

The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: A prospective, randomized, double-blind, placebo-controlled trial

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Background: Wet-wrap treatment (WWT) has been advocated as a relatively effective treatment in children with severe atopic dermatitis (AD). WWT often serves as crisis intervention for AD.

Objectives: We sought to evaluate the use of WWT with diluted corticosteroids in comparison with emollient in children with severe AD during 4 weeks in a proactive schedule during which the frequency of corticosteroid applications was tapered.

Methods: A randomized, double-blind, placebo-controlled study was performed in children aged 6 months to 10 years with severe AD (objective SCORAD at least 40 ± 5), comparing WWT with diluted corticosteroids (1:3 mometasone furoate 0.1% ointment and for the face 1:19 mometasone furoate 0.1% ointment under a mask) with emollient (petrolatum 20% in cetomacrogol cream). The primary outcome was improvement of the objective SCORAD; secondary outcomes included Patient-Oriented Eczema Measure and quality-of-life index.

Results: WWT with diluted corticosteroids acted faster and was more efficacious than WWT with emollients. Best results were obtained in age groups 6 to 9 years and 0 to 3 years. The difference in efficacy evaluated by objective SCORAD was significant at all measuring points. This also applied to the quality-of-life index.

Limitations: The study group was relatively small.

Conclusions: WWT for severe AD is an effective therapy option for at least a period of 4 weeks. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.01.898>.)

Key words: atopic dermatitis; diluted corticosteroids; emollients; eczema; long-term-intervention; wet-wrap treatment.

Atopic dermatitis (AD) is characterized by exacerbations and remissions that, when severe, may require a multifaceted treatment strategy.¹ Wet-wrap treatment (WWT) to reduce

severe AD is currently applied without solid evidence.^{2,3} WWT has a prominent place as crisis intervention in routine practice.^{2,4} Dry occlusive therapy has also been advocated, but the few

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available studies show no benefit over conventional open therapy.⁵ WWT applied for a few days or weeks is considered as a relatively safe and efficacious crisis intervention in severe therapy-resistant childhood AD.² There is little evidence of the efficacy of WWT with diluted corticosteroids and emollients combined or with emollients alone. In a randomized controlled trial in 40 children comparing mometasone furoate 0.1% ointment and fluticasone propionate 0.005% ointment first without wraps (4 weeks) and next under wet wraps (2 weeks), both corticosteroids performed better under WWT.⁶ In another controlled trial in 20 children investigating WWT with mometasone furoate 0.1% ointment and a vehicle preparation in a 5-day treatment period, results were significantly better in the corticosteroid group.⁷ In a pilot study in 19 children comparing WWT with conventional therapy with hydrocortisone acetate 1% cream and emollients, the different regimens were equally effective in moderately severe AD.⁸ In a left-right comparative study in 24 adults and children experiencing an acute episode of AD, 24 to 72 hours of WWT with undiluted prednicarbate performed significantly better than did standard prednicarbate only.⁹ Hindley et al¹⁰ did not find differences in outcome between application of wet-wrap bandages versus conventional topically applied corticosteroid or emollient ointments in 50 children with AD. Our group has performed many observational case series in which diluted fluticasone propionate 0.05% cream was applied, showing benefits of this treatment.^{2-4,11}

This study was undertaken to prove the long-term (4 weeks) efficacy of diluted mometasone furoate 0.1% ointment in the treatment of AD with wet wraps, compared with treatment using wet wraps and emollients alone.^{12,13}

METHODS

Study design

From February 1, 2009, until February 1, 2012, we performed a multicenter, randomized, placebo-controlled, double-blind, prospective study in the Erasmus MC, Sophia Children's Hospital, and the KinderHaven outpatient clinic of Havenziekenhuis, both in Rotterdam, The Netherlands. Patients of the dermatology departments of the Sint Franciscus Gasthuis and Maastad Hospitals in Rotterdam were

referred to KinderHaven if wet-wrap therapy was indicated. Duration of treatment was 4 weeks (28 days). Computerized randomization was performed by our statistician (D.R.).

