Clinical and ImmunoLogic Assessment of Patients With Psoriasis in a Randomized, Double-blind, Placebo-Controlled Trial Using Recombinant Human Interleukin 10

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Background: In several open-label studies, recombinant human interleukin 10 (rhIL-10), a type 2 anti-inflammatory cytokine, has been reported to improve psoriasis, a disease characterized by type 1 cytokine inflammation.

Objective: To evaluate the safety, efficacy, and immunologic parameters in individuals with psoriasis treated with rhIL-10.

Design and Intervention: Patients received rhIL-10 (20 µg/kg) or placebo subcutaneously 3 times weekly for 12 weeks in a randomized, double-blind manner.

Setting and Patients: National Institutes of Health Clinical Center in Bethesda. Twenty-eight patients with moderate-to-severe psoriasis as defined by a Psoriasis Area Severity Index (PASI) score of 10 or higher.

Main Outcome Measure: The primary clinical end point was the mean percentage change in the PASI score comparing baseline and week 12 scores. Intracellular cytokine production by peripheral blood mononuclear cells (PBMCs) was measured by flow cytometry.

Results: There was no significant difference in the mean percentage change in the PASI score from baseline to week 12 between the rhIL-10–treated group and control patients (17% vs 13% improvement, respectively; P = .69), although a modest trend toward improvement in patients receiving rhIL-10 was documented at both the 6- and 8-week points. Interestingly, proinflammatory and type 1 cytokine production by PBMCs progressively declined in the rhIL-10–treated patients during the entire 12-week study period.

Conclusions: Treatment with rhIL-10 resulted in only temporary clinical improvement in psoriasis, despite sustained systemic decreases in proinflammatory and type 1 cytokine production. These data suggest that immunotherapy that decreases the ratio of systemic type 1 and type 2 cytokine production does not necessarily lead to improvement of type 1 cytokine–mediated disease.

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A IMPORTANT role for T cells in the pathogenesis of psoriasis is supported by both the clinical benefits of treatments that specifically target T cells and the documentation of clonal T-cell proliferation within lesions. The T-cell–driven inflammatory response in psoriasis is dominated by type 1 cytokines, with high levels of interleukin 2 (IL-2), interferon γ (IFN-γ), and other proinflammatory cytokines detected within lesions. By contrast, IL-10, a type 2 cytokine with a broad spectrum of immunosuppressive and anti-inflammatory effects in vitro and in vivo, is absent or markedly diminished in psoriatic skin when compared with normal skin. Because of these findings, recombinant human IL-10 (rhIL-10) has been tested as a possible treatment for psoriasis.

In several small studies, patients with psoriasis were treated with varying doses of rhIL-10 for relatively short periods (≤6 weeks) with reported efficacy. Given this background, we designed a randomized, double-blind, placebo-controlled trial to evaluate safety, efficacy, and immunologic parameters of rhIL-10 treatment in patients with moderate-to-severe psoriasis.

SUBJECTS AND METHODS

Patients
Eligibility criteria included stable classic psoriatic skin lesions, a Psoriasis Area and Severity Index (PASI) score of 10 or higher, an affected total body surface area of more than 10%, weight less than 110 kg, and cessation of systemic psoriatic medications for 4 weeks and topical psoriasis medications for 2 weeks before entry.
All PBMCs gathered from individual patients were thawed and assayed for intracellular cytokine staining on the same day using monoclonal antibody (mAb) staining (PharMingen, San Diego, Calif) and flow cytometry. Briefly, thawed PBMCs were restimulated for 6 hours with 4-α-phorbol 12-myristate 13-acetate, 25 ng/mL (Sigma Aldrich Corp) and ionomycin, 1 µg/mL (Sigma Aldrich Corp). Two hours before harvesting, brefeldin A, 3 µg/mL (Sigma Aldrich Corp), was added to cultures to prevent cytokine secretion. Following stimulation, cells were incubated with Cy-chrome–conjugated anti-CD4 mAbs, fixed and permeablized with Cytofix/Cytoperm (PharMingen), incubated with fluorescein isothiocyanate–conjugated anti–IFN-γ mAbs, 10 µg/mL, and phycoerythrin–conjugated anti–IL-4 mAbs or phycoerythrin–conjugated anti–tumor necrosis factor α (TNF-α) mAbs, and examined by flow cytometry (FACScan; Becton Dickinson, Mountain View, Calif) using Lysys II software (Becton Dickinson).

