrolled before, during and after sun exposure. Moreover, this parameter may be present even as a simple final evolution of AD.

Changes in pruritus severity was also considered during the entire period of treatment. A 10 cm visual analog scale (VAS) was used for record the patients' pruritus intensity: 0 cm= "no itching", 10 cm= "worst imaginable itching".

All outcome measures were assessed at baseline, day 15 and day 30.

Safety outcome measures

Safety and tolerability end points were assessed on the basis of potential adverse events reported by the patients or caregivers (parents/guardians) or observed by the investigator.

Adverse events were recorded after the application of AR-GG27[®] cream or placebo at baseline and at each subsequent visit for the entire period of the study.

Sample-Size Estimation

The sample size was empirically set at 60 subjects, 30 per group.

Statistical analysis

The statistical analysis was performed on the ITT population (Intention To Treat population), defined as "all randomized subjects who received at least one dose of the study product, with baseline evaluation and with at least one post-baseline efficacy measurement".

The results were presented using descriptive statistics (mean, SD, minimum and maximum values, or frequency tables, as appropriate) and the comparison between treatment groups performed on the changes, vs baseline values, obtained at visit V1 (15 days) and V2 (30 days), by using parametric (Student's t-test) or non-parametric (Wilcoxon Ranks Sum test) test and Fisher exact test (for evaluation of erythema, desquamation and excoriation) as appropriate.

A $p < 0.05$, two-tailed, was considered as statistically significant.

Results at recruitment.

A total of 60 patients all with PA associated with AD were enrolled in the study (30 in the AR-GG27[®] group and 30 in the placebo), but 8 patients (3 of AR-GG27 group and 5 of placebo group) withdrew prematurely (before visit 1) and were excluded from statistical analysis.

Patient demographics and baseline disease characteristics.

Patient demographics and baseline characteristics were similar between the 2 groups.

The white and the black race were respectively 89% and absent in the ARG27 group; 92% and 4 % in the placebo group . Asian race was absent in the placebo group and 3,70% in the ARG27 group. Other races were 7,40% in ARG27 group and 4% in placebo group.

The mean age for both groups was ~ 4 years with comparable proportion of males and females in AR-GG27[®] group, while in placebo group the majority of subjects was females.

At baseline, physician assessment of individual signs in the different areas was comparable between the 2 groups.

Itching was present in 67% (20 patients) in the AR-GG27 group and 44% (13 patients) in the placebo group.

The itching score was not different between AR-GG27[®] and placebo group in total ITT (intention-to-treat) population.

Efficacy Results

At the first visit of follow-up (day 15), 27 patients of group AR-GG27 and 25 patients of placebo group were evaluated. At the end of the study the number of patients who withdrew from the study between day 15 and day 30 were respectively 23 in the group AR-GG27 and 21 in the placebo group.

At baseline, in AR-GG27 group, in 24/27 patients (89%) the IGA score was 2 (=mild AD) and in 3/27 patients (11%) it was 3 (=moderate AD). In placebo group there were 23/25 patients (92%) with IGA 2 (=mild AD) and 2/25 patients (8%) with IGA 3 (=moderate AD).

After 15 days of treatment (V1) a reduction of IGA was observed. In particular the difference of IGA between baseline (V0) and V1 was significantly higher for the AR-GG27[®] group than for the placebo-treated group (-6.30 ± 3.27 vs -2.80 ± 3.19 ; $p=0.0007$).

Greater effectiveness of AR-GG27[®] cream respect to placebo remained at the second visit (V2) with a reduction of -7.78 ± 3.96 in AR-GG27[®] treated patients and -4.24 ± 4.01 in placebo-treated patients (Wilcoxon Sum Ranks test: $p = 0.0053$). (Table III) .

The results of the second endpoint (regarding the differences in values of the individual signs) between baseline (V0), V1 and V2 are summarized in figures 1,2,3 . In these figures the total changes of the value of erythema, excoriation and desquamation in the two groups are reported. This total value is referred to all the 27 AR-GG27 group of patients and to all the 25 placebo group of patients. It derives from the sum of all the single values of this sign evaluated for every patient in the 4 different considered areas.