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Dutch Medical Research Involving

Human Subjects Act (WMO) and good clinical practice and was approved by the Medical Ethics Committee of Erasmus MC. All parents gave written informed consent for participation of their children. The study results were structured according to the CONSORT statement 2010.

Wet-wrap therapy

WWT was applied in children with severe AD aged 10 years or younger. Severe AD is defined by an objective SCORAD greater than 40 ± 5 (see below for information on the SCORAD). WWT is normally performed with diluted corticosteroids and tapered off during several months. Earlier we have published our WWT protocol with Tubifast garments (Mölnlycke Health Care, Gothenburg, Sweden) in which ready-to-go suits are used for the body and the parents themselves cut the holes in the facemask using Tubifast.¹⁴ For the face, mometasone furoate 0.1% ointment was diluted 1:19, although pimecrolimus 1% cream was used in some patients. For the body, a 1:3 dilution was used. These concentrations (diluted with petrolatum 20% cetomacrogol cream) were based on earlier studies with fluticasone propionate 0.005% cream.¹¹

Patient selection

A total of 39 children 6 months or older and 10 years or younger with severe AD (Hanifin and Rajka¹⁵ criteria) were recruited in the above-mentioned sites. All parents of patients who qualified for WWT were invited to participate. The objective SCORAD was 35 to 40 or higher (indicating severe eczema) on 2 measuring points before start of treatment. In all, 35 children finished the complete study protocol.

Excluded were patients known with underlying severe illness, (secondary) infected eczema or signs of systemic infection, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis. In addition those receiving systemic therapy with corticosteroids and those showing severe growth retardation were excluded. In case of overt

CAPSULE SUMMARY

- Wet-wrap treatment (WWT) is a crisis intervention modality in severe atopic dermatitis.
- WWT with diluted topical corticosteroids is more efficacious than WWT with emollients only in atopic dermatitis (evidence level 3, grade B).
- WWT should be considered in therapy-resistant severe childhood atopic dermatitis if nurse support is available.

Abbreviations used:

AD:	atopic dermatitis
HPA:	hypothalamic-pituitary-adrenal
POEM:	Patient-Oriented Eczema Measure
QOL:	quality of life
WWT:	wet-wrap treatment

impetiginization, wet wrapping could be delayed until 72 hours after commencing antibiotics. Eczema herpeticum was a contraindication for the use of wet dressings.

Patients were studied for 4 weeks after randomization to receive either WWT with verum (diluted mometasone furoate 1:3 body and 1:19 face) or emollient (petroleum 20% in cetomacrogol cream). The concentration/dilution of the corticosteroid was chosen based on earlier studies with fluticasone propionate 0.005% cream.¹¹

In week 1 the study cream was applied once daily on the whole body using the finger tip unit method.¹⁶ In weeks 2 to 4, the cream was likewise applied on lesions only, ie, once daily for 4 consecutive days per week. Emollients were used in both groups on the other 3 days in weeks 2 to 4. Skin condition was checked at day 0 (initial visit), day 1 (1-3 days after day 0), day 4, day 7, day 14, and day 28 (end of study).

Outcome measures were objective SCORAD, Patient-Oriented Eczema Measure (POEM)/quality of life (QOL) (parents), adverse events, and medication consumption. Patients were not allowed to use other emollients or topical agents.

For fasting cortisol, blood samples were taken between 8 and 9 AM at day 0 or day 1, day 7, day 21, and day 28.

Criteria for withdrawal

Subjects were withdrawn from the study in case of the following adverse events: severe suppression of HPA (early morning serum cortisol in 2 consecutive samples >2 SD under reference value, followed by an anomalous ACTH stimulation test and/or metyrapone test), overt impetiginization, or eczema herpeticum. Furthermore, symptoms of systemic infection with skin involvement and severe local skin reactions were reasons for withdrawal. Lastly, deviation from the protocol, including lack of compliance with dosing or visit schedule, lost to follow-up, and lack of efficacy defined by a SCORAD not decreased by 10% on day 7 were reasons for withdrawal.

