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# Chitosan Conjugated CLA Gel For Treatment of Stable Chronic Psoriasis Vulgaris

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## Summary

A new gel containing Conjugated Linoleic Acid (CLA) used in adult patients with chronic stable psoriasis vulgaris, showed promising therapeutic results. The duration of the study was 4 weeks. Forty patients were included; 20 received in a randomised manner treatment with the new gel and 20 got placebo. The study was carried out as a double blind trial.

Thirty-eight patients concluded the study according to the protocol. The two withdrawals were in the placebo group and were due to deterioration of the disease. The treatment with the CLA gave significant improvements in the psoriasis disease while the results in the placebo group were not significant.

The results were judged through clinical evaluation by the investigator (AL) as well as with objective measurements using Dermascan C. A significant correlation between the subjective clinical evaluation and the objective measurements is observed.

The tolerability was good in both groups. However, several patients in both groups were of the opinion that the vehicle had a drying effect on the skin. Based on these observations it is recommended that the present vehicle should be changed in order to avoid the drying effect on the skin.

## Riassunto

Un nuovo gel contenente acido linoleico coniugato (CLA) utilizzato per pazienti adulti affetti da una forma cronica e stabile di psoriasi vulgaris, ha mostrato di possedere una promettente attività terapeutica.

La durata dello studio è stata di 4 settimane. 40 pazienti suddivisi in 2 gruppi di 20, selezionati in modo casuale, sono stati trattati in doppio ceco con il prodotto in studio o con il placebo. 38 pazienti hanno concluso la terapia in accordo al protocollo. 2 pazienti appartenenti al gruppo del placebo hanno interrotto la terapia per il peggioramento osservato.

Il trattamento con CLA ha fatto registrare buoni miglioramenti che non si sono avuti con il placebo.

I risultati ottenuti sono stati valutati clinicamente e con l'uso del Dermascan C.

Buona è stata sia la correlazione tra i risultati dell'indagine soggettiva e quella oggettiva, che la tollerabilità del prodotto e del placebo. Comunque molti pazienti di entrambi i gruppi hanno affermato che il veicolo provocava loro secchezza cutanea. Dati questi giudizi si stanno studiando veicoli alternativi.

# INTRODUCTION

Psoriasis is a common, genetically skin disorder. Between 80 to 90 percent of the patients suffer from localised, stable plaque-type lesions. This patient group is commonly treated with topical steroids, calcipotriol or home phototherapy. Patients with severe, widespread lesions are usually treated with ambulatory phototherapy or oral therapy such as retinoids, cyclosporin or methotrexate. In rare cases hospitalisation is needed. The pathogenesis of psoriasis is still unclear. High amounts of saturated fatty acids, e.g. arachidonic acid, in psoriatic epidermis may be of importance. In a pilot study oral administration of chitosan conjugated CLA had a beneficial effect on psoriasis of the stable type. The aim or the present study was to evaluate the effect of topically used chitosan conjugated CLA of chronic psoriasis plaques in a placebo-controlled way.

# MATERIAL AND METHOD

The study was carried out as a randomised vehicle (placebo) controlled study in
40 patients with chronic stable psoriasis. The administration of the formulations was randomised meaning that half of the patients received the active preparation and the other half received the vehicle (placebo). The duration of the treatment was 4 weeks and the formulations were applied b.i.d. (in the morning and in the evening during the study period.

## *Investigational formulations*

The patented formulation (approved June 5 2001;Norwegian patent no. 310176) used in this study were made according to a formula developed by one of the authors (JW). The conjugation is made as follows: 100g CLA (Tonalin 80,Natural ASA Norway) is heated to 70°C under pressure with 30 g Chitosan (Chitoclear 400,Primex AS Norway). When conjugation has taken place (milky appearance of the solution ) it is cooled down to 50°C and the other ingredients are added. Retinyl palmitate (RA) is conjugated with chitosan in the same way as for CLA. The gel base is of a standard type and is used as placebo. Other ingredients are Vitamin E as stabiliser and preservative and lactic acid used for pH adjustment. to 6.5.
To our knowledge this is the first gel containing CLA and RA conjugated with chitosan. Substances sensitive to oxidation, as both CLA and RA are can be successfully protected through conjugation. It has further been shown that skin penetration of the active compounds (CLA and RA ) is improved when the substances are used in a conjugated form.
The CLA gel and the placebo gel were produced by Regina Cosmetics AB, Halmstad Sweden.
Polar PHARMA OY Espoo Finland delivered the drugs in similar containers to keep the blindness. The appearance and cosmetic properties of the two gels were identical. Code envelopes accompanied the drug deliveries. The code envelopes should only be opened in emergency situations. All envelopes, opened and unopened should be returned to the sponsor at the conclusion of the study.

