Treatment of active psoriatic arthritis with the PPARγ ligand pioglitazone: an open-label pilot study

T. Bongartz, B. Coras1, T. Vogt1, J. Schölmerich and U. Müller-Ladner

Objectives. Psoriatic arthritis (PsA) is an inflammatory joint disease, in which early neovascularization of affected skin and synovial tissue represents an important pathogenetic step in the disease process. Activation of the peroxisome proliferator activated receptor γ (PPARγ) showed anti-inflammatory effects in several in vitro and in vivo models (e.g. collagen-induced arthritis) by inhibition of angiogenesis and suppression of proinflammatory cytokines. Therefore, we studied the use of pioglitazone, a PPARγ agonist originally developed for the treatment of diabetes, in patients with PsA.

Methods. Ten patients with active PsA, seven males and three females, who showed at least two tender and two swollen joints despite stable treatment with an NSAID, were enrolled in this open-label study. All patients received a daily dose of 60 mg pioglitazone while continuing their current NSAID therapy. The primary endpoint was the PsARC (Psoriatic Arthritis Response Criterion); the secondary endpoints included the ACR20 response and improvement in the Psoriasis Area and Severity Index (PASI) in patients with more than 2% skin involvement. Patients were evaluated for endpoints at baseline and after 12 weeks.

Results. After 12 weeks, six of 10 patients met the PsARC. The ACR20 response was achieved in five patients. The mean percentage reduction in PASI was 38%, with a clinically meaningful PASI 50 response in two of six patients. Median tender joint count (interquartile range) decreased from 12.0 (8.0–18.0) to 4.0 (2.0–10.0), and the median swollen joint count from 5.0 (4.0–8.0) to 2.0 (1.0–7.0) (P < 0.05 for both). Median Health Assessment Questionnaire score changed from 1.0 (0.375–1.375) to 0.75 (0.375–1.0) (P < 0.05). Three patients had to be withdrawn from the study due to inefficacy and side-effects. Major side-effects were oedema of the lower extremities and increase in weight.

Conclusions. Treatment with a PPARγ agonist appears to be a promising therapeutic principle in PsA, but the use of PPARγ ligands might be limited by side-effects such as increase in weight and fluid retention.

Key words: Psoriatic arthritis, Pioglitazone, Peroxisome proliferator activated receptor γ agonists.
Patients with active PsA, defined as having at least two painful and two swollen joints despite a minimum of 4 weeks of therapy with an NSAID prior to the initiation of study medication, were eligible for inclusion. During the entire study, NSAID therapy was maintained at a stable dose. Patients were excluded if they have been treated with disease-modifying drugs within the last 3 months.

### Protocol

The protocol was approved by the local ethics committee of the University Hospital of Regensburg and all patients had to give written informed consent prior to entering the study. Throughout the study, patients were treated with 30 mg pioglitazone (Takeda Pharma, Aachen, Germany) twice daily and evaluated at week 0, 6 and 12 for response to therapy and for the occurrence of side-effects. Patient assessment consisted of physical examination, measurements of disease activity (arthritis and psoriasis), concomitant medication and laboratory parameters (haematology, serum chemistry, urine analysis). Evaluation of disease activity included assessment of 78 joints (including iliosacral joints) for tenderness and 76 joints for swelling, patient’s and physician’s global health assessments (1–5 Likert scale), patient’s assessment of pain [visual analogue scale (VAS)], patient’s assessment of disability using the Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In addition, patients with cutaneous manifestations of psoriasis affecting at least 2% of the body surface area were assessed for activity of skin disease.

### Study endpoints

The primary endpoint addressing efficacy in PsA was the number of patients who met the Psoriatic Arthritis Response Criterion (PsARC, adapted from Clegg et al. [1]) after 12 weeks of pioglitazone therapy. Meeting this response criterion requires improvement in two parameters (at least one being a joint score) and worsening in none of the following four parameters: patient’s and physician’s global assessments (improvement was defined as a decrease of ≥1 unit and worsening as an increase of ≥1 unit) and tender and swollen joint counts (the sum of all joints scored; improvement was defined as a decrease of ≥30% and worsening as an increase of ≥30%).

The secondary endpoint for the assessment of PsA was the number of patients meeting the American College of Rheumatology preliminary criteria for improvement of RA (the ACR20 criterion) after 12 weeks [21]. This index requires a reduction of at least 20% in swollen and tender joint counts and a 20% reduction in at least three of the following criteria: patient’s assessment of pain (VAS), patient’s global assessment, physician’s global assessment, ESR and health-associated quality of life.

