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XP-828L in the Treatment of Mild-to-Moderate Psoriasis: A Randomized, Double-blind, Placebo-controlled Study

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Abstract

Background: XP-828L, a protein extract obtained from sweet whey, has demonstrated potential benefit for the treatment of mild to moderate psoriasis in an open-label study. Objective: To study in a randomized, double-blind, placebo-controlled study the safety and efficacy of XP-828L in the treatment of mild to moderate psoriasis. Design: XP-828L 5 g/d (group A, n=42) or placebo (group B, n=42) was given orally for 56 days followed by XP-828L 5 g/d in group A and by XP-828L 10 g/d in group B for an additional 56 days. Results: Patients receiving XP-828L 5 g/d for 56 days had an improved Physician's Global Assessment (PGA) score compared with patients under placebo ($p < 0.05$). Considering the data of group A only, the PGA score improved from day 1 to day 56 ($p < 0.01$); the Psoriasis Area and Severity Index score improved as well, but to a lesser extent ($p < 0.05$). Conclusion: Oral administration of 5 g/d XP-828L compared with a placebo significantly improved the PGA score of patients with mild to moderate psoriasis. (*Altern Med Rev* 2007;12(4):352-359)

The therapeutic challenge is to achieve a compromise between the efficacy and the safety of a product, especially in mild to moderate psoriasis. In current practice, therapies for psoriasis are often rotated to take advantage of unique features and benefits to minimize the development of adverse events.

Nutraceutical products are commonly used to support the usual treatments of many health disorders.

In general, nutraceutical targets are less specific than pharmaceutical products, which makes them relatively less effective for a specific disease. Nutraceuticals are associated with fewer side effects and may represent a good long-term reinforcement to the usual pharmacologic treatments. Clinical data on the use of nutraceutical products for psoriasis are still scarce. Conflicting and nonconclusive results were reported in clinical trials studying the effects against a placebo of fish oil supplementation alone,¹⁻³ with ultraviolet B (UVB),⁴ or with corticosteroids.⁵

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Advitech is the developer of XP-828L.



Original Research

XP-828L is a patented new dietary ingredient made of a protein extract obtained from bovine whey. The bioactive profile of XP-828L could be related to the presence of growth factors, active peptides, and immunoglobulins in the extract. *In vitro* experiments showed that XP-828L inhibits production of T helper 1 cytokines (interferon (IFN)- γ and interleukin (IL)-2), suggesting that XP-828L could improve T helper 1-related disorders, such as psoriasis.⁶ Recently, an open-label clinical trial suggested some potential for XP-828L to reduce psoriasis severity.⁷ Today, protein complexes derived from whey have been shown to have clinically proven health benefits in cancer, hepatitis, human immunodeficiency virus (HIV), cardiovascular disease, and osteoporosis.⁸

The primary objective of the study was to confirm the efficacy of XP-828L to reduce psoriasis severity in a randomized, double-blind, placebo-controlled clinical trial in patients with mild to moderate psoriasis. The secondary objectives consisted in assessing the efficacy of a dose of 10 g/d and determining the safety profile of the treatment at all of the dosages used.

Methods

Protocol

This was a double-blind, randomized, placebo-controlled, parallel-arm dose comparison study conducted in two independent centers (Centre de Recherche Dermatologique du Quebec, Quebec, and Innovaderm Research, Montreal) by two independent dermatologists between December 2004 and June 2005.

Women (n=27) and men (n=57) adult patients (18 years or older) with a clinical diagnosis of stable psoriasis involving $\geq 4\%$ of body surface were recruited. The required sample size was determined by a biostatistician based on results from a previous open-label clinical trial.⁷ Patients with pustular, erythrodermic, or palmoplantar psoriasis or active psoriatic arthritis were excluded. Pregnant or nursing mothers or those not using dependable contraceptive means were not eligible. Patients with a skin disease that could interfere with the evaluation of psoriasis, who were not compliant owing to alcoholism, or with a history of drug-abuse or intellectual deficiency were excluded. Patients using lithium, who had a history of cancer in the past 5 years,