In figure 1, the difference of erythema sign between baseline (V0) and V1 was significantly higher for the AR-GG27[®] group than for the placebo group (Fisher exact test: V1 p-value 0,0285). The

effectiveness of AR-GG27[®] cream respect to placebo was not statistically significant V2 (Fisher exact test : p-value 0,6063).

In figure 2, the difference of excoriation between baseline (V0) and V1 and V2 did not show a statistically differences between AR-GG27[®] group and placebo group (V1 Fisher exact test: V1 p-value 0,2010). (V2 Fisher exact test : p-value 0.6063).

In figure 3, the difference of desquamation between baseline (V0) and V1 was significantly higher for the AR-GG27[®] group respect to the placebo group (Fisher exact test: V1 p-value 0,0140). The effectiveness of AR-GG27[®] cream respect to placebo was not statistically significant V2 (Fisher exact test : p-value 0.2264)

VAS score

To better evaluate pruritus, two statistical analysis were performed: the first included all the ITT population, while the second included only subjects affected by mild/moderate AD and PA associated with itching at baseline in the two groups. VAS was above 0 in 18 patients of the AR-GG27[®] group and in 11 patients of the placebo group at baseline.

In both analysis, the mean itch score (VAS) at baseline was not significantly different for the two groups (Fig.4 and fig.5).

After 15 days of treatment, the itching decreased in AR-GG27[®] group respect to baseline (-2.048 ± 2.330 in ITT population and -3.200 ± 1.991), more than in placebo group (-0.388 ± 2.22 in ITT population and -1.345 ± 2.918).

The difference in the intensity of pruritus, comparing the two groups, was statistically significant at this time ($p=0.011$ AR-GG27[®] in ITT population)

At T30 the VAS score reduction was more marked for AR-GG27[®] group, when we considered total ITT population (-2.326 ± 2.637 AR-GG27[®] group vs -0.976 ± 2.941 placebo group; Fig. 4) or the subgroup where pruritus was present since the beginning of the study (-3.583 ± 2.347 AR-GG27[®] group vs -3.00 ± 3.100 placebo group; Fig. 5).

Safety

There were no serious adverse events.

The overall adverse event incidence was limited to placebo group, while no adverse events were reported in AR-GG27[®] group.

In particular, 6/30 patients in the placebo group had one or more adverse events during the study, with a total of 7 events (1 subject had 2 events): 2 of them, classified as a “possible correlation” to treatment, caused the discontinuation of treatment (urticaria, worsening of AD/PA), while the remaining 5 events were considered “not related” and they were of mild intensity.

DISCUSSION

The treatments most commonly used for AD are topical corticosteroids and topical calcineurin inhibitors (TIMs), that should control flares and extend the periods of remission via the proactive therapy (i.e. in “week-end therapy”), but the continuous use of corticosteroids is actually charged by the presence of corticophobia¹² and the use of TIMs is restricted to AD not responsive to topical steroids. In addition, TIMs must not be used in patients younger than 2 years¹³. Therefore, the objective of the research is maintaining the remission and treating mild AD, without risk of side effects, especially for younger children in which the use of effective dermato-cosmetic products should play an important role in long-term management of the disease¹⁴⁻¹⁵.

PA is usually treated with emollients¹⁶⁻¹⁷ and mild topical corticosteroids with particular attention to different body area involved¹⁸.

In this double blind randomized trial we evaluated the effectiveness of AR-GG27[®], patented active ingredient, presented in the new Dermolichtena[®] Cream. This product is chemically and pharmacologically developed for clinical use in therapeutic dermatological affections characterized by inflammation and oxidative stress¹. Its use in PA associated with AD represents a new and innovative approach to a frequent association in AD children. Again PA and mild AD the use of steroids and TIMs may be excessive and not justified given to the peculiarity of the clinical picture which is certainly not severe, but aesthetically unpleasant and, sometimes, itchy.