In patients with cutaneous psoriasis affecting at least 2% of their body surface, the mean percentage decrease in the Psoriatic Area and Severity Index (PASI), was assessed as another secondary endpoint [22]. Clinically meaningful improvement was defined as a decrease of at least 50% in the PASI.

### Statistical methods

Clinical parameters were compared between study entry and after 12 weeks by the Wilcoxon rank sum test. A P value <0.05 was regarded as statistically significant. All statistical analyses were done using SPSS software version 11.5 (Lead Technologies, Chicago, IL, USA).

### Results

Baseline characteristics of the 10 patients enrolled in the study are summarized in Table 1. The outcome measurements of the seven patients who completed the study are depicted in Table 2. After 12 weeks, the median joint count decreased from 12.0 tender and 5.0 swollen joints to 4.0 and 2.0, respectively (P<0.05 for both). Although not significant, patient’s median global assessment of disease activity decreased from 4.0 to 2.0 on the five-point Likert scale. In contrast, physician’s median global assessment showed a significant reduction, from 3.0 to 2.0 (P<0.05). Patient’s median assessment of disability according to the HAQ and median joint pain assessed by the patient on a 100 mm VAS dropped from 1.0 to 0.75 (P<0.05) and from 7.2 to 5.2 (P=0.063), respectively. ESR and CRP showed a decrease that was not statistically significant.

### Table 1. Demographic parameters of the 10 patients enrolled in the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Enrolled patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr): median and interquartile range</td>
<td>37.0 (33.5–48.0)</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Weight (kg): median and interquartile range</td>
<td>78.3 (75.3–88.2)</td>
</tr>
<tr>
<td>Duration of psoriatic arthritis (yr): median and interquartile range</td>
<td>2.0 (1.0–3.8)</td>
</tr>
<tr>
<td>Duration of psoriasis (yr): median and interquartile range</td>
<td>12.5 (3.5–15.8)</td>
</tr>
<tr>
<td>HLA B27-positive</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Concomitant NSAID therapy</td>
<td>Rofecoxib 7</td>
</tr>
<tr>
<td></td>
<td>Diclofenac 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study entry</th>
<th>6 weeks</th>
<th>12 weeks</th>
<th>12 weeks vs baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count</td>
<td>12.0 (8.0–18.0)</td>
<td>9.0 (1.0–16.0)</td>
<td>4.0 (2.0–10.0)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>5.0 (4.0–8.0)</td>
<td>4.0 (3.0–9.0)</td>
<td>2.0 (1.0–7.0)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Patients global assessment (1–5 Likert scale)</td>
<td>4.0 (3.0–4.0)</td>
<td>3.0 (2.0–3.0)</td>
<td>2.0 (2.0–3.0)</td>
<td>0.0014*</td>
</tr>
<tr>
<td>Physicians global assessment (1–5 Likert scale)</td>
<td>3.0 (3.0–4.0)</td>
<td>3.0 (2.0–3.0)</td>
<td>2.0 (2.0–3.0)</td>
<td>0.0014*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>12.6 (5.0–13.8)</td>
<td>7.5 (4.9–13.0)</td>
<td>6.4 (4.0–10.1)</td>
<td>0.345</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>16.0 (7.0–24.0)</td>
<td>12.0 (7.0–24.0)</td>
<td>14.0 (3.0–23.0)</td>
<td>0.735</td>
</tr>
<tr>
<td>Pain (VAS 0–10 cm)</td>
<td>7.2 (5.9–7.6)</td>
<td>6.0 (5.0–6.2)</td>
<td>5.2 (4.0–6.5)</td>
<td>0.063</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.0 (0.375–1.375)</td>
<td>1.0 (0.625–1.125)</td>
<td>0.75 (0.375–1.0)</td>
<td>0.045*</td>
</tr>
<tr>
<td>PASI</td>
<td>3.6 (1.98–5.95)</td>
<td>2.95 (1.9–2.9)</td>
<td>2.05 (1.9–2.9)</td>
<td>0.046*</td>
</tr>
</tbody>
</table>

*Patients with psoriatic skin disease affecting >2% of body surface (n=6). *P-value <0.05.
Primary and secondary endpoints

Six patients achieved the primary endpoint criterion (PsARC) and five patients an ACR 20 response. Three patients had to be withdrawn from the study due to inefficacy and side-effects (see below).

The mean percentage reduction in PASI was 38%, with a clinically meaningful PASI 50 response in two of the six patients. Of the three patients who had to be withdrawn from the study prematurely, two showed an increase in disease activity despite pioglitazone treatment: one patient with generalized erythematous psoriasis had to be withdrawn at week 2 due to an extension of his skin involvement and received systemic immunosuppressive therapy. A second patient with severe mutilating arthritis already refractory to methotrexate, sulphasalazine and cyclosporin treatment presented with a flare of his joint disease at week 8.

