Efficacy and Safety of Combination Acitretin and Pioglitazone Therapy in Patients With Moderate to Severe Chronic Plaque-Type Psoriasis

A Randomized, Double-blind, Placebo-Controlled Clinical Trial

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Objective: To evaluate the efficacy and safety of combination therapy with acitretin and pioglitazone hydrochloride in patients with moderate to severe chronic plaque-type psoriasis.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: A tertiary care referral hospital.

Patients: The study included patients of either sex (age range, 18-65 years) with moderate to severe chronic plaque-type psoriasis. Patients were excluded if they were of child-bearing potential or if they had impaired liver or renal function, hyperlipidemia, diabetes mellitus, coronary artery disease, or a body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared). Of the 62 patients screened, 41 were randomly assigned to 2 groups: 22 to an acitretin (25 mg) plus placebo group and 19 to an acitretin (25 mg) plus pioglitazone hydrochloride (15 mg) group.

Main Outcome Measure: Change in Psoriasis Area and Severity Index score between the 2 groups from baseline to 12 weeks.

Results: After 12 weeks of therapy, the percentage of reduction in the Psoriasis Area and Severity Index score was 64.2% in the acitretin plus pioglitazone group and 51.7% in the acitretin plus placebo group. The majority of the adverse events were mild to moderate except for 1 possibly unrelated episode of acute myocardial infarction in a 49-year-old woman in the acitretin plus placebo group.

Conclusions: Pioglitazone has a potential beneficial antipsoriatic effect and may provide a convenient, efficacious, and relatively safe option to combine with acitretin, although further studies are needed.

Trial Registration: clinicaltrials.gov Identifier: NCT00395941

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SORIASIS IS A CHRONIC, inflammatory, immune-mediated skin disorder that can cause considerable morbidity and have an adverse impact on quality of life. It affects 2% to 3% of the world's population, with chronic plaque-type psoriasis accounting for approximately 90% of the cases. The course of the disease is unpredictable, with patients generally having multiple remissions and relapses that require repeated and prolonged courses of therapy throughout life. However, potential serious toxic effects, eg, end-organ damage, which are associated with long-term use of currently available therapeutic modalities such as methotrexate, cyclosporine, and phototherapy, limit the use of most drugs as monotherapy. Therefore, one way to overcome these limitations is by the use of combination therapy to provide safe and effective care and to minimize cumulative toxic effects.

For editorial comment see page ded90001

Acitretin, a synthetic retinoid, is a widely used systemic antipsoriatic drug. It acts by decreasing proliferation, by normalizing the differentiation of epidermal keratinocytes, and by exerting anti-inflammatory effects. Although acitretin is largely devoid of serious and irreversible toxic effects, which have been observed with other antipsoriatic drugs, its use as monotherapy in patients with chronic plaque-type psoriasis is associated with a slow and often incomplete response. Also, the toxicity of acitretin is dose-related, thereby limiting the use of...
higher, more efficacious doses. Therefore, acitretin is often used in combination with other topical or systemic agents, such as calcipotriol, phototherapy, and cyclosporine. Such combination treatment strategies allow the use of lower doses of acitretin and thereby decrease adverse effects and enhance efficacy.

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, have potential beneficial therapeutic effects in psoriasis. Pioglitazone hydrochloride is a TZD that is used as an insulin sensitizer in patients with type 2 diabetes mellitus. Thiazolidinediones have been shown to inhibit proliferation and to induce differentiation in various in vitro and murine models of psoriasis. Also, it has been suggested that the anti-inflammatory and antiangiogenic properties of TZDs underlie their beneficial effects in psoriasis.

A number of recent clinical studies, including 3 open-label studies and 1 randomized, double-blind, placebo-controlled, prospective study, have provided evidence of some therapeutic benefit of TZDs in psoriasis. Further evidence in support of a role for TZDs in psoriasis was provided in a recently published population-based case-control study involving 36,702 patients with a first-time diagnosis of psoriasis. In that study, Brauchli et al found that there was a statistically significant decrease in the risk for the development of psoriasis in long-term users of TZDs compared with non-users (adjusted odds ratio, 0.33; 95% confidence interval [CI], 0.16-0.66).

Because both acitretin and pioglitazone act by normalizing cellular proliferation and differentiation, by inhibiting angiogenesis, and by exerting anti-inflammatory actions in psoriatic skin through different mechanisms at the nuclear level, we hypothesized that pioglitazone and acitretin therapy might lead to additive efficacy in patients with psoriasis. Therefore, we conducted this study to evaluate the safety and efficacy of combination therapy with pioglitazone and acitretin in patients with moderate to severe chronic plaque-type psoriasis.

