Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial

Paolo Gisondi, Micol Del Giglio, Vincenzo Di Francesco, Mauro Zamboni, and Giampiero Girolomoni

ABSTRACT

Background: Chronic plaque psoriasis is frequently associated with obesity. The effect of a hypoenergetic diet on psoriasis has not been investigated.

Objective: The objective was to investigate whether moderate weight loss (ie, 5–10% of body weight) increases the therapeutic response to a low dose of cyclosporine in obese patients with moderate-to-severe chronic plaque psoriasis.

Design: A 24-wk randomized, controlled, investigator-blinded clinical trial was conducted in 61 patients. The efficacy of 2.5 mg · kg⁻¹ · d⁻¹ cyclosporine combined with a low-calorie diet (intervention group) was compared with cyclosporine alone (control group) in obese patients [body mass index (in kg/m²) > 30] with moderate-to-severe psoriasis. The primary endpoint was an improvement from baseline of ≥75% in the Psoriasis Area and Severity Index (PASI 75 response) at week 24.

Results: At week 24, the mean (± SD) reduction in body weight was 7.0% ± 3.5 in the intervention group and was 0.2% ± 0.9 in the control group (P < 0.001). The PASI 75 response was achieved by 20 of 30 patients (66.7%) treated with cyclosporine plus a low-calorie diet and by 9 of 31 (29.0%) patients treated with cyclosporine alone (P < 0.001). Four patients (13.3%) from the intervention group and 14 (45.1%) from the control group withdrew prematurely from the study (P < 0.001).

Conclusions: Obese patients with moderate-to-severe psoriasis increase their response to low-dose cyclosporine if a calorie-controlled diet is included in the treatment regimen. Lifestyle modifications, including a low-calorie diet, may supplement the pharmacologic treatment of obese psoriasis patients. This trial was registered at clinicaltrials.gov as NCT00512187.


INTRODUCTION

Chronic plaque psoriasis is an inflammatory skin disease that is associated with obesity in 13–34% of cases (1, 2). The relative risk of psoriasis has been reported to be directly related to body mass index (BMI), and a positive correlation between psoriasis severity and BMI has been established (3). As far as the directional-ity of the psoriasis-obesity association is concerned, a prospective study recently suggested that obesity could be a risk factor for incident psoriasis (4). However, others suggest that lifestyles associated with psoriasis may favor obesity (5). Worldwide, the incidence of obesity has increased dramatically in recent decades (6). Obesity is associated with a propensity to develop dyslipidemia, insulin resistance, hyperglycemia, hypertension, and a state of chronic low-grade inflammation, which leads to an increased risk of cardiovascular morbidity and mortality (7). Indeed, psoriasis has also been reported to be related to the metabolic syndrome (8, 9), and severe psoriasis is associated with an increased risk of cardiovascular disease (10). Gelfand et al (11) reported psoriasis to be an independent risk factor for myocardial infarction, especially in young patients.

Human adipose tissue not only acts as a storage organ for excess energy, but is also an active endocrine organ that produces and releases many bioactive proteins, such as adipokines (eg, adiponectin and leptin) and cytokines [eg, tumor necrosis factor-α (TNF-α) and interleukin (IL)-6], and chemokines [IL-8 and monocyte chemotactic protein (MCP)-1], which exert paracrine and endocrine effects (12). Obesity-associated inflammation is characterized by increased concentrations of IL-6, TNF-α, IL-8, and MCP-1 as well as parallel decreases in antiinflammatory adipokines, especially adiponectin, which may contribute to the development of metabolic changes, endothelial dysfunction, and atherosclerosis (12). Weight loss in obese patients is associated with decreases in the serum concentrations of inflammatory mediators, including TNF-α, IL-6, C-reactive protein, fibrinogen, and markers of endothelial dysfunction, and with a concomitant increase in adiponectin and IL-10, which exert antiinflammatory and insulin-sensitizing effects (13–15). The aim of this study was to investigate whether moderate weight loss induced by a calorie-restrictive diet could improve the therapeutic response to a low dose of cyclosporine in obese patients with moderate-to-severe psoriasis.
SUBJECTS AND METHODS