## *Efficacy measurements*

The investigator (AL) carried out the clinical evaluation the patients with respect to the psoriasis disease initially, after 2 and 4 weeks using a 4 –point scale (0=absent, 1=mild, 2=moderate and 3=severe). The following items were scored: Crnsting,thickness erythema and itching.
Dermascan C (Cortex,Århus,Denmark) was used for measuring crusting and acanthisis (mm). Erythema index was measured using a photospectrometer.

## *Ethics*

The study was carried out in accordance with the Hong Kong (1989) amendment to the Decla-

ration of Helsinki (1964). The study was monitored in accordance with GCP (Good Clinical Pratice) standards. The trial protocol, the patient information and the informed consent form were approved by an ethics committee before enrolment of any patient into the study.
All patients signed an informed consent before inclusion in the study.

### Statistical methods

A significance level of 5% was used in the tests and two-tailed tests were applied. Mean was used for estimation over continuos and near continuos variables

## RESULTS

Forty Caucasian patients were included in the study, 25 males and 15 females with an average age of 56.0 years. All patients fulfilled the requirements for participation and all gave their informed consent before being included in the study. Two patients in the placebo group did not complete the study according to the protocol due to deterioration of the disease. The investigator therefore decided to withdraw these patients from the study and start alternative treatments. This decision was taken after the 2 week control for both patients. One patient in the group treated with the CLA gel stopped treatment after 2 weeks due to complete healing.
Demographic data for the two treatment groups are presented in Table I.

**Table I.**
*Demographic data for the two treatment groups. Average values with SD in brackets.*

| PARAMETER | CLA GROUP | PLACEBO GROUP |
|---|---|---|
| Gender | 11 males / 9 females | 14 males / 6 females |
| Age (years) | 58.4 (8.8) | 53.6 (70) |
| Duration of the disease (years) | 22.7 (3.4) | 23.9 (3.1) |

The two treatment groups are comparable with respect to demographic parameters at baseline. The patients in the CLA group are somewhat older than in the placebo group, but the difference is not statistically significant ($p>0.05$). The patients in both groups had had psoriasis for more than 20 years (22.7 years and 23.9 years in the two groups, respectively).
Table II lists the medical background history at inclusion.

**Table II.**
*Medical background history at inclusion; Number of patients.*

| | CLA GROUP | PLACEBO GROUP |
|---|---|---|
| Onychopathia (Y/N) | 10 / 10 | 12 / 8 |
| Arthopathia (Y/N) | 7 / 14 | 8 / 12 |
| Concomitant disease (Y/N) | 6 / 14 | 2 / 18 |

As can be seen from the table, the distribution of patients with and without onychopathia, arthopathia and concomitant disease is similar in the two treatment groups. There is no significant difference in any of the parameters between the groups.
All patients fulfilled the inclusion criteria in the study protocol. With respect to concomitant disease, none of the patients had diseases and/or pharmacological treatments conflicting the inclusion criteria. Based on demographic data (Table I) and the medical background history (Table II) the two patient groups are well matched at the start of the study, and no significant differences are found in any of these parameters.
None of the patients had received treatment for their psoriasis within 2 weeks prior to entering the study. The majority of the patients had previously been treated with topical steroids and phototherapy.

Table III lists parameters describing the severity of the psoriasis disease at inclusion in the study. As can be seen from the table, the different parameters are quite similar expect for the grade of itching, which is reported to be significantly higher in the group receiving CLA treatment ($p<0.05$). However, for the other parameters it is no significant difference in the psoriasis disease at baseline.