METHODS

We conducted this study at the Postgraduate Institute of Medical Education and Research, Chandigarh, India, between January 2007 and December 2007 after obtaining approval from the institutional ethics committee. The study was an investigator-initiated, prospective, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose clinical trial of 12 weeks’ duration.

PATIENTS

Patients of either sex, 18 to 65 years of age, with moderate to severe chronic plaque-type psoriasis (body surface area involvement >20%) who were attending the psoriasis clinic were screened regarding their eligibility for inclusion in the study. Only women who had completed their family and had undergone a tubectomy or were postmenopausal were eligible for the study. Patients were excluded from the study if they were of child-bearing potential or if they had (1) a history of hypersensitivity to acitretin or pioglitazone; (2) impaired hepatic function (serum bilirubin level >50% of the normal value and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels >1.5 times the upper limit of normal); impaired renal function (serum creatinine >1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4] in men and >1.4 mg/dL in women); (3) hyperlipidemia requiring systemic therapy; (4) a body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared); (5) a history of excessive alcohol use; (6) diabetes mellitus; (7) congestive heart failure; or (8) ischemic heart disease.

Written informed consent was obtained from the patients before inclusion in the trial. A detailed clinical examination and evaluation of Psoriasis Area and Severity Index (PASI) scores were performed for all patients. Laboratory investigations, including a complete blood cell count, serum electrolyte levels, liver function tests (LFTs), renal function tests (RFTs), fasting serum lipid profile, fasting blood glucose levels, urinalysis, electrocardiography, and radiography of the patients’ right ankle joints and lumbosacral spines, were also performed.

THERAPY AND FOLLOW-UP

Following a washout period of 2 weeks’ duration for topical therapy and 4 weeks’ duration for systemic therapy, the eligible patients were randomized to either of the treatment arms: acitretin plus placebo or acitretin plus pioglitazone. A randomization list was generated using a random numbers table, and the code was kept with an investigator who was not directly involved in the assessment of end points. Acitretin was administered at a dosage of 25 mg/d in both groups. Pioglitazone hydrochloride was administered at a dosage of 15 mg/d to one group, while the other group received a matching placebo. The drugs or placebo were supplied in sealed containers bearing the code for each patient according to the randomization list. All participants were advised to take the drugs once a day after breakfast. The treatment was continued until the patient achieved complete clearance of lesions or for 12 weeks, whichever came first. No concomitant antipsoriatic therapy was allowed, except for emollients and antihistamines. Patients were advised against unsupervised exposure to excessive sunlight or sunlamps.

The patients were followed up at 2, 4, 8, and 12 weeks after randomization. At each visit, efficacy, safety, and compliance were checked. Compliance was assessed at each follow-up visit by direct questioning of the patients about any missed doses and by pill count. Consumption of more than 80% of study medications was taken as a measure of adequate compliance.

EFFICACY AND SAFETY ASSESSMENT

The primary efficacy parameter was a change in PASI score between the 2 groups from baseline to 12 weeks. The secondary efficacy parameter was the proportion of subjects who achieved marked improvement, ie, at least 75% decrease in PASI score (PASI 75) by week 2, 4, 8, or 12.

Adverse events were elicited at each follow-up visit by open method, by asking leading questions, and by detailed physical examination. Laboratory investigations, including complete blood cell counts, LFTs, RFTs, fasting lipid profiles, fasting blood glucose levels, and serum electrolyte levels, were repeated at 4 weekly intervals; x-ray films of the lumbosacral spines and right ankle joints were repeated at the end of the study period to assess any adverse effects of the use of acitretin on the bones.

STATISTICAL ANALYSIS

Assuming an SD of 10 in PASI scores and a difference of 10 in the PASI score between the drug and the placebo arms at 12

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Sixty-two patients with moderate to severe chronic plaque-type psoriasis were screened for eligibility. Forty-one patients satisfied the entry criteria and were randomly assigned to the 2 treatment arms: 22 to the acitretin (25 mg) placebo group and 19 to the acitretin (25 mg) plus pioglitazone hydrochloride (15 mg) group (Figure 1). The 2 treatment groups were similar with respect to majority of the baseline parameters, including duration of disease, body surface area involved, PASI score, and laboratory indices (Table 1).