who were known to be HIV positive, who were allergic to lactose and/or proteins of milk, who planned to expose themselves to the sun or to sun lamps to treat psoriasis, or with unstable diabetes were also excluded. Patients with increased creatinine, systolic arterial pressure > 140 mm Hg, diastolic arterial pressure > 90 mm Hg, or a heart rate > 100 /min were not eligible. Patients had to stop systemic treatments (including psoralen plus ultraviolet A) for psoriasis at least 28 days prior to randomization and topical treatments including UVB phototherapy for at least 14 days before randomization to be eligible. Tar shampoos were allowed for scalp psoriasis, as well as tar and low-potency topical steroids for facial and genital psoriasis. The study was approved by an ethics committee, and written informed consent was obtained from each patient before initiating any study procedure.

XP-828L is a whitish powder with an odorless to slightly milky odor manufactured from a commercial whey protein isolate obtained from cow's milk (Armor Proteines, Elle et Vire, Conde sur Vire, France). The placebo consisted of food-grade microcrystalline cellulose (Wiler PCCA Inc., London, ON). A double-blind test product was provided as 2.5 g pouches (Pet Foil Poly containing a polyethylene liner to protect from ambient humidity) filled either with XP-828L or placebo. The powder was to be taken orally twice daily before morning and evening meals.

Patients were randomly allocated to receive XP-828L 2.5 g twice daily (group A) or placebo (group B) for the first 56 days. During the following 56 days, group A continued to receive XP-828L 2.5 g twice daily, whereas group B received XP-828L 5 g twice daily. The random allocation of patients to active treatment or to placebo was determined according to a computer-generated list of randomization. This list was made available only to the sponsor's clinical coordinator involved in the preparation and distribution of pouches of study medication to study sites. Neither the participant in the study, the investigators, nor the personnel of the different sites were aware of the code. A sealed copy of the randomization list was provided to the study manager and could be opened only in case of a serious adverse event.

Efficacy Assessments

Efficacy was based primarily on the Physician's Global Assessment (PGA), an assessment of overall lesion severity comprising six categories, ranging from none (category 0) to very severe (category 5), based on plaque elevation, scaling, and erythema.^{9,10} Other efficacy assessments included the Psoriasis Area and Severity Index (PASI), body surface area (BSA) covered with psoriasis, and itch severity (0=no itch and 3=severe, bothersome with difficulty in performing daily activities and causing sleep disturbances). The PASI is a physician-assessed outcome based on the extent of involved skin surface and severity of erythema, desquamation, and plaque induration, with a score ranging from 0 to 72.^{9,10} Efficacy assessments were done at day 1 (baseline), day 56, and day 112. If a value was missing, the last available observation was carried forward for analysis.