Adverse events

Six out of 10 patients participating in the study reported an adverse event. Three patients developed oedema of the lower extremities and a weight gain of more than 2 kg. One of these patients presented with an increase in weight of 14 kg at the final visit. Of interest, she suffered from obesity before the study and reported a massive increase in appetite throughout the study. As her oedema of the lower extremities was only mild, the increase in weight gain was attributed to an increase in body mass. Two patients had episodes of nervousness that lasted for 5–10 min and resolved spontaneously. Neither of them showed decreased blood glucose levels at the time of the visits. One patient had an asymptomatic increase in creatine kinase following an alcohol excess and enhanced physical exercise, which resolved despite continuation of study medication. No serious adverse event was observed.

One patient had to be withdrawn from the study prematurely because of severe oedema of the lower extremities, although this patient had responded clinically according to the PsARC prior to the onset of oedema.

Discussion

To our knowledge, this is the first study addressing the effects of a PPARγ agonist as therapy for a rheumatic disease. Of the eight clinical and laboratory parameters used to evaluate the efficacy of pioglitazone in PsA over a period of 12 weeks, four improved significantly in the patients who completed the study: tender and swollen joint counts, physician’s global assessment and patient’s assessment of disability. The two objective parameters reflecting disease activity, ESR and CRP, did not show a statistically significant decrease. Since ESR and CRP were elevated in only three and six patients respectively at baseline (two of whom had to be withdrawn from the study prematurely), it is difficult to conclude whether there is a biological effect on inflammatory parameters. This would request a larger number of patients with raised values at baseline.

Six patients met the PsARC and five an ACR 20 response. Furthermore, an improvement of skin involvement was demonstrated by a mean decrease in PASI of 38%; a clinically meaningful improvement (PASI 50) was achieved in two patients. Owing to the open-label, single-arm design, it is not possible to confirm the general efficacy of PPARγ treatment in psoriatic arthritis.

The pleiotropic function of PPARγ activation raised some concerns about possible side-effects. Of these, liver toxicity in particular has been a rare but severe adverse event during troglitazone treatment and resulted in withdrawal of the drug in 2001 [23, 24]. None of our patients developed abnormal liver enzymes during therapy.

In the present study, increase in body weight and peripheral oedema were the major side-effects. Both of these side-effects have been reported in the diabetes studies with pioglitazone, rosiglitazone and troglitazone, suggesting a class effect of these drugs [25–28]. It should be noted that the number of patients showing these side-effects in our study appears rather high compared with observations in the diabetes studies.

A possible explanation for this phenomenon might be the high dose of 60 mg pioglitazone/day, which exceeds the maximum dose used in diabetes by 15 mg. Another reason could be the co-medication with NSAIDs, which can also cause fluid retention and might have amplified this side-effect [29]. In one patient, a significant elevation of the creatine kinase appeared after excessive alcohol consumption and physical exercise, and resolved quickly despite continuation of therapy.

The observation that major clinical improvement appeared between week 6 and week 12 suggests that patients may require at least 3 months to achieve a significant clinical response.

There are two major problems associated with the currently available in vitro and in vivo data addressing the mechanism of action by which PPARγ ligands may exert their anti-inflammatory effects. First, these models differ substantially from human disease and the doses of thiazolidinediones used in these studies are at least 100-fold higher than those used for antidiabetic therapy in humans. Our study revealed that a dose exceeding 60 mg/day is limited due to the side-effects observed.

Secondly, there are indications that some of the anti-inflammatory effects of thiazolidinediones are PPARγ-independent. Chawla et al. [30] were able to show in PPARγ-null mice that thiazolidinediones exert anti-inflammatory effects independent of PPARγ activation. In addition, despite the high affinity of thiazolidinediones for PPARγ, their anti-inflammatory effects are weaker compared with those of the low-affinity ligand 15d-PGJ2 in different in vitro and in vivo models.

Further investigations should also focus on PPARγ-independent anti-inflammatory mechanisms, leading to the development of drugs with a better risk/benefit ratio than thiazolidinediones in high doses.

In summary, since their discovery in the early 1990s, it has become clear that PPARs take part in the complex regulation of lipogenesis, glucose haemostasis and inflammation. The present study supports the hypothesis that patients with PsA may benefit from therapy with PPARγ ligands. This needs to be evaluated in larger controlled trials.

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The authors have declared no conflicts of interest.

References