Objective SCORAD

The objective SCORAD described by Oranje et al¹⁷ served as clinical scoring system. It is based on the

SCORAD Index developed by the European Task Force on Atopic Dermatitis, excluding the subjective symptoms.^{18,19}

POEM/QOL

Dutch-language versions of the POEM²⁰ and Infant's Dermatitis QOL Index²¹ were produced by forward/backward translation (English to Dutch, Dutch to English, and then in Dutch again). These questionnaires are intended to gain insight into the QOL of children with AD. The latter is designed for children younger than 4 years. Comparing scores before and after treatment reveals the influence of treatment on QOL. Higher scores denote worse quality.

Statistical analysis

To account for the correlation in the measurements taken from the same patient, we performed a repeated measurements analysis for each parameter using linear mixed effects models as described by Verbeke and Molenberghs.^{22,23} In the specification of the fixed effects part we used time as a categorical variable and its interaction with the treatment group. In the random- part we used random slopes (treating time as continuous variable). The models' assumptions were validated using residuals plots. The analysis was performed in R Version 2.15.2 (2012-10-26) using package nlme (Version 3.1-108), and the significance level was set at 5%. Calculations were made with Fisher exact test and Mann-Whitney test.

RESULTS

Baseline characteristics

In all, 56 patients were eligible based on an objective SCORAD (twice scored with at least a day's interval) equal to or more than 35 to 40. Parents of 2 patients declined participation and parents of 3 other patients did not agree with WWT. Furthermore, 12 other patients were not included: 5 because the objective SCORAD was too low at day 1; 1 whose face was mainly affected; 1 who did not cooperate; and 5 for logistic reasons such as lack of hospital facilities or conflicting holidays. Thus, 39 patients were included and labeled as intention to treat. A total of 35 patients finished the complete study protocol and were labeled as per protocol. Reasons for noncompletion were the following: in 2 cases the objective SCORAD had not decreased by 10% or more after 1 week; in 1 case the mother declined further participation; and in 1 case the child refused further WWT. After randomization, the verum group consisted of 19 patients and the placebo group of 20 patients (Table 1).

Table I. Inclusion of subjects for the wet-wrap study, diluted mometasone furoate versus emollient as described in this report

Wet-wrap therapy indicated (objective SCORAD >35-40)	56
Declined by parents	5
Not started in study	12
Included in study	39
Randomization	Placebo: 20 Verum: 19
Finished per protocol	35 (4 dropouts before study end) Placebo: 16 Verum: 19

Characteristics of the 39 included cases are given in Table II. Fifteen in the placebo group were male (75%) versus 10 in the verum group (53%). Seventeen in the placebo group (85%) and 16 in the verum group (84%) started therapy with a mask (because of very severe AD). Twelve in the placebo group (60%) and 8 in the verum group (42%) started WWT with emollients only between day 0 and day 1, because fasting cortisol could not be tested at day 0 but had to be performed on day 1; 11 in the placebo group (55%) and 13 in the verum group (68%) started WWT in the clinic (1 week). There were no significant differences between the groups treated in the different settings ($P > .05$, Fisher exact test). Mean age in the placebo group was 43 versus 38 months in the verum group. The mean objective SCORAD at day 0 in the placebo group was 42 versus 44 in the verum group. These differences also were not significant ($P > .05$, Mann-Whitney test). There was an age-dependent effect, in that the most statistically significant results were obtained in the age group 6 to 9 years, followed by the age group 0 to 3 years (Supplemental data available at <http://www.jaad.org>).