**Table III.**

*Psoriasis related parameters in the two groups of patients at baseline. SD in brackets. N=20+20.*

| CLINICAL EVALUATION | CLA GROUP | PLACEBO GROUP |
|---|---|---|
| Grade of crusting | 2.1 (0.3) | 2.0 (0.4) |
| Grade of thickness | 2.6 (0.3) | 2.6 (0.4) |
| Grade of erythema | 2.7 (0.5) | 2.8 (0.5) |
| Grade of itching | 1.2 (0.2) | 0.8 (0.3) |
| DERMASCAN MEASUREMENTS | | |
| Munro's microabscesses | 2.20 (0.4) | 2.35 (0.3) |
| Acanthosis (mm) | 0.44 (0.1) | 0.49 (0.2) |
| Subepidermal oedema | 0.25 (0.1) | 0.25 (0.2) |
| Erythemal index | 20.3 (2.4) | 18.3 (2.1) |

The conclusion to be drawn when using the data from Tables I-III is that the two patient groups are clinically comparable with respect to demographic data, medical background history and the severity of the psoriasis disease. The only deviation observed is that the grade of itching is significantly higher in the group receiving CLA treatment.

In Table IV we have listed the development of the disease during the 4 week treatment period in the two treatment groups based on the clinical evaluation. As can be seen from the table, it is an improvement in all the 4 clinical parameters evaluated in the CLA group. The improvements are statistically significant as compared to the baseline values for all parameters in the CLA group, but not in the placebo group where the changes are negligible or not existing. The improvement in the 4 clinical parameters in the CLA treated group is sizeable amounting to 40-50% as compared to baseline situation.

**Table IV.**

*The development of the psoriasis disease during the treatment period based on the clinical evaluation. SD in brackets.*

| GROUP | PARAMETER | BASELINE (week 0) | At week 2 0 - week 4 | At week 4 | Diff. Week | p-values |
|---|---|---|---|---|---|---|
| CLA group | Grade of crusting | 2.1(0.3) | 1.2(0.1) | 1.2(0.1) | 0.9 | p<0.05 |
| | Grade of thickness | 2.6(0.3) | 1.8(0.1) | 1.6(0.1) | 1.0 | p<0.05 |
| | Grade of erythema | 2.7(0.5) | 1.8(0.1) | 1.7(0.1) | 1.0 | p<0.05 |
| | Grade of itching | 1.2(0.2) | 0.6(0.1) | 0.6(0.1) | 0.6 | p<0.05 |
| Placebo group | Grade of crusting | 2.0(0.4) | 1.9(0.3) | 2.0(0.3) | 0 | ns |
| | Grade of thickness | 2.6(0.4) | 2.6(0.4) | 2.4(0.4) | 0.2 | ns |
| | Grade of erythema | 2.8(0.5) | 2.7(0.4) | 2.6(0.3) | 0.2 | ns |
| | Grade of itching | 0.8(0.3) | 0.5(0.2) | 0.6(0.2) | 0.2 | ns |

In table V we have listed the measurement done by Dermascan C and the erythermal index at baseline and throughout the study. When comparing the baseline values for the two groups, no statistical significant difference in any of the parameters can be found. Also from this point of view, the two groups are clinically comparable.

However, as can be seen from the table, it is a significant improvement in the four parameters in the CLA group during the treatment period, while this is not the case with the placebo groups where none of the changes reach statistical significance.

**Table V.**
*The development of the psoriasis disease during the treatment period based on Dermascan C measurements and erythemal index.*

| GROUP | PARAMETER | BASELINE (week 0) | At week 2 | At week 4 | Diff. Week 0 - week 4 | p-values |
|---|---|---|---|---|---|---|
| CLA group | Monro's microabsesses | 2.20 | 1.16 | 1.25 | 0.95 | p<0.05 |
| | Acanthosis (mm) | 0.44 | 0.34 | 0.36 | 0.08 | p<0.05 |
| | Subepidermal oedema | 0.25 | 0.11 | 0.11 | 0.14 | p<0.05 |
| | Erythemal index | 20.3 | 17.3 | 18.3 | 2.0 | p<0.05 |
| Placebo group | Monro's microabsesses | 2.35 | 2.2 | 2.0 | 0.15 | ns |
| | Acanthosis (mm) | 0.49 | 0.40 | 0.46 | 0.03 | ns |
| | Subepidermal oedema | 0.25 | 0.26 | 0.23 | 0.02 | ns |
| | Erythemal index | 18.3 | 17.7 | 18:2 | 0.2 | ns |

In table VI the results from the investigators' global assessment of the two groups of patients are listed. As can be seen from the table, 15 patients in the CLA group were evaluated as having effect of the treatment and 5 patients to have no effect. It is impressing that 9 patients (45%) were rated as completely cured/almost cured. After all, these patients had had psoriasis in average for more than 20 years. The results in the placebo group show that 6 patients bad effect while 14 had no effect.