Safety Assessment

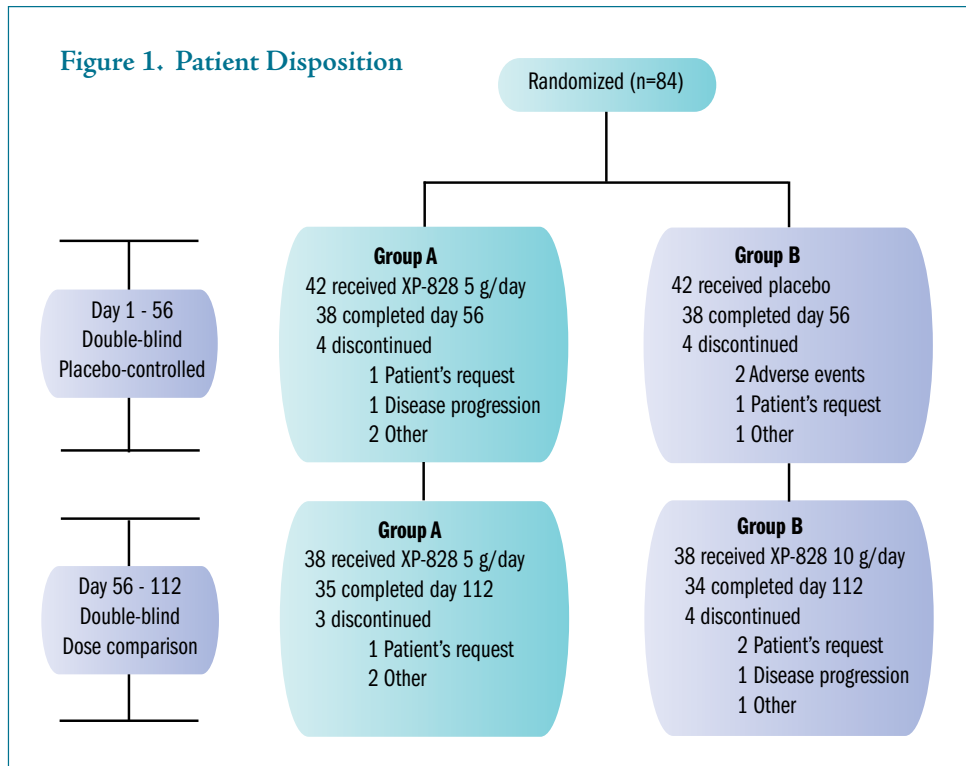
Safety was assessed by evaluating adverse events at each visit. Blood samples for hematology and chemistry analysis and urine samples were collected before randomization and at days 4, 7, 28, 56, 59, 62, 84, and 112 and were analyzed by a central laboratory.

Statistical Analysis

PGA and PASI scores for patients who received XP-828L were compared with those from patients under placebo at days 56 and 112 for each tested dose. Gender, age, and baseline PASI score were included as covariables when appropriate.

Continuous end-point variables were analyzed using mixed-model analyses of variance or analyses of

Figure 1. Patient Disposition



covariance, controlling for baseline values. Score changes over time were analyzed using two-tailed Student's unpaired t-tests. Dichotomous end points and safety parameters were analyzed using chi-square tests. All statistical analyses were performed on an intent-to-treat and on a per protocol basis (completers with $\geq 80\%$ compliance). In all cases, a p value < 0.05 was considered statistically significant. Data were analyzed by the procedure MIXED for repeated measurements in SAS, version 8.2 (SAS Institute, Cary, NC), plus StatView, version 5.0.1 (SAS Institute), and Systat 11.0.

Results

Patient Characteristics

Eighty-four patients were enrolled for this study and randomly assigned to both groups (Figure 1). No difference was found between both groups in gender (31 and 26% male for group A and group B, respectively), race (98 and 95% Caucasian for group A and group B, respectively), age (46.5 ± 13.4 years and 47.1 ± 12.6 years for group A and group B, respectively) or weight (81.6 ± 17.5 kg and 84.1 ± 22.7 kg for group A and group B, respectively). Fifteen patients (18%) did

not complete the entire study. Five patients discontinued following consent withdrawal, two patients because of unrelated adverse events, and two patients discontinued owing to disease progression. Compliance with the test product was 93% in both groups. The per protocol data set excluded six patients for whom compliance with testing the product was less than 80%.

Treatment Efficacy

A clinical improvement in the psoriasis plaque severity was associated with a decrease in PGA, PASI, BSA, and the severity of the itch.

Physician's Global Assessment: Intergroup Analysis

In the intent-to-treat data set, the PGA score at day 56 was lower in XP-828L-treated patients than in the placebo group ($p < 0.05$). However, no change was observed at day 112. In the per protocol data set, although a strong tendency was observed at day 56, the difference between the PGA scores of group A and group B was not statistically significant ($p = 0.089$) (Table 1).

Physician's Global Assessment: Intragroup Analysis

In the intent-to-treat data set of group A, the PGA score decreased from 3.05 ± 0.44 at day 1 to 2.79 ± 0.61 at day 56 ($p < 0.005$) and remained identical at day 112 (2.79 ± 0.69 , $p < 0.005$). In the intent-to-treat data set of group B, no significant change in the PGA score was observed between days 1, 56, and 112. In the per protocol data set of group A, the PGA score decreased from 3.03 ± 0.43 at day 1 to 2.75 ± 0.60 at day 56 ($p < 0.01$) and remained stable at day 112 (2.76 ± 0.68 , $p < 0.005$), whereas no change was observed in group B (Table 1).