Although our study showed that the use of placebo, promoting hydration, may improve some patients, the AR-GG27[®] cream is statistically more effective, especially for the presence of the active ingredient AR-GG27[®] in its formulation. In addition, the AR-GG27[®] cream is faster than placebo in the control both of the considered signs and of the pruritus in patients affected by AD associated with PA. Moreover the efficacy is maintained even after 30 days of therapy.

To the best of our knowledge, this is the first double-blind clinical trial designed to evaluate the use of a molecule with antioxidant capacity in the treatment of dermatoses with inflammatory component (such as PA associated with AD), a frequent reason for dermatologic consultation, particularly in childhood.

The quality of results and the high tolerance are a good rationale for the planning of further clinical studies with AR-GG27[®] cream in other dermatological diseases with inflammatory component, such as contact dermatitis, psoriasis and seborrhoeic dermatitis.

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Table I : Investigator's Global Assessment (IGA) score

0 = Clear No inflammatory signs of atopic dermatitis
1 = Almost clear. Just perceptible erythema, and just perceptible papulation/infiltration
3 = Moderate disease. Moderate erythema and moderate papulation/infiltration
4 = Severe disease. Severe erythema and severe papulation/infiltration
5 = Very severe disease. Severe erythema and severe papulation/infiltration with oozing/crusting

Table II: Physician assessment of individual signs in the areas of PA.

	Absent	Almost absent	Mild	Moderate	Severe
Signs, <i>n</i>	0	1	2	3	4
Erythema	No signs of inflammation	Slight perceptible erythema and / or faint desquamation	Erythema and / or mild scaling	Erythema and / or moderate desquamation	Intense erythema, severe desquamation, excoriations
Excoriations					
Desquamation					

Table III: The difference of IGA score between baseline,V1,V2 in the AR-GG27 group and placebo group. The difference of IGA between baseline (V0) and V1 was significantly higher for the AR-GG27® group than for the placebo group (-6.30 ± 3.27 vs -2.80 ± 3.19; p=0.0007). Greater effectiveness of AR-GG27® cream respect to placebo remained at the second visit (V2) Wilcoxon Sum Ranks test: p = 0.0053)

		V0	V1	V2
IGA AR-GG27	Mild	24 (89%) (pz 27)	6 (22,2%) (pz n°27)	4 (17%) (pz n °23)
	Moderate	3 (11%) (pz n° 27)	0 (pz n°27)	0 (pz n °23)
IGA PLACEBO	Mild	23 (92%) (pz n °25)	12 (48%) (pz n °25)	3 (14%) (pz n °21)
	Moderate	2 (8%) ((pz n °25)	6 (24%) (pz n °25)	0(pz n °21)