Subjects

A 24-wk randomized, controlled, investigator-blinded clinical trial was performed. Patients were recruited from those consecutively admitted to the psoriasis outpatient clinic of the University Hospital of Verona. Patients were eligible if they were ≥18 y of age, had active but clinically stable plaque psoriasis involving ≥10% of the body surface area (BSA) and a Psoriasis Area and Severity Index (PASI) score ≥10, and a BMI (kg/m²) ≥30 but <45. Exclusion criteria were other types of psoriasis (guttate, erythrodermic, and pustular psoriasis); uncontrolled hypertension; severe congestive heart failure; renal and liver impairment; active or chronic severe infections, including HIV, hepatitis B virus, and hepatitis C virus infections and latent tuberculosis; previous or active malignancies; previous treatment with cyclosporine; phototherapy; or any systemic or topical therapy for psoriasis within the 4 wk before enrollment. Pregnant or lactating women were also excluded. All patients gave their written informed consent before any study-related procedures were performed. All subjects were visited by 2 dermatologists who recorded demographic, biometrical, and other relevant data on a case report form. Visits were scheduled at screening, baseline, and every 4 wk up to week 24. Collected data included age, sex, weight, height, BMI, age of psoriasis onset, type and severity of psoriasis, and concomitant medications. The clinical diagnosis of psoriasis was confirmed by a dermatologist. The severity of psoriasis was assessed according to the BSA and PASI indexes. The study was investigator blinded, ie, the dermatologist who performed the PASI scoring was unaware of the randomization assignment.

Anthropometric measurements

While the subjects were wearing light indoor clothing and no shoes, body weight was measured to the nearest 0.1 kg (Salus, Milan, Italy), and height was measured to the nearest 0.5 cm with a stadiometer (Salus). BMI was calculated as body weight divided by stature squared (kg/m²). Waist circumferences were obtained with a measuring tape at the narrowest circumference of the abdomen. Noninvasive brachial blood pressure was measured 3 times within a 15-min time frame using a traditional sphygmomanometer on the left arm of the subject, who was in the supine position. The recorded blood pressure was taken as the mean of the 3 readings.

Biochemical analysis

Standard serum laboratory tests, including measurements of complete blood count, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, creatinine, cholesterol, triglycerides, uric acid, folic acid, homocysteine, and C-reactive protein, were performed at baseline and again at weeks 12 and 24. Blood samples were taken at the baseline visit and every 3 mo thereafter; in all cases, subjects had fasted overnight for ≥8 h before blood samples were taken. All biochemical markers were measured by the central laboratory of the University Hospital.

Therapeutic interventions

Patients were randomly assigned to 1 of 2 groups: the first group received 2.5 mg cyclosporine · kg⁻¹ · d⁻¹ orally together with a low-calorie diet administered by a dietitian (intervention group); the second group received 2.5 mg cyclosporine · kg⁻¹ · d⁻¹ alone (control group). Patients underwent clinical and nutritional follow-up every month. The total dose of cyclosporine was adjusted monthly, taking into account changes in body weight. The low-calorie diet was designed to achieve a loss of 5–10% of initial body weight. The caloric restriction was 500 kcal below the resting energy expenditure, as evaluated by the Harris-Benedict equation (16). Patients received a balanced diet scheme, based on a caloric intake reduction related to BMI and sex (range: 1200–1500 kcal/d for women, 1300–1600 kcal/d for men). Calorie intake consisted of ≈60% carbohydrates, 25% fat, and 15% protein. Subjects were advised to eat 3 meals a day (breakfast, lunch, and dinner). Breakfast consisted of skim milk and bread; lunch consisted of pasta or rice, vegetables, and fruit; and dinner consisted of fish or meat and legumes and bread, vegetables, and fruit. Fruit juices, especially grape fruit and orange juice, were excluded because of their possible interaction with cyclosporine pharmacokinetics via inactivation of intestinal cytochrome P450 3A4 (CYP3A4). Alcohol beverages were also excluded. The only beverage allowed was water. All of the subjects were also encouraged to perform moderate physical exercise for ≥40 min, ≥4 times/wk.

The primary endpoint was an improvement from baseline in the PASI of ≥75% (PASI 75 response) at week 24. Secondary endpoints were an improvement from baseline in the PASI of ≥50% (PASI 50 response) and premature withdrawal from the study at week 24. Randomization was performed with the use of computer-generated random numbers and block size of 4 patients. The study was approved by the local ethical committee.