RESULTS

There was clinical improvement in both groups, as shown by a decrease in the PASI score from week 0 to week 12 (P < .05 for both groups). An initial worsening of the disease, observed as an increase in the PASI score at 2 weeks, was seen in 7 patients (37%) in the acitretin plus pioglitazone group vs 11 patients (50%) in the acitretin plus placebo group (P = .53). At the end of 12 weeks, the reduction in the mean PASI score was significantly greater in the acitretin plus pioglitazone group than in the acitretin plus placebo group (P = .04) (Table 2 and Figure 2). The percentage of reduction in the PASI score from baseline to 12 weeks of treatment was 64.2% (95% CI, 49.2%-79.3%) in the acitretin plus pioglitazone group compared with 51.7% (95% CI, 38.7%-64.7%) in the acitretin plus placebo group. Overall, the lesions cleared or almost cleared in 7 patients (37%) in the acitretin plus pioglitazone group compared with 2 patients (9%) in the acitretin plus placebo group (P = .06).

Furthermore, at 12 weeks, PASI 75 was achieved in 8 patients (42%) in the acitretin plus pioglitazone group compared with 5 patients (23%) in the acitretin plus placebo group (P = .31). Also, PASI 75 was attained earlier, ie, by week 8 in 2 patients (11%) in the acitretin plus pioglitazone group compared with 1 patient (4%) in the acitretin plus placebo group (P = .59). Compliance with study medication, as determined by direct questioning and pill count, was greater than 95% for all patients included in the trial.

Clinically, improvement was seen as a decrease in erythema, scaling, induration, and the body surface area involved (Figures 3, 4, and 5). Scaling was the first pa-
skeletal changes in either treatment group. Spines and right ankle joints also did not reveal any evidence of abnormalities. Baseline and end-of-study x-ray films of the lumbosacral region were examined at 0, 2, 4, 8, and 12 weeks of therapy in both groups. An asterisk indicates significance at P=.04 when the acitretin plus pioglitazone group was compared with the acitretin plus placebo group.

Figure 2. Median Psoriasis Area and Severity Index (PASI) score in the 2 treatment groups at 0, 2, 4, 8, and 12 weeks. Asterisk indicates P=.04 when the acitretin plus pioglitazone hydrochloride group was compared with the acitretin plus placebo group.

The model of complete to almost complete remission with acitretin plus placebo (9%) observed in our study is comparable to that reported by Kragballe et al,9 who observed complete remissions with acitretin monotherapy in 11% of patients. Furthermore, the approximately 50% reduction in the PASI score observed in the acitretin plus placebo group is in agreement with a previous study by Olsen et al,15 who observed a similar improvement in erythema, scaling, and induration after 20 weeks of acitretin therapy.

There was gradual clinical improvement during the study period, which is in agreement with previously reported findings that treatment with retinoids results in considerable improvement in psoriasis over 6 to 12 weeks.27 We also observed that the addition of pioglitazone to the regimen led to a decrease in the initial flare-up of disease, as fewer patients in the acitretin plus pioglitazone group (37%) than in the acitretin plus placebo group (50%) had an increase in their PASI scores at 2 weeks of therapy. Since the baseline demographics and the disease parameters were comparable in the 2 groups in our study, the observed differences could be ascribed to the additive effect of acitretin and pioglitazone.

From a mechanistic viewpoint, the combination of retinoids and PPAR-γ agonists is particularly appealing as both groups of drugs have antiproliferative, prodifferentiating, anti-inflammatory, and antiangiogenic activity7,25 and thus may provide additive efficacy in patients with psoriasis. Furthermore, both retinoic acid receptors and PPARs act on DNA as heterodimers with retinoid receptors, which may be involved in the additive effects of acitretin and pioglitazone, although this speculation needs further elucidation.

In our study, most of the adverse events observed were mild and tolerable. Common adverse events involved muco-cutaneous and musculoskeletal complaints, which are frequent and known side effects of acitretin therapy.7,28,29 We did not observe any remarkable abnormalities in laboratory parameters, including serum lipid levels, LFT results, and fasting blood glucose levels, in either group. However, there was an episode of acute myocardial infarction (AMI) in a 49-year-old woman in the acitretin plus placebo group after just 5 days of therapy. It is unlikely, however, that the event was related to the drug therapy. Furthermore, in comparison to the general population, patients with psoriasis have been shown to be at a higher risk for myocardial infarction (hazard ratio, 1.21; 95% CI, 1.10–1.32).30 Although, to our knowledge, there are no published reports of acitretin therapy being associated with AMI, the prescription information leaflet for Soriatane (acitretin, Connectics Corporation, Palo Alto, California) reports the development of AMI in a few patients, but causality has not been established.31 Because of the seriousness of

SAFETY

Adverse events were seen in 15 patients in each group. Most were mild, although 1 patient (a 49-year-old woman) had an episode of acute myocardial infarction (AMI) after just 5 days of therapy. Commonly observed adverse effects were increased erythema, dry skin, dry mouth, thirst, increased pruritus, cheilitis, myalgia, arthralgia, and weight gain (Table 3).