Objective SCORAD results

Overall, the 2 treatment groups statistically significantly differed in the mean longitudinal evolutions of the objective SCORAD (likelihood ratio test = 84, d.f. = 6, P value < .0001). The estimated differences in the mean SCORAD per time point are presented in Table III. Fig 1 shows the fitted mean longitudinal evolutions for the objective SCORAD. The values of the objective SCORAD declined in both groups, albeit much faster and more pronounced in the verum group.

QOL and POEM

QOL significantly differed between the 2 treatment groups (likelihood ratio test = 17, d.f. = 2, P value .0002). This did not hold true for the POEM

Table II. Characteristics of study population of wet-wrap treatment comparing diluted mometasone furoate versus emollient divided into verum (corticosteroids) and placebo (emollients) groups

Variable	Placebo		Verum	
	N	%	N	%
Sex				
Male	15	75	10	53
Female	5	25	9	47
$P = .19^*$				
Mask				
Yes	17	85	16	84
No	3	15	3	16
$P = 1.00^*$				
WWT with emollient 1-3 d				
Yes	12	60	8	42
No	8	40	11	58
$P = .34^*$				
Treatment start in clinic				
Yes	11	55	13	68
No	9	45	6	32
$P = .51^*$				
	Mean (q1-q3)	Range	Mean (q1-q3)	Range
Age, mo	42.9 (7.8-80.2)	6-124	37.8 (13.0-50.0)	7-104
$P = .89^\dagger$				
Objective SCORAD	42.0 (36.8-44.2)	35-60	43.8 (40.0-48.5)	35-54
$P = .25^\dagger$				

Q1, Quarter 1; q3, quarter 3; WWT, wet-wrap treatment.

*Fischer exact test.

† Mann-Whitney test.

Table III. Difference in average objective SCORAD between placebo (emollient) and verum (diluted mometasone furoate) per time point after randomization

Day	Difference	SE	P value
1	0.552	2.355	.8150
4	-14.358	2.526	<.0001
7	-16.308	2.489	<.0001
14	-12.171	2.699	<.0001
28	-9.927	3.268	.0028

(likelihood ratio test = 3.6, d.f. = 2, P value .1668). Figs 2 and 3 show the fitted average longitudinal evolutions for the QOL and POEM.

Dropouts

Four patients, all in the placebo group, dropped out during the study ($P = .11$, Fisher exact test). Treatment setting did not have any influence on the number of dropouts ($P = .63$, Fisher exact test).

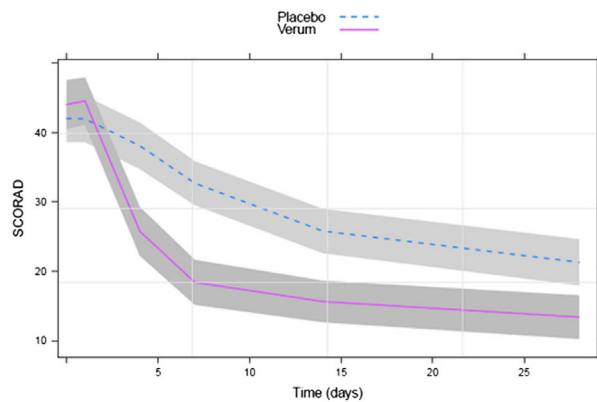


Fig 1. Fitted average longitudinal profiles for objective SCORAD. The *gray* and *light gray* areas denote 95% pointwise confidence intervals.

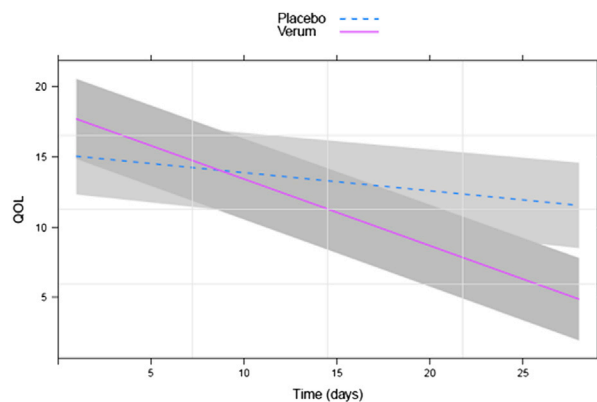


Fig 2. Fitted average longitudinal profiles for quality of life (QOL). The *gray* and *light gray* areas denote 95% pointwise confidence intervals.