**STATISTICAL ANALYSIS**

The 2-sample t test was used to determine the statistical significance of differences from baseline for PASI scores, SAPASI scores, and laboratory parameters between groups of patients randomized to placebo or rhIL-10. If the variances were not equal, then the standard Satterthwaite method for modifying the t test was used. Otherwise, if the data were not normally distributed, a Wilcoxon rank sum test was performed. Categorical demographic and prior treatment variables were compared between the 2 groups using the χ2 test as appropriate. All P values are reported without correction for multiple comparisons, but only the 12-week PASI score difference should be interpreted without any caveats. All other test results are exploratory and should be considered in the context of the number of evaluations performed and the likelihood of identifying a small P value by chance when many are calculated. All P values are 2-tailed.

**RESULTS**

**DEMOGRAPHICS AND COMPLIANCE**

Twenty-eight patients with moderate-to-severe psoriasis enrolled in this study, with 10 randomly assigned to receive placebo and 18 randomly assigned to receive rhIL-10 (Figure 1). Baseline PASI scores ranged from 9.3 (in a patient subsequently determined to be ineligible) to 45.0, with an overall mean PASI score of 19.3. The mean PASI scores were 19.9 for rhIL-10–treated patients and 19.2 for placebo-treated patients. The mean age was 44.9 years, and the overall ratio of men to women was 1.8:1. Randomization resulted in 2 groups that differed somewhat in several aspects; the rhIL-10–treated group was significantly older, had a slightly greater proportion of men, and reported more alcohol use (Table 1). Most patients had been undergoing some form of systemic psoriasis treatment in the past.

Of the 28 patients who enrolled in the trial, 21 were able to complete all 12 weeks of therapy (Figure 1). Two patients in the placebo arm withdrew from the study at 6 weeks because of worsening skin disease (an increase of PASI score of >30%), 2 left the study early because of adverse events (one case each of anemia and pancreatitis, details follow), and 2 discontinued the trial because of early study termination by the US Food and Drug Administration. Two patients were considered statistically
unevaluable because they both received fewer than 3 doses of rhIL-10 or placebo (Figure 1).

Compliance throughout the study was excellent. Because of noncompliance and not medical reasons, 5 patients in the rhIL-10 group missed a total of 9 doses and 2 patients in the placebo group missed 2 doses. No patient missed more than 3 doses while enrolled in the study.

rhIL-10 LEADS TO TRANSIENT CLINICAL IMPROVEMENT IN PATIENTS WITH PSORIASIS

All patients, whether they were receiving placebo or rhIL-10, improved slightly during the initial weeks of treatment (Table 2). The rhIL-10–treated patients but not the placebo-treated patients continued to improve during the second month of treatment (Table 2 and Figure 2). However, most patients receiving rhIL-10 experienced rebound flares in their psoriasis following 8 weeks of therapy. This was reflected in their 12-week PASI scores (Table 2). At this point, there was no statistically significant difference between the rhIL-10 and placebo groups (P=.69). Although the SAPASI scores tended to be higher than the investigator scores, the SAPASI scores showed similar trends to PASI scores (data not shown).

Histologic review of target lesions at weeks 0, 4, and 12 revealed changes consistent with classic psoriasis or partially treated psoriasis (data not shown) and were consistent with the clinical score at the time of the biopsy.

Table 1. Baseline Characteristics of Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 10)</th>
<th>rhIL-10 (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SEM, y</td>
<td>35.8 ± 3.2</td>
<td>50 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (50)</td>
<td>13 (72)</td>
<td>.11</td>
</tr>
<tr>
<td>Female</td>
<td>5 (50)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td>Baseline PASI score, mean ± SEM</td>
<td>19.2 ± 2.8</td>
<td>19.9 ± 2.4</td>
<td>.90</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10)</td>
<td>1 (6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>African American</td>
<td>1 (10)</td>
<td>1 (6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>White</td>
<td>8 (80)</td>
<td>14 (77)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>6 (60)</td>
<td>11 (61)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>3 (30)</td>
<td>6 (33)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Smoker</td>
<td>4 (40)</td>
<td>10 (55)</td>
<td>.44</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>4 (40)</td>
<td>15 (83)</td>
<td>.03</td>
</tr>
<tr>
<td>Prior therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriene</td>
<td>8 (80)</td>
<td>12 (67)</td>
<td>.67</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2 (20)</td>
<td>1 (6)</td>
<td>.28</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5 (50)</td>
<td>8 (44)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>PUVA</td>
<td>6 (60)</td>
<td>8 (44)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Systemic retinoids</td>
<td>3 (30)</td>
<td>7 (39)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>3 (30)</td>
<td>4 (22)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>UV-B</td>
<td>5 (50)</td>
<td>11 (61)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>9 (90)</td>
<td>13 (72)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated. rhIL-10 indicates recombinant human interleukin 10; PASI, Psoriasis Area Severity Index; and PUVA, psoralen–UV-A.