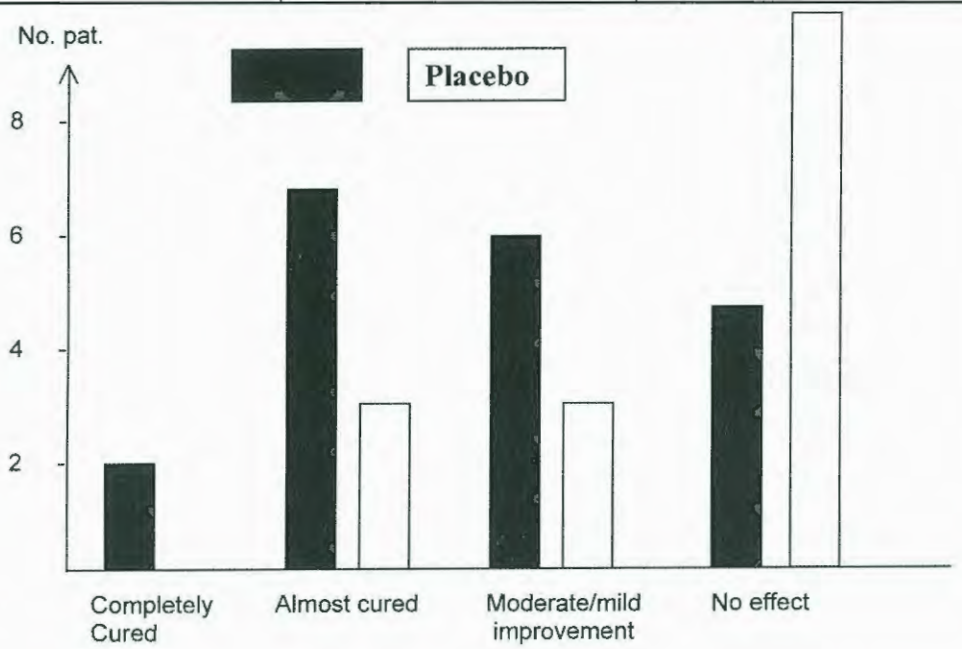
A comparison of the results in the two groups of patients is highly statistically significant in favour of the CLA treatment ($p<0.001$).

The results from the clinical evaluation by the investigator during the study (weeks 2 and 4) and the objective measurements carried out at the same visits, are highly correlated to the investigator's global evaluation of the status of the disease at the end of the study. The results show an improvement in the CLA groups, but not in the placebo treated group.

Based on the results from this study, the CLA gel seems to be an interesting treatment alternative for patients with psoriasis. As mentioned later in the report (Tolerability), some changes need to be made in the present galenical formulation in order to avoid the drying effect this formulation has on the skin.

**Table VI.**
*Clinical judgement by the investigator at the conclusion of the study (Number of patients).*

| RESULT | CLA GROUP | PLACEBO GROUP |
|---|---|---|
| Completely cured | 2 | 0 |
| Almost cured | 7 | 3 |
| Moderate/mild improvement | 6 | 3 |
| No effect | 5 | 14 |




## TOLERABILITY

No severe adverse events of the treatment were reported in either of the two groups. However, a number of patients reported that the gel had a drying effect on the skin. In the placebo group, 14 patients reported a drying effect on the skin, while one reported pruritus and another irritation. Both the last ones can of course be related to the drying effect. In the CLA group, 16 patients reported a similar drying effect. The lesson to learn from this is to add more lipids to the gel in order to avoid the drying effect. From the above mentioned it is obvious that the present concentration of CLA in the gel in itself is not able to reduce the drying effect. Other galenical formulation techniqnes have to be considered in order to avoid this effect on the skin and give the gel an improved dermatological tolerability.

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