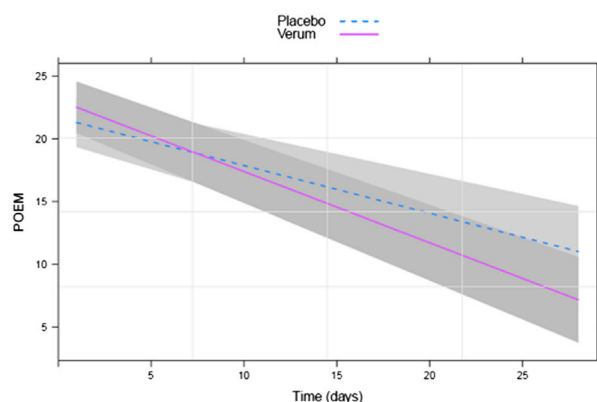


Fig 3. Fitted average longitudinal profiles for Patient-Oriented Eczema Measure (POEM). The *gray* and *light gray* areas denote 95% pointwise confidence intervals.

Adverse events

Mild to moderate folliculitis was seen in 2 patients in the placebo group and 9 patients in the verum group ($P = .01$). Severe folliculitis was seen in only 1

Table IV. Number of adverse effects in the wet-wrap therapy study comparing diluted mometasone furoate versus emollient between the placebo (emollients) and verum (mometasone furoate) groups

Variable	Placebo		Verum	
	N	%	N	%
Mild to moderate folliculitis				
Yes	2	10	9	47
No	18	90	10	53
$P = .01$				
Severe folliculitis				
Yes	0	0	1	5
No	20	100	18	95
$P = .49$				
Secondary infected eczema				
Yes	2	10	0	0
No	18	90	19	100
$P = .49$				
Suppression of HPA axis				
Yes	0	0	3	16
No	20	100	16	84
$P = .11$				
Mild/beginning decubitus				
Yes	2	10.0	0	0.0
No	18	90.0	19	100.0
$P = .49$				
Decubitus				
Yes	1	5.0	2	10.5
No	19	95.0	17	89.5
$P = .60$				

P values based on Fisher exact test.

HPA, Hypothalamic-pituitary-adrenal (assessed by measuring early morning cortisol).

patient in the verum group. Other adverse events were secondary infected eczema in 2 patients (not cultured) in the placebo group, mild or beginning decubitus by the mask in 2 patients in the placebo group, and decubitus by the mask in 1 patient in the placebo group and 2 patients in the verum group. At 1 measuring moment suppression of the HPA axis was observed in 3 patients in the verum group. None of the patients had eczema herpeticum (Table IV).

Amount of cream used during weeks 2 to 4

During week 1 the same amount of cream was applied in both groups (according to the protocol).

The treatment consisted of a 4-week lasting proactive schedule during which the frequency of corticosteroid applications was tapered.

Differences were calculated between weeks 2 to 4.

In the placebo group the mean amount of cream applied to the body was 67.5 versus 39.4 g in the

Table V. Amount of cream used in grams (emollient or diluted mometasone furoate [corticosteroids] 1:3 for the body and 1:19 for the face) with wet-wrap therapy in the placebo (emollients) and the verum (mometasone furoate) groups during weeks 2 to 4

	Minimum	Q1	Mean	Q3	Maximum
Cream on the body					
Placebo	13	34.2	67.5	91.5	117
Verum	10	16.0	39.4	62.2	71
$P = .07^*$					
Cream on the face					
Placebo	0	0.0	4.0	1.5	22
Verum	0	0.0	4.5	7.0	14
$P = .31^*$					

Q1, Quarter 1; Q3, quarter 3.