Statistical analysis

Analyses were performed using the STATA (version 10.0; StatCorp LP, College Station, TX) and Graphpad (version 4.0; GraphPad Software, El Camino Real, San Diego, CA) software packages. When designing this trial, we calculated that ≥30 patients would be needed in each group for the study to have a 95% power to rule out a difference of ≥20% in the PASI 75 response rate after 24 wk. An intention-to-treat analysis was performed. The intention-to-treat population included all patients who received at least one dose. Differences in mean values of selected variables along time were evaluated by using mixed-effects regression models for longitudinal data. For the binary endpoints (ie, PASI 75 response, PASI 50 response, and withdrawal rate from the study), the Cochran-Mantel-Haenszel analysis was performed at all time points investigated. Standard descriptive statistics, such as the mean and SD, were computed. Log transformations were performed for nonnormal variables. Differences in age, BMI, waist circumference, psoriasis duration, PASI score, and %BSA between groups were compared by using the unpaired t test. Differences in the mean serum variables within group at baseline and week 24 were analyzed by using the paired t test. Pearson’s correlation was used to test the association between mean percentage body weight and reduction in PASI score. All P values were 2-sided, and P < 0.05 was considered statistically significant.

RESULTS

Seventy-one patients were screened, and 61 patients were enrolled in the study. Six patients refused to participate in the study, and 4 patients were ineligible because of the clinically
significant deviation from the normal range in baseline serum variables. In particular, serum creatinine concentrations increased to ≥20% of the normal range (44–100 μmol/L) in 3 patients, and serum liver enzymes were 3-fold higher than the normal range (aspartate aminotransferase: 5–45 U/L; alanine aminotransferase: 5–50 U/L) in 1 patient. At enrollment, no significant differences in age, sex distribution, body weight, BMI, waist circumference, psoriasis duration, or PASI score were observed between the 2 groups (Table 1). Thirty patients were randomly assigned to receive 2.5 mg cyclosporine · kg⁻¹ · d⁻¹ orally in 2 divided doses plus a low-calorie diet (intervention group), whereas 31 patients received only 2.5 mg cyclosporine · kg⁻¹ · d⁻¹ (control group). At week 24, the PASI 75 response was achieved by 20 patients (66.7%) in the intervention group and by 9 patients (29.0%) in the control group (P < 0.001). Differences in the PASI 75 response were already significant at week 8 (Figure 1A). At week 24, the PASI 50 response was achieved by 26 patients (86.7%) in the intervention group and by 15 patients (48.3%) in the control group (P < 0.001) (Figure 1B). Mean PASI scores for the study population at each time point are shown in Figure 2A. The mean (± SD) PASI scores at week 24 were 2.5 ± 6.3 and 8.1 ± 5.4 and the BSA values were 2.9% ± 4.4 and 7.5% ± 4.9% in the intervention group and control group, respectively (P < 0.001). The mean (± SD) reduction in body weight was 7.0 ± 3.5 kg in the intervention group and was 0.2 ± 0.9 kg in the control group (P < 0.001; Figure 2B). There was a concomitant mean (± SD) reduction in waist circumference of 3.5 ± 2.7 cm in patients in the diet group compared with no reduction in the other group (P = 0.001). There was also a significant linear correlation between mean percentage of body weight and PASI score reduction at each time point (Pearson correlation: 0.96; P = 0.001). Withdrawal from the study rate was also significantly different between the groups. In particular, 4 patients in the intervention group (13.3%) dropped out of the study because of side effects caused by cyclosporine, including uncontrolled hypertension (2 patients), gingival hypertrophy (1 patient), and withdrawal of consent (1 patient) compared with 14 patients (45.1%) in the control group, mainly because of unsatisfactory therapeutic results (10 patients) or adverse events of cyclosporine (uncontrolled hypertension; 4 patients) (P < 0.001). At week 24 a significant reduction in C-reactive protein was observed in the intervention group compared with no reduction in the other group (P < 0.001). Differences between the groups at all time points investigated were compared by Cochran-Mantel-Haenszel analysis. *Significantly different from the control group, P < 0.001. Differences in the prevalence of PASI 50 and PASI 75 responses with time were evaluated by using mixed-effects regression models for longitudinal data. A significant time-by-treatment interaction was found for both PASI 75 and PASI 50 responses (P < 0.001). The difference between the percentages of responders in the 2 groups increased with time.

patients were encouraged to discontinue cyclosporine therapy but to maintain their diet; however, by week 52 of the observational period, 24 patients (80%) had returned to their baseline weight. Moreover, in these patients, psoriasis relapsed and the patients were switched to other systemic treatments.