Table 2. Mean Percentage Improvement in PASI Scores Over Time*

<table>
<thead>
<tr>
<th>Time Point, wk</th>
<th>Placebo</th>
<th>rhIL-10</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>12.1 ± 8.0 (9)</td>
<td>18.7 ± 3.1 (17)</td>
<td>.46</td>
</tr>
<tr>
<td>4</td>
<td>20.0 ± 9.3 (9)</td>
<td>30.2 ± 5.0 (17)</td>
<td>.30</td>
</tr>
<tr>
<td>6</td>
<td>6.9 ± 13.0 (9)</td>
<td>31.8 ± 5.8 (16)</td>
<td>.06</td>
</tr>
<tr>
<td>8</td>
<td>13.3 ± 10.5 (7)</td>
<td>35.6 ± 4.3 (16)</td>
<td>.03</td>
</tr>
<tr>
<td>12</td>
<td>12.9 ± 9.2 (7)</td>
<td>17.3 ± 6.2 (14)</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Values shown are means ± SEMs (number) calculated by comparing baseline Psoriasis Area Severity Index (PASI) scores with the PASI scores at weeks 2, 4, 6, 8, or 12. P values are based on the 2-sample t test. rhIL-10 indicates recombinant human interleukin 10.

Figure 2. Recombinant human interleukin 10 (rhIL-10) leads to transient clinical improvement. Representative clinical photographs of an rhIL-10–treated patient showing significant improvement at week 6 (Psoriasis Area Severity Index [PASI] score = 6.6) compared with baseline (PASI score = 31.8) and disease flare at week 12 (PASI score = 19.1).
rhIL-10 IS RELATIVELY WELL TOLERATED

Overall, there were no differences in the type or frequency of adverse events between the 2 study groups, including headaches, fever, and gastrointestinal symptoms (data not shown). Serious adverse events observed in this study included gallstone pancreatitis in an rhIL-10–treated patient and cellulitis in a placebo-treated patient. The former patient underwent laparoscopic cholecystectomy, and the latter received 2 days of intravenous antibiotics and both recovered completely.

rhIL-10 LEADS TO ANEMIA, THROMBOCYTOPENIA, AND REDUCTIONS IN SERUM CHOLESTEROL LEVELS

Statistically significant changes in hemoglobin levels, reticulocyte counts, platelet counts, and cholesterol levels were observed during the study between the rhIL-10 and placebo groups (Figure 3). Changes in hemoglobin levels were statistically lower in the rhIL-10–treated group during weeks 2 to 8 compared with baseline (range in P values: .001 to .02, unadjusted for multiple comparisons) but returned to levels similar to placebo.

Figure 3. Recombinant human interleukin 10 (rhIL-10) leads to decreases in platelet counts, hemoglobin levels, and cholesterol levels and increases in serum IgE levels. Absolute mean values ± SEMs for either rhIL-10–treated (closed diamonds or closed bars) or placebo-treated (open circles or open bars) patients during the study are shown. To convert cholesterol to millimoles per liter, multiply by 0.0259.
treated patients by week 12. One patient demonstrated a gradual decline in hemoglobin levels throughout 8 weeks of rhIL-10 therapy (to a nadir of 9.9 g/dL), was discontinued from the study for this reason, and had return of his hemoglobin levels to baseline values 1 month after stopping use of the drug. No other patient demonstrated laboratory-defined anemia (hemoglobin levels <12 g/dL). Perhaps in compensation for mild drug-associated anemia, changes in reticulocyte counts were statistically higher in the rhIL-10–treated group from weeks 6 to 12 (range in P values: .001 to .13, unadjusted for multiple comparisons), but only rarely exceeded the upper limit of normal. As has been previously observed, platelet levels dropped in the first week of rhIL-10 therapy (P < .001) but returned to normal by week 2.

One of the most unexpected laboratory findings of this study was a marked decline in cholesterol levels seen in the rhIL-10–treated group (mean change, 50-67 mg/dL [1.30-1.74 mmol/L]; <.001 ≤ P ≤ .01) at every point in the study (Figure 3C). Mean triglyceride levels were unaffected by rhIL-10.