Table 1. Physician's Global Assessment Score over Time

Physician's Global Assessment	Group A	Group B
<i>Intent-to-treat</i>		
Day 1	3.05 ± 0.44	3.12 ± 0.45
Day 56	2.79 ± 0.61^{bc}	3.05 ± 0.54
Day 112 ^a	2.79 ± 0.69^c	2.98 ± 0.75
<i>Per protocol^d</i>		
Day 1	3.03 ± 0.43	3.13 ± 0.46
Day 56	2.75 ± 0.60^c	2.97 ± 0.50
Day 112 ^a	2.76 ± 0.68^c	2.95 ± 0.76

Data are expressed as mean \pm SD. ^a Group B received 10g/day of XP-828L between days 56 and 112. ^b $p < 0.05$ versus Group B at day 56, ^c $p < 0.005$ versus day 1 for Group A. ^d Group A: $n = 36$, and Group B: $n = 37$.

Table 2. Psoriasis Area and Severity Index Score over Time

PASI score	Group A	Group B
<i>Intent-to-treat</i>		
Day 1	8.94 ± 3.97	8.79 ± 2.94
Day 56	8.36 ± 4.31^b	8.61 ± 3.97
Day 112 ^a	8.38 ± 4.53	8.44 ± 4.70
<i>Per protocol^c</i>		
Day 1	8.77 ± 3.99	8.82 ± 3.01
Day 56	8.35 ± 4.52	8.72 ± 4.20
Day 112 ^a	8.49 ± 4.56	8.51 ± 4.85

Data are expressed as mean \pm SD. ^a Group B received 10 g/day of XP-828L between days 56 and 112. ^b $p < 0.05$ versus day 1 for Group A. ^c Group A: $n = 36$, and Group B: $n = 37$.

Psoriasis Area and Severity Index: Intergroup Analysis

In the intent-to-treat or per protocol data set (Table 2), no change in the PASI score was observed between XP-828L- and placebo-treated patients. Five of 42 patients (11.9%) improved their PASI score by $\geq 40\%$ in group A compared with 2 of 42 patients (4.8%) in group B ($p = 0.4326$). Between day 1 and day 112, 8 of 42 patients (19%) improved their PASI score by $\geq 40\%$ in group A compared with 5 of 42 patients (11.9%) in group B ($p = 0.5477$) (Table 2). A PASI score of 50 was attained in four patients in group A at day 84 compared with only one patient in group B. However, at day 112, a PASI score of 50 was attained in six patients in group A and four patients in group B.

Psoriasis Area and Severity Index: Intragroup Analysis

In the intent-to-treat data set of group A, the PASI score decreased from 8.94 ± 3.97 at day 1 to 8.36 ± 4.31 at day 56 ($p < 0.05$). There was no additional improvement observed at day 112. In group B, no change was observed between days 1, 56, and 112 (Table 2).

Body Surface Area: Intergroup Analysis

In the intent-to-treat or per protocol data set, no change in BSA was observed between XP-828L- and placebo-treated patients (Table 3).

Body Surface Area: Intragroup Analysis

In the intent-to-treat data set of group A, no change in the BSA was observed between days 1, 56, and 112. At best, the decrease in BSA at day 56 tended to be statistically significant ($p = 0.0973$). In group B, no change in BSA was seen between days 1, 56, and 112 (Table 3).

Severity of the Itch: Intergroup Analysis

In the intent-to-treat or per protocol data set, no change in the severity of the itch was shown between XP-828L- and placebo-treated patients (Table 4).

Severity of the Itch: Intragroup Analysis

In the intent-to-treat data set of group A, no change in the severity of the itch was observed from day 1 to day 56, but a significant clinical improvement was demonstrated at day 112 (Table 4). In group B, no change in itch severity was recorded from day 1 to day 56, but an improvement was observed at day 112 ($p < 0.05$). However, no difference was seen between days 56 and 112 in both groups (Table 4).