**DISCUSSION**

The main finding of this study was that moderate weight loss renders obese patients with moderate-to-severe chronic plaque psoriasis highly responsive to low doses of cyclosporine. Indeed, PASI 75 or PASI 50 responses were achieved by 66.7% and 86.7% of the patients in the intervention group compared with 29% and 48.3% of the patients in the control group. Moreover, the withdrawal rate was higher in the control group, mainly because of unsatisfactory therapeutic results. The clinical response to low-dose cyclosporine in our study was particularly impressive when compared with the published data. Cyclosporine is usually used at a dose of 3 to 5 mg · kg⁻¹ · d⁻¹ in the treatment of chronic plaque psoriasis (17–22). Doses lower than 3 mg cyclosporine · kg⁻¹ · d⁻¹ are often ineffective, particularly for severe forms of the disease. Few data concerning the efficacy of low-dose cyclosporine are available. Laburte et al (23) compared the efficacy of the 2 different dose regimens (ie, 2.5 and 5 mg · kg⁻¹ · d⁻¹) for a 12-wk continuous treatment. The PASI 75 response was 47.9% and 88.8% with the low and high doses, respectively. Meffert et al (24) found that 10% and 30% of patients treated with 1.25 and 2.5 mg cyclosporine · kg⁻¹ · d⁻¹, respectively, achieved a PASI 75 response at week 10. In other

![Figure 1](https://academic.oup.com/ajcn/article-abstract/88/5/1242/4649024/figure1)

**FIGURE 1.** Improvement from baseline of ≥75% (A) or ≥50% (B) in the Psoriasis Area and Severity Index (PASI 75 and PSAI 50 responses, respectively) at 6 mo in the intervention group (■) and the control group (○). Differences between the groups at all time points investigated were compared by Cochran-Mantel-Haenszel analysis. *Significantly different from the control group, P < 0.001. Differences in the prevalence of PASI 50 and PASI 75 responses with time were evaluated by using mixed-effects regression models for longitudinal data. A significant time-by-treatment interaction was found for both PASI 75 and PASI 50 responses (P < 0.001). The difference between the percentages of responders in the 2 groups increased with time.

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**TABLE 1**

Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine alone</th>
<th>Cyclosporine + low-calorie diet</th>
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<tr>
<td></td>
<td>(n = 15 M, 16 F)</td>
<td>(n = 15 M, 15 F)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.3 ± 14.5</td>
<td>50.9 ± 10.5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>94.8 ± 14.9</td>
<td>93.4 ± 12.8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>34.03 ± 4.9</td>
<td>33.4 ± 3.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>104.6 ± 7.9</td>
<td>105.2 ± 8.9</td>
</tr>
<tr>
<td>Psoriasis duration (y)</td>
<td>15.1 ± 5.3</td>
<td>14.1 ± 6.4</td>
</tr>
<tr>
<td>Body surface area (%)</td>
<td>21.5 ± 16.2</td>
<td>22.5 ± 14.2</td>
</tr>
</tbody>
</table>

1 All values are arithmetic x ± SD. PASI, Psoriasis Area and Severity Index.

2 Reflects the significance of the between-group differences in baseline characteristics determined with an unpaired t-test.
Weigh loss was fairly stable in the control group during the considered period. Reduction in mean body weight up to 4 mo; on the other hand, body weight was significantly higher in subjects who consumed a low-calorie diet. Also, when body weight was considered, a significant time-by-treatment interaction was found (P < 0.001). Mean values decreased with time in both groups, but the reduction rate was significantly higher in those who consumed a low-calorie diet. Also, when body weight was considered, a significant time-by-treatment interaction was found (P < 0.001). Subjects who underwent a low-calorie diet showed a significant reduction in mean body weight up to 4 mo; on the other hand, body weight was fairly stable in the control group during the considered period.

Differences in mean PASI scores and body weight over time were evaluated by using mixed-effects regression models for longitudinal data. A significant time-by-treatment interaction was found for PASI score (P = 0.001). Differences between the groups at all time points investigated were compared by Cochran-Mantel-Haenszel analysis. Reflects the significance of the differences within groups at baseline and week 24 determined with a paired t test.

Clinical trials, cyclosporine was initially given at a dose of 2.5 mg · kg⁻¹ · d⁻¹, but this dosage had to be incrementally increased up to 5 mg · kg⁻¹ · d⁻¹ to achieve a satisfactory therapeutic response (25–27). This does not allow a realistic comparison with our data, where doses of cyclosporine were only adjusted to compensate for changes in body weight. Our findings suggest that moderate weight loss achieved by a low-calorie diet can improve the therapeutic response to cyclosporine. Weight loss through calorie restriction induces decreases in insulin, leptin, C-reactive protein, and MCP-1 and increases adiponectin concentrations, which results in an antiinflammatory effect (14, 28–33). Whereas weight loss has