There was no consistent trend in triglyceride levels among either group at various time intervals, although an increase of 10% to 41% was seen in 10 patients (46%) in the acitretin plus placebo group and an increase of 14% to 39% was seen in 5 patients (26%) in the acitretin plus pioglitazone group (P=.33). No significant change was noted in the results of the other laboratory investigations, including LFTs or fasting blood glucose levels, throughout the study period in the 2 groups (P > .05). Comparison of the baseline and end-of-study x-ray films of the lumbosacral spines and right ankle joints also did not reveal any evidence of skeletal changes in either treatment group.

COMMENT

This investigator-initiated, randomized, double-blind, placebo-controlled, parallel group, fixed-dose clinical trial for evaluating the efficacy and safety of combination therapy with acitretin plus pioglitazone in patients with moderate to severe plaque-type psoriasis shows that the use of acitretin and pioglitazone combined led to a significantly greater reduction in PASI score at 12 weeks than the use of acitretin plus placebo. To the best of our knowledge, this is the first such study in patients with chronic plaque-type psoriasis.

The frequency of complete to almost complete remission with acitretin plus placebo (9%) observed in our study is comparable to that reported by Kragballe et al,9 who observed complete remissions with acitretin monotherapy in 11% of patients. Furthermore, the approximately 50% reduction in the PASI score observed in the acitretin plus placebo group is in agreement with a previous study by Olsen et al,15 who observed a similar improvement in erythema, scaling, and induration after 20 weeks of acitretin therapy.

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From a mechanistic viewpoint, the combination of retinoids and PPAR-γ agonists is particularly appealing as both groups of drugs have antiproliferative, prodifferentiating, anti-inflammatory, and antiangiogenic activity7,25 and thus may provide additive efficacy in patients with psoriasis. Furthermore, both retinoic acid receptors and PPARs act on DNA as heterodimers with retinoid X receptors.15,27 Such cooperativity at the receptor level due to heterodimerization of PPAR and retinoid receptors may be involved in the additive effects of acitretin and pioglitazone, although this speculation needs further elucidation.

In our study, most of the adverse events observed were mild and tolerable. Common adverse events involved mucocutaneous and musculoskeletal complaints, which are frequent and known side effects of acitretin therapy.7,28,29 We did not observe any remarkable abnormalities in laboratory parameters, including serum lipid levels, LFT results, and fasting blood glucose levels, in either group. However, there was an episode of AMI in a 49-year-old woman in the acitretin plus placebo group after just 5 days of therapy. It is unlikely, however, that the event was related to the drug therapy. Furthermore, in comparison to the general population, patients with psoriasis have been shown to be at a higher risk for myocardial infarction (hazard ratio, 1.21; 95% CI, 1.10–1.32).30 Although, to our knowledge, there are no published reports of acitretin therapy being associated with AMI, the prescription information leaflet for Soriatane (acitretin, Connectics Corporation, Palo Alto, California) reports the development of AMI in a few patients, but causality has not been established.31 Because of the seriousness of
the event, however, the patient was withdrawn from our study.

Acitretin is an established antipsoriatic drug, and there is growing evidence of a potential therapeutic role of TZDs in psoriasis. In a randomized, double-blind, placebo-controlled, prospective study, Shafiq et al demonstrated the efficacy and safety of pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis. The percentages of reduction in the mean PASI scores observed in the study were 21.5%, 41.1%, and 47.5% in the placebo, 15-mg pioglitazone hydrochloride, and 30-mg pioglitazone hydrochloride groups, respectively. Furthermore, a trend toward greater antipsoriatic response with the use of rosiglitazone was seen in 2 clinical trials, although the observed difference for the primary end point (PASI 75) was not statistically significant when compared with placebo (P = .44 and P = .27 for rosiglitazone 2-mg and 4-mg groups, respectively). The lack of statistical significance in these trials could be attributable to a large placebo response (in about one-third of the patients) and to the use of topical corticosteroids that could diminish the difference between the 2 groups. Also, as suggested by Ellis et al, there is the possibility that an optimal dose of rosiglitazone for antipsoriatic activity was not achieved.