*Mann-Whitney test.

verum group ($P = .07$, Mann-Whitney test). The mean amount of cream applied to the face was 4.0 g in the placebo group versus 4.5 g in the verum group ($P = .31$, Mann-Whitney test) (Table V).

Mask

In all, 33 of all 39 patients started with a mask for facial WWT. Parents of 26 patients stopped this treatment because the child developed psychological problems. Therefore, only 13 patients continued during the full 4 weeks of treatment, 5 in the placebo group and 8 in the verum group ($P = .30$, Fisher exact test). Nine of all 13 had started treatment in the clinic versus 4 in the outpatient setting ($P = 1.00$, Fisher exact test).

DISCUSSION

This was a relatively long-term (4 weeks) study comparing WWT with diluted corticosteroids versus placebo. The results show that WWT with diluted corticosteroids acts faster and is more efficacious than WWT with emollients. Wolkerstorfer et al¹¹ and Devillers et al³ described WWT for eczema in observational case study series and showed that it was effective and well tolerated. Beattie and Lewis-Jones⁸ studied WWT in moderately severe eczema and concluded that outcome did not exceed that of conventional therapy. This is likely because of the use of hydrocortisone acetate 1%, which is a weak corticosteroid.²

In our study, objective SCORAD values declined in both groups of patients, albeit much faster and more pronounced in the verum group. This also held true for the QOL index. In contrast, the difference in POEM outcome was not statistically significant, although a positive trend toward better outcome in the verum group was found. Analysis showed that

most of the more problematic patients (less progress and more pruritus) indeed had received the placebo. This would also explain why statistically more cream was used in weeks 2 to 4 in the placebo group.

Adverse effects of WWT observed mainly concerned folliculitis, but usually very mild and not burdensome to the patients. Hindley et al¹⁰ reported significantly more skin infections in the WWT group, even requiring antibiotics.

In this study, the HPA axis was suppressed in 3 patients only during 1 evaluation only in the first week, when relatively the greatest amount of cream was applied.

For most patients or parents the mask eventually presented a psychological problem and was discarded. Face treatment was then often continued with pimecrolimus 1% cream and this obtained satisfactory outcome in most of them.

Limitations of our study are the relatively small group of patients and the limited duration of treatment, ie, 4 weeks only. We recommend future studies investigate options such as 1 to 2 weeks treatment with diluted corticosteroids and then continuation with emollients. We would like to speculate that proactive long-term treatment for 3 to 6 months will be beneficial.

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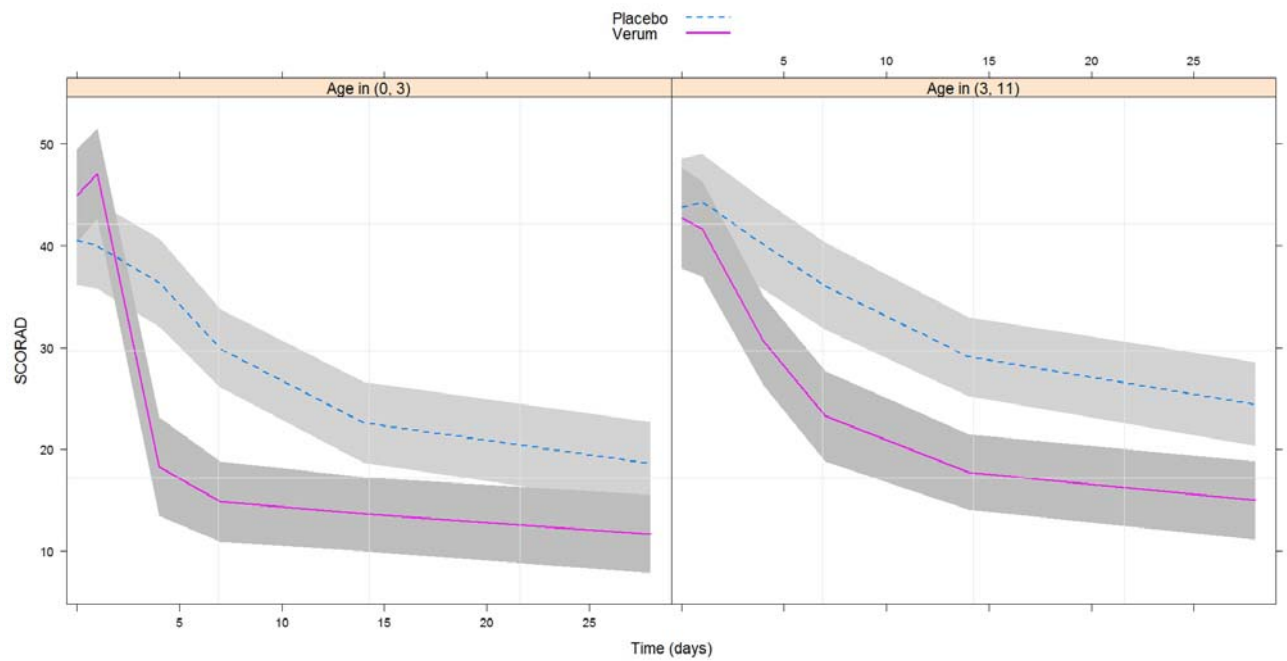
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ANALYSIS 1 – Age in 2 categories: (0, 3) & (3, 11)