![FIGURE 2. Mean (± SD) Psoriasis Area and Severity Index (PASI) scores (A) and body weight (B) at each time point in the intervention group (■) and the control group (●). Differences between the groups at all time points investigated were compared by Cochran-Mantel-Haenszel analysis. Differences in mean PASI scores and body weight over time were evaluated by using mixed-effects regression models for longitudinal data. A significant time-by-treatment interaction was found for PASI score (P < 0.001). Mean values decreased with time in both groups, but the reduction rate was significantly higher in subjects who consumed a low-calorie diet. Also, when body weight was considered, a significant time-by-treatment interaction was found (P < 0.001). Subjects who underwent a low-calorie diet showed a significant reduction in mean body weight up to 4 mo; on the other hand, body weight was fairly stable in the control group during the considered period.](image)

![FIGURE 3. Photographs of a 48-y-old obese female patient with severe chronic plaque psoriasis who was treated with 2.5 mg cyclosporine · kg⁻¹ · d⁻¹ and a dietary regimen (1250 kcal/d). At baseline, the PASI score was 20.2 and body weight was 90.5 kg. At 6 mo, the PASI score was 4.7 (–77%) and body weight was 80.4 kg (–11.2%).](image)

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Serum variables for the study population at baseline and week 24[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclosporine + low-calorie diet</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>White blood cells (10³/mL)</td>
<td>7.9 ± 1.5</td>
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<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13.5 ± 1.4</td>
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<tr>
<td>AST (U/L)</td>
<td>24.1 ± 7.9</td>
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<tr>
<td>ALT (U/L)</td>
<td>33.2 ± 13.5</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>77.9 ± 18.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.5 ± 1.06</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.7 ± 0.8</td>
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<tr>
<td>Uric acid (mg/dL)</td>
<td>6.4 ± 3.6</td>
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<tr>
<td>Folic acid (mg/dL)</td>
<td>7.02 ± 7.0</td>
</tr>
<tr>
<td>Homocysteine (mg/dL)</td>
<td>11.4 ± 6.8</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>6.1 ± 2.4</td>
</tr>
</tbody>
</table>

[^1]: All values are arithmetic x ± SD. AST, aspartate aminotransferase; ALT, alanine aminotransferase. Baseline values were not significantly different between groups.

[^2]: Reflects the significance of the differences within groups at baseline and week 24 determined with a paired t test.

[^3]: Differences in mean values of all variables over time were evaluated by using mixed-effects regression models for longitudinal data. A significant time-by-treatment interaction was found for ALT (P = 0.004) and C-reactive protein (P = 0.01).
been shown to improve the clinical outcomes of chronic inflammatory diseases, such as rheumatoid arthritis and asthma (34–38), only anecdotal evidence is available to suggest that weight loss may also be beneficial to psoriasis patients (39, 40). Two case reports describe the complete resolution of psoriasis after significant weight loss in 2 individuals who underwent gastric bypass surgery for obesity. Moreover, a prospective 5-wk open study showed that fasting and a vegetarian diet improved the signs and symptoms of different types of skin disorders, including atopic eczema and psoriasis (41). Excessive alcohol intake is a known risk factor for the development of psoriasis and may have an adverse effect on treatment outcome (42, 43), and alcohol abstinence in our patients could also have had a role in psoriasis improvement.

Because obesity is on the increase and is frequently associated with psoriasis, further studies will be necessary to elucidate the relation between the effect of weight loss in psoriasis patients receiving traditional or biological therapies. Clark et al (44) reported that the 2 biologies that are weight doses, infliximab and efalizumab, do not seem to lose efficacy with increasing body weight, but etanercept and alefacept may have had a reduced efficacy in heavier individuals.

Our study had some limitations, such as the relatively small number of patients and the failure to directly measure blood cyclosporine concentrations during the study. It is thus possible that the serum concentrations of cyclosporine may have differed between the 2 groups, possibly favored by the weight loss. However, cyclosporine adsorption is not impaired in obese patients; on the contrary, Shibata et al (45) have shown that serum concentrations of cyclosporine are significantly greater in obese than in normal-weight psoriasis patients. We were unable to include a control group of patients treated only with a low-calorie diet because this was judged to be unethical.

In conclusion, our study showed that weight loss increases the responsiveness of obese patients with moderate-to-severe chronic plaque psoriasis to low doses of cyclosporine and supports the concept that lifestyle modifications, including a low-calorie diet, may supplement traditional pharmacologic approaches in the treatment of obese psoriasis patients.

We are grateful to Rocco Micciolo (University of Trento) for assistance with the data analysis.

The authors’ responsibilities were as follows—PG and GG: designed the study and wrote the manuscript; MDG and VDF: collected the data and supervised its collection; and PG and MZ: analyzed and interpreted the data. None of the authors had a conflict of interest.

REFERENCES

restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA 2006;295:1539–48.