According to our study results, the addition of pioglitazone to acitretin therapy can enhance antipsoriatic efficacy. In comparison to other antipsoriatic drugs that have been used in combination with acitretin, pioglitazone may offer a safer alternative as it has been used in patients with diabetes mellitus for several years, and most of the placebo-controlled trials have shown the incidence of adverse effects due to pioglitazone therapy to be approximately equal to that found with placebo. Furthermore, PPAR-γ agonists are known to possess an array of beneficial effects, including a decrease in blood pressure, an increase in high-density lipoprotein levels, and an improvement of fibrinolysis. Moreover, the occurrence of diabetes, hypertension, and metabolic syndrome in patients with psoriasis is not uncommon, and these conditions may coexist more often than is typically predicted from the prevalence of either disorder alone. Pioglitazone therapy may be particularly useful in these subsets of patients.

Our study has several important advantages. Its randomized, double-blind, placebo-controlled design al-
The study also has some limitations. The lowest dose of pioglitazone (15 mg/d) was used. It would be interesting to evaluate 30- and 45-mg doses of pioglitazone with acitretin to clarify any dose-response relationship. Also, there was an underrepresentation of females in our study, probably because of the strict entry criteria, as acitretin is a pregnancy category X drug, not suitable for females of child-bearing potential. The study was also underpowered to detect smaller differences in response.

In conclusion, the present study provides important insights into the beneficial effect of pioglitazone in combination with acitretin for therapy of moderate to severe chronic plaque-type psoriasis. Pioglitazone may offer a convenient, efficacious, and relatively safer alternative for combining with acitretin than currently available immunosuppressive agents, although this theory needs to be proved by further studies. Also, the long-term safety of pioglitazone therapy in patients with chronic plaque-type psoriasis needs to be established.

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Author Contributions: Dr Mittal had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mittal, Malhotra, Pandhi, Kaur, and Dogra. Acquisition of data: Mittal and Kaur. Analysis and interpretation of data: Mittal, Malhotra, Pandhi, and Dogra. Drafting of the manuscript: Mittal, Malhotra, and Kaur. Critical revision of the manuscript for important intellectual content: Mittal, Malhotra, Pandhi, and Dogra. Statistical analysis: Malhotra. Obtained funding: Mittal, Malhotra, and Pandhi. Administrative, technical, and material support: Mittal, Malhotra, and Pandhi.

Table 3. Adverse Events Observed During the Study in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total No. (%)</th>
<th>Acitretin (25 mg) + Placebo Group (n=22)</th>
<th>Acitretin (25 mg) + Pioglitazone Hydrochloride (15 mg) Group (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>15 (68)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>Thirst</td>
<td>15 (68)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>14 (64)</td>
<td>13 (68)</td>
<td></td>
</tr>
<tr>
<td>Increased erythema</td>
<td>14 (64)</td>
<td>8 (42)</td>
<td></td>
</tr>
<tr>
<td>Cheilitis</td>
<td>12 (54)</td>
<td>3 (16)</td>
<td></td>
</tr>
<tr>
<td>Increased pruritus</td>
<td>6 (27)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (27)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Weight gain of &gt;1 kg</td>
<td>5 (23)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>5 (23)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (18)</td>
<td>5 (26)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (18)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td>Blurred night vision</td>
<td>2 (9)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Other adverse events included somnolence, insomnia, sun burns, skin fissuring, low back pain, dyspepsia, fatigue, xerophthalmia, laryngitis, pharyngitis, malaise, headache, pedal edema, and abdominal pain in 1 or 2 patients each in the 2 groups.

P<.05 compared with the acitretin (25 mg) plus placebo group.
support: Mittal, Malhotra, Pandhi, Kaur, and Dogra. Study supervision: Malhotra, Pandhi, Kaur, and Dogra. Financial Disclosure: None reported. Funding/Support: Acitretin (25 mg) was donated by Innova, a division of Ipca Laboratories Ltd, Mumbai, India, and pioglitazone (15 mg) was donated by Ind-Swift Ltd, Chandigarh. Role of the Sponsor: The pharmaceutical companies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

**REFERENCES**


12. Tanew A, Guggenbichler A, Honigsmann H, Geiger JM, Fritsch P. Topical treatment with thiazolidinediones, and pioglitazone (15 mg) was donated by Ind-Swift Ltd, Chandigarh.


17. Demerjian M, Man MQ, Choi EH, et al. Topical treatment with thiazolidinediones, and pioglitazone (15 mg) was donated by Ind-Swift Ltd, Chandigarh.