- Treatment effect (LRT = 117.6, df = 12, $p < 0.001$)

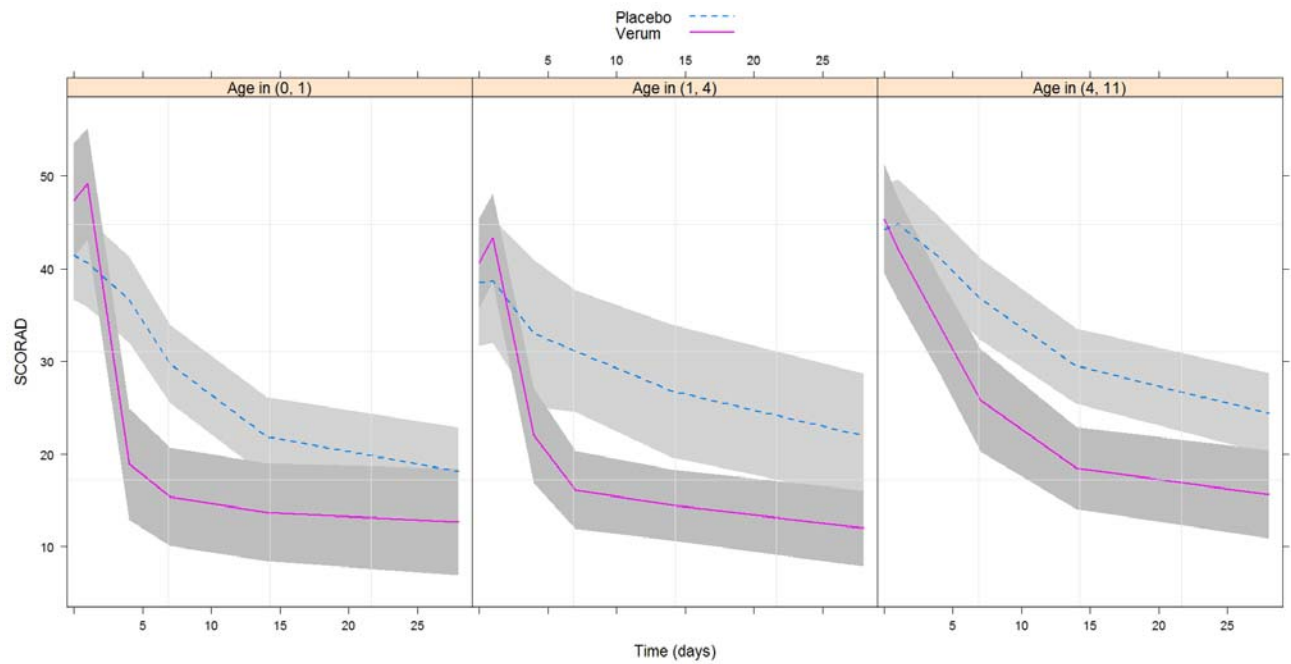
- *Age effect (LRT = 49.5, df = 12, $p < 0.001$)