Safety

Creatinine, total bilirubin, aspartate transaminase, and alanine transaminase concentrations did not vary in both groups through the study period (Table 5). During the first 56 days, there were no differences in the number of adverse events experienced by patients of group A (17 patients (40.5%)) and group B (19 patients (45.3%)). Between days 56 and 112, 25 patients (59.5%) in each group reported at least one adverse event. The most commonly reported adverse events

Table 3. Body Surface Area of Psoriasis over Time

Body Surface Area of Psoriasis	Group A	Group B
<i>Intent-to-treat</i>		
Day 1	9.07 ± 4.32	8.96 ± 5.85
Day 56	8.65 ± 4.78	9.36 ± 7.98
Day 112 ^a	8.66 ± 5.53	9.35 ± 9.22
<i>Per protocol^b</i>		
Day 1	8.99 ± 4.43	9.07 ± 5.97
Day 56	8.54 ± 4.70	9.79 ± 8.41
Day 112 ^a	8.55 ± 5.72	9.56 ± 9.54

Data are expressed as mean \pm SD. ^a Group B received 10 g/day of XP-828L between days 56 and 112. ^b Group A: n=36, and Group B: n=37.

Table 4. Itch over Time

Itch	Group A	Group B
<i>Intent-to-treat</i>		
Day 1	1.57 ± 0.86	1.67 ± 0.90
Day 56	1.38 ± 0.96	1.48 ± 1.09
Day 112 ^a	1.26 ± 0.91^b	1.41 ± 0.91^b
<i>Per protocol^c</i>		
Day 1	1.53 ± 0.86	1.65 ± 0.92
Day 56	1.25 ± 0.87	1.43 ± 1.09
Day 112 ^a	1.34 ± 0.91	1.41 ± 0.94

Data are expressed as mean \pm SD. ^a Group B received 10 g/day of XP-828L between days 56 and 112. ^b $p < 0.05$ versus day 1 (intra group analysis). ^c Group A: n=36, and Group B: n=37.

were infection (26% and 29% for group A and group B, respectively), headache (9% and 25% for group A and group B, respectively), and pharyngitis (13% and 4% for group A and group B, respectively). One serious adverse event was reported in group A and consisted of severe pain owing to a bladder calculus in a patient with a history of nephrolithiasis. It was judged as unrelated to the study product.

Table 5. Biochemical Data

Ref. values	Day 1		Day 56		Day 112	
	Group A (n=42)	Group B (n=42)	Group A (n=39)	Group B (n=38)	Group A (n=35)	Group (n=34)
Creatinine ($\mu\text{mol/L}$) (44-106)	78.7 \pm 12.6	75.5 \pm 14.6	73.0 \pm 11.6	72.3 \pm 12.2	73.4 \pm 12.4	71.1 \pm 11.9
Total Bilirubin ($\mu\text{mol/L}$) (0-20)	9.9 \pm 4.8	9.9 \pm 4.6	9.3 \pm 3.6	9.0 \pm 3.2	8.6 \pm 2.8	8.8 \pm 2.7
AST (U/L) (10-35)	24.1 \pm 10.1	21.7 \pm 5.9	24.3 \pm 6.7	22.5 \pm 5.6	24.2 \pm 7.7	21.8 \pm 6.0
ALT (U/L) (5-40)	30.8 \pm 23.2	25.1 \pm 12.7	29.0 \pm 13.1	24.8 \pm 11.2	29.0 \pm 16.5	24.3 \pm 12.8

Data are expressed as mean \pm SD. ALT = alanine transferase; AST = aspartate transaminase

Discussion

Whey used to be considered a waste product from cheese and curd manufacturing. However, with its discovery as a functional food with potential health benefits, whey is now considered a coproduct of cheese manufacturing.⁸ Proteins contained in whey, such as β -lactoglobulin, α -lactalbumin, bovine serum albumin, lactoferrin, immunoglobulins, glycomacropeptide, and growth factors, are known to have health benefits⁸ and to modulate the immune system.^{11,12}