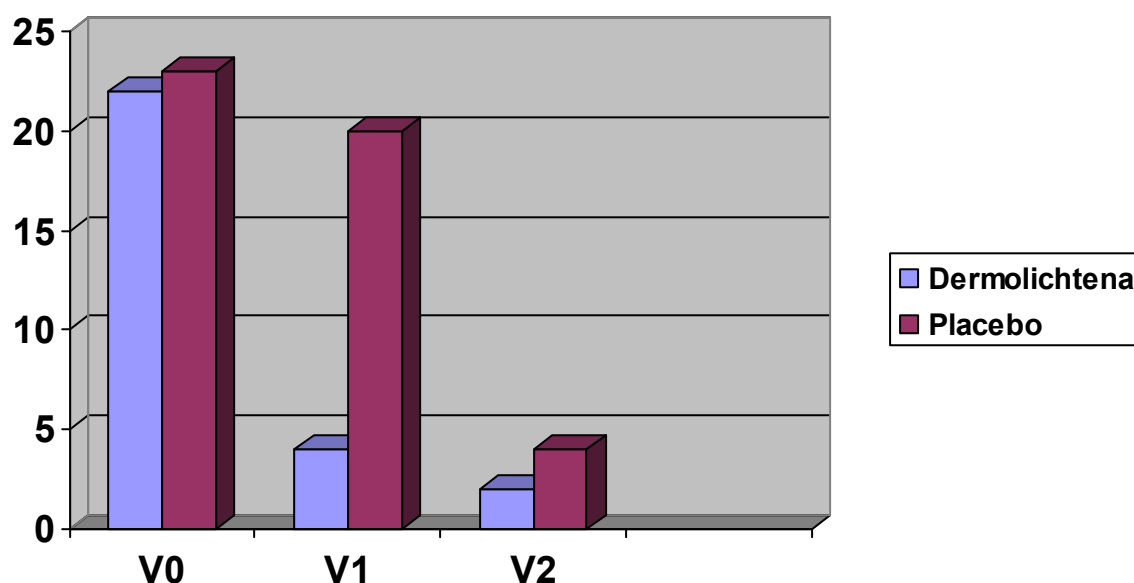


Fig. 1: variation of total value of the intensity of the sign ERYTHEMA at V0, V1, V2.

The difference between baseline (V0) and V1 was significantly higher for the AR-GG27® group than for the placebo group (Fisher exact test: V1 p-value 0,0285). The effectiveness of AR-GG27® cream respect to placebo did not remain at the second visit (V2) (Fisher exact test : p-value 0,6063).

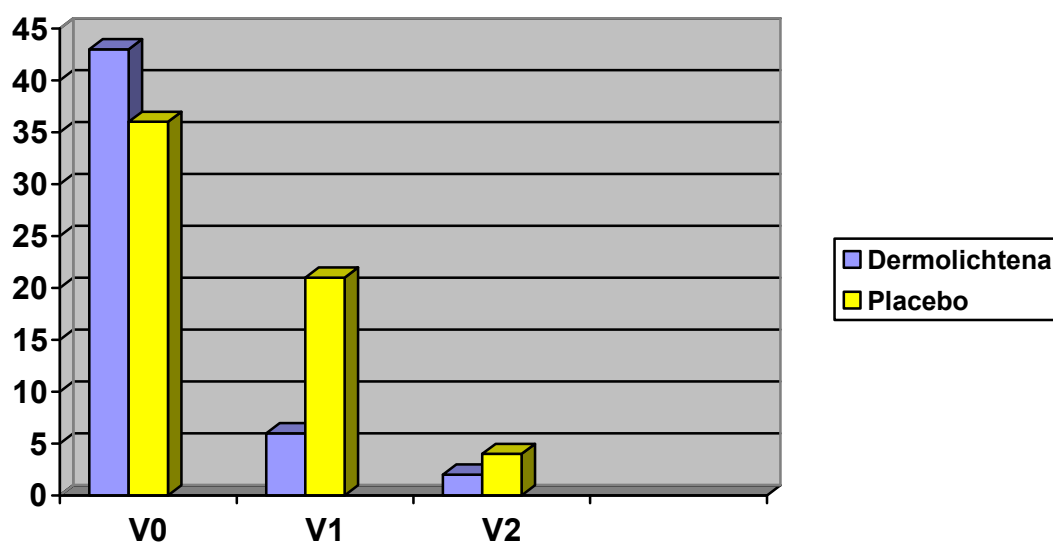


Fig.2: variation of total value of the intensity of the sign EXCORIATION at V0, V1, V2.

The difference of excoriation sign between baseline (V0) and V1 did not show a statistically differences between AR-GG27® group and placebo group (Fisher exact test: V1 p-value 0,2010). It was not significant even at the second time (V2) (Fisher exact test : p-value 0.6063).