ANALYSIS 2 – Age in 3 categories: (0, 1), (1, 4) & (4, 11)

- Treatment effect (LRT = 111.7, df = 18, $p < 0.001$)

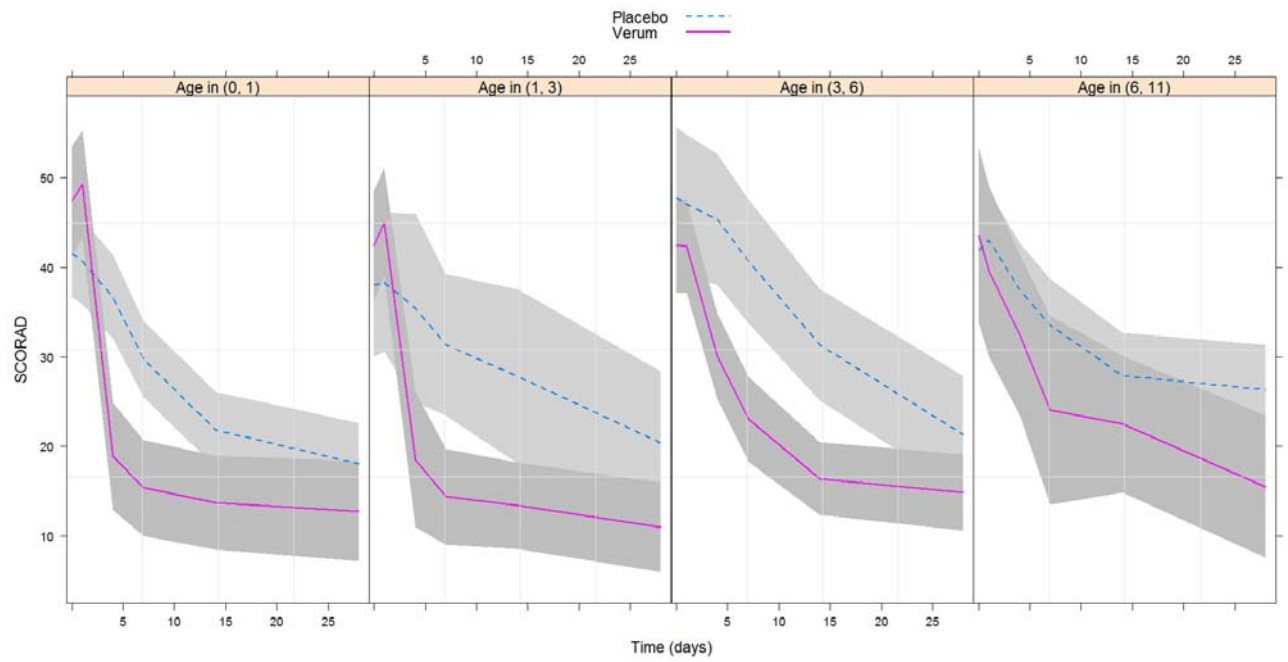
- *Age effect (LRT = 55.2, df = 24, $p < 0.001$)



ANALYSIS 3 – Age in 4 categories: (0, 1), (1, 3), (3, 6) & (6, 11)

- Treatment effect (LRT = 124.0, df = 24, $p < 0.001$)

- *Age effect (LRT = 64.6, df = 36, $p = 0.002$)



*P-values (calculated by statistician) for age effect are about the interaction terms between treatment and age, i.e. under the null hypothesis there is no difference in treatment effect between the different age categories