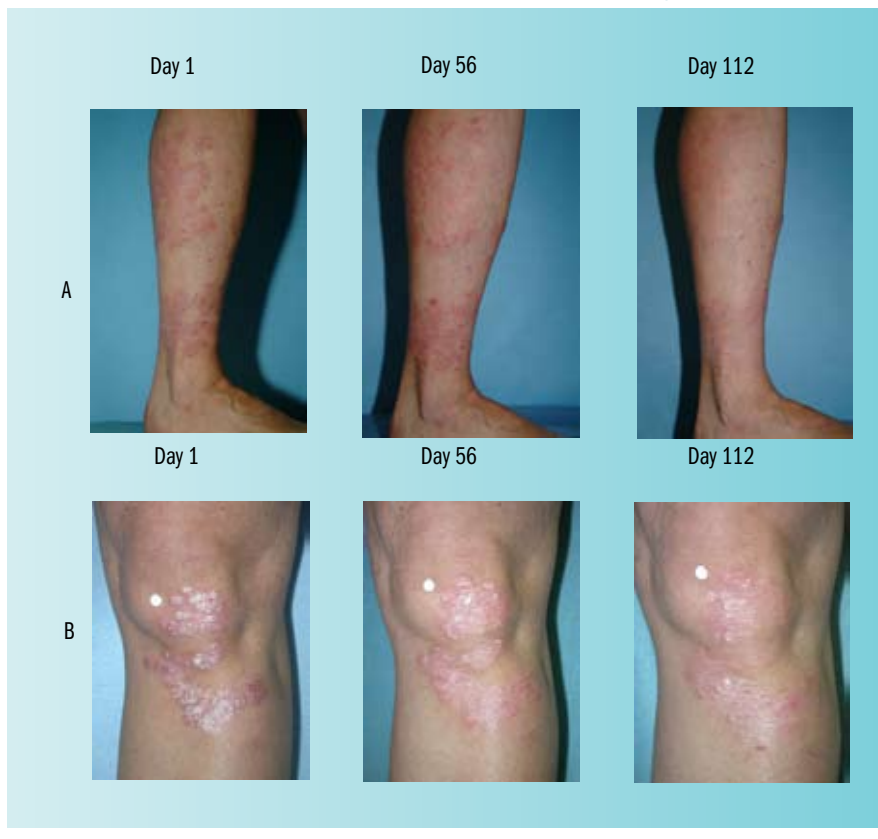
In this study, the clinical benefit of XP-828L therapy in patients with mild to moderate psoriasis was shown mainly by the PGA score (primary efficacy variable), which was improved at day 56 in patients who received 5 g/d of the product. Also, the intragroup analysis revealed that both PGA and PASI scores were improved at day 56 in patients using XP-828L (Tables 1 and 2), whereas no change was observed in the placebo group. These data suggest that a period of 56 days of treatment with 5 g/d of XP-828L is sufficient to induce and maintain a clinical improvement of mild to moderate psoriasis insofar as 112 days of treatment did not additionally improve PGA scores (Table 1). During the second phase of the study, in which the patients in group B received 10 g of XP-828L daily, no additional effect on PGA or PASI scores was observed with the double dose of XP-828L. The initial improvement was maintained by continuing to receive 5 g/d XP-828L, but future studies would be required to evaluate how long the improvement can be maintained and how fast

the disease will return following treatment interruption. At the present time, although a strong tendency of improvement has been observed, the reason why a dose of 10 g/d of XP-828L did not statistically improve psoriasis is unknown. No studies on efficacy-dose relationship studies have been performed on humans with XP-828L. Further studies should be conducted to determine the optimal dose of XP-828L for the treatment of psoriasis. However, the fact that the placebo group had been untreated for 56 days prior to XP-828L treatment may have worsened their condition, even though it was not revealed by BSA or PASI or PGA scores. During the entire 112-day study, no related serious adverse event was reported under XP-828L treatment, and no statistically significant difference was observed between the XP-828L group and the placebo group for laboratory values or for the total number of adverse events.