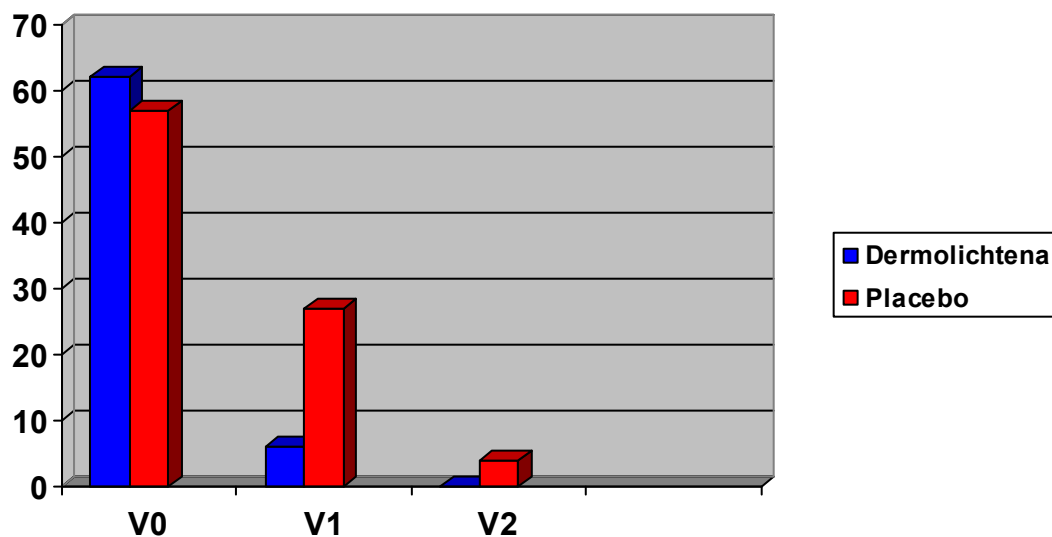


Fig. 3: variation of total value of the intensity of the sign DESQUAMATION at V0, V1, V2.

The difference of desquamation sign between baseline (V0) and V1 was significantly higher for the AR-GG27® group than for the placebo group (Fisher exact test: V1 p-value 0,0140). The effectiveness of AR-GG27® cream respect to placebo did not remain at the second visit (V2) (Fisher exact test : p-value 0.2264).

Figure 4 – Changes of VAS in total ITT population. The difference in the intensity of pruritus, comparing the two groups, was statistically significant at V1 (p=0.011 AR-GG27® in ITT population) but no at V2 (p=0,08)

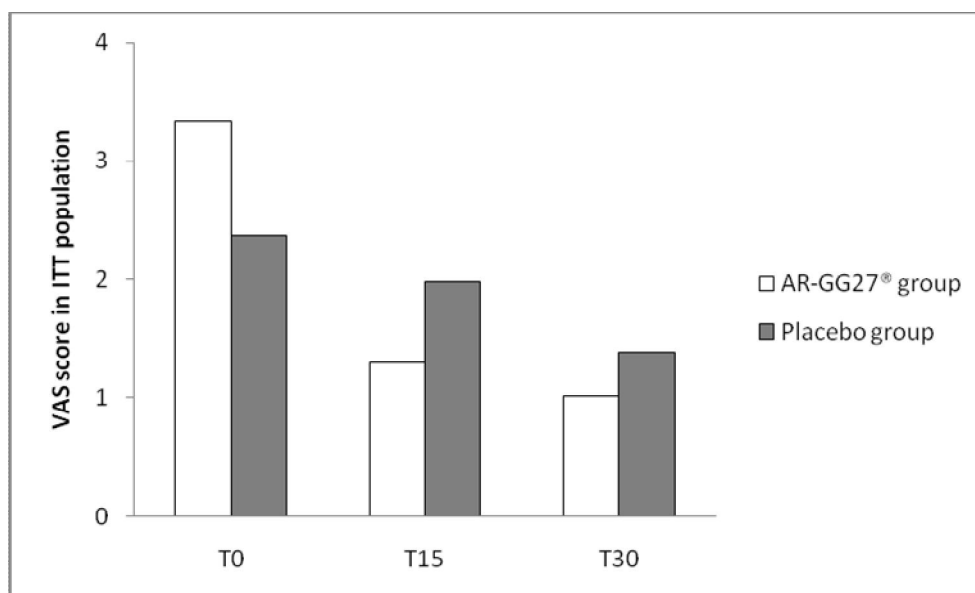


Figure 5 – Changes of VAS in the subgroup with VAS>0 at the beginning of the study.