As there is no cure for psoriasis, the multiple treatment options currently available are only attempting to control the severity of signs and symptoms. The therapeutic challenge is to find an ideal compromise between the effectiveness and the side effects of a product to increase the general well-being of the patients. The nature, extent, location, side effects, and convenience are all factors that influence the choice of treatment for patients, particularly for patients with mild psoriasis. In general, therapies with the fewest side effects are preferred by these patients.¹³ One potential option is the use of natural products or nutraceuticals with clinical proof of efficacy and safety. As such, clinical trials on psoriasis against a placebo present a great challenge for a

nutraceutical product. The only clinical data against a placebo concerning the potential efficacy of a natural or nutraceutical product for chronic plaque psoriasis are data on fish oil supplementation (omega-3 fatty acid). Maysers and colleagues demonstrated that intravenous administration of omega-3-fatty acid for 14 days was efficacious in the treatment of chronic plaque psoriasis.¹ The main result of this study was a decrease in the PASI score in the omega-3 group (11.2 ± 9.8) compared with placebo (7.5 ± 8.8). Also, a PASI score of 50 was reached in 37% of patients receiving the omega-3 fatty acid solution compared with 27% for those receiving the placebo lipid emulsion. Although these results look promising, the need for intravenous administration remains a deterrent for the treatment of mild to moderate psoriasis. Gupta and colleagues also demonstrated the health-promoting features of fish oil for psoriasis.⁴ In this study, oral administration of fish oil was used in addition to phototherapy (UVB) and the improvement in the fish oil group was statistically greater for all parameters compared with placebo with UVB. This study suggests that a natural product, taken orally, could support traditional therapies for psoriasis. Conversely, used alone^{2,3,14} or with topical corticosteroids,⁵ the efficacy of fish oil for psoriasis was not confirmed. Thus, data on the use of fish oil for psoriasis treatment remain inconsistent. The present study demonstrated that XP-828L can reduce the symptoms associated with mild to moderate psoriasis. Additional studies would be required to evaluate the potential of XP-828L to complement traditional treatments for psoriasis. From its safety and efficacy profiles, a natural product such as XP-828L could be a good addition to traditional therapies for mild to moderate psoriasis.

Figure 2. Two patients treated with XP-828L (2.5 g twice daily). A) Patient MB001 of Group A. B) Patient LT036 of group A.



Psoriasis has a T lymphocyte-based immunopathogenesis.¹⁵ The response of psoriasis to treatment compounds that act on lymphocytes such as cyclosporine,¹⁶ DAB389IL-2,¹⁷ alefacept,¹⁸ efalizumab,¹⁹ or, in some cases, CD4 antibodies²⁰ confirms the major role of T cells in the pathogenesis of psoriasis. Anti-tumor necrosis factor agents (etanercept, infliximab, adalimumab) also have a proven efficacy.²¹ However, these specific products are not appropriate for mild psoriasis owing to potential side effects and the high costs of treatment. There is a need for a safer and more appropriate therapy for patients with psoriasis. The bioactive profile of XP-828L could be related to the presence of growth factors, active peptides, and immunoglobulins in the extract. *In vitro* experiments showed that XP-828L inhibits the production of T helper 1 cytokines (IFN- γ and IL-2), suggesting that XP-828L could improve T helper

1-related disorders, such as psoriasis.⁶ The exact mechanism of action of XP-828L is still unknown. However, we suspect that the high concentration of transforming growth factor (TGF)- β 2 could be, at least in part, responsible for the inhibition of T helper 1 cytokines by lymphocytes. In fact, TGF- β plays an essential role in T-cell homeostasis, and its abrogation leads to autoimmune disease.²² For instance, TGF- β -based diets have been shown to reduce the symptoms associated with inflammatory bowel disease.²³⁻²⁵

In conclusion, oral administration of XP-828L at a dose of 2.5 g twice daily for 56 days reduced PGA and PASI scores compared with day 1, whereas no change was observed in the placebo group. Furthermore, XP-828L is safe and well tolerated by patients with mild to moderate stable psoriasis. It is a novel therapeutic agent to add to the armamentarium to be used as a complement for long-term treatment of psoriasis.

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