No other statistically significant differences were found in other routine laboratory tests, or if statistically significant changes were seen, they were not clinically relevant because the values all remained within normal limits. These laboratory evaluations included chemistry panels, liver function tests, and urinalyses.

**rhIL-10 LEADS TO INCREASED SERUM IgE LEVELS AND DECREASED PRODUCTION OF TYPE 1 CYTOKINES**

Serum IgE levels doubled in the rhIL-10 group by 12 weeks (from a mean of 104.3 mg/dL at baseline to 208.78 mg/dL at week 12; mean difference of 96.0 mg/dL for those with paired observations; P = .002 by Wilcoxon signed rank test) (Figure 3D). Furthermore, consistent with this, intracellular cytokine staining of PBMCs from the rhIL-10–treated patients revealed progressive declines in the IFN-γ/IL-4 ratio and TNF-α production in CD4+ T cells and decreases in TNF-α production in monocytes during the 12-week period (Figure 4). The combination of these immunologic findings indicates that rhIL-10 therapy induced a decrease in the ratio of systemic type 1 and type 2 cytokine production.

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**COMMENT**

Because of its anti-inflammatory and immunomodulatory properties, rhIL-10 has been tested as a treatment for a variety of inflammatory disease states, including Crohn disease and rheumatoid arthritis. These have been relatively small open-label studies. To date, significant clinical utility has not been established in either of these conditions. In the first report on the use of rhIL-10 in psoriasis, 3 patients received subcutaneous rhIL-10, 8 µg/kg per day, for 24 days and were described as experiencing clinical efficacy without major adverse effects. In a subsequent open-label study, 10 patients with psoriasis received subcutaneous rhIL-10, 4 µg/kg per day, for 42 days with clinical improvement. In the largest reported study to date, 10 patients with psoriasis received subcutaneous rhIL-10 during a 7-week period at a dose of 8 µg/kg daily (n = 5) or 20 µg/kg 3 times per week (n = 5). Again, substantial improvement in PASI scores was reported. The authors of these studies have posited that a defect in the production of IL-10 within lesions may cause or contribute to psoriasis. Others have suggested that rhIL-10 may be working by decreasing proinflammatory cytokine production by PBMCs. Whether local skin or systemic cytokine production is more important in the pathogenesis of psoriasis remains subject to debate.

Herein, we report the first (to our knowledge) randomized, double-blind, placebo-controlled study to evaluate the effects of rhIL-10 as a treatment option for a human disease. In patients with moderate to severe psoriasis, use of rhIL-10 for 12 weeks did not lead to sustained clinical efficacy, although there were favorable differences between placebo- and rhIL-10–treated patients at both the 6- and 8-week points. Our 6- and 8-week data are consistent with the reported efficacy of rhIL-10 in several smaller studies, since patients were only treated for 6 weeks or less in these studies. The findings that rhIL-10–treated patients experience flares in psoriasis despite continued use of the drug and despite persistent suppression of type 1 and proinflammatory cytokine production are novel. Our study also emphasizes the importance of blinded controlled studies in evaluating the effects of such novel agents.
clinical efficacy and immunologic effects of new therapeutic agents for psoriasis.

In general, the subcutaneous injections of rhIL-10 were well tolerated. No patients withdrew because they disliked the treatment; instead, patients withdrew because of worsening skin disease or adverse events that precluded continuing with the study. As with previous experience with this medication, predictable declines in hemoglobin levels and platelet counts were seen soon after the initiation of treatment (Figure 3). However, the declines in cholesterol levels were surprising and striking (Figure 3), especially considering that current cholesterol-lowering agents decreased levels by approximately 25% on average.24 In our study, an average decrease of 30% (59 points) was noted in rhIL-10 patients.

With a few notable exceptions, cytokine therapy has been somewhat disappointing in the treatment of immunemediated diseases. In our study, rhIL-10 demonstrated significant antipsoriatic effects for 6 to 8 weeks of treatment (Table 2, Figure 2) and induced distinct immunologic changes (Figures 3 and 4). However, clinical responses were not maintained with continued use of the drug, despite persistent reduction of proinflammatory and type 1 cytokine production by PBMCs. This is one of the more interesting findings of our study, yet we are unsure why cytokine production did not correlate with clinical disease severity at the 12-week point. This may reflect compensatory mechanisms and/or redundancy in cytokine pathways within the skin. Regardless, our data suggest that immunotherapy that decreases the ratio of systemic type 1 and type 2 cytokine production does not necessarily correlate with improvement of type 1 cytokine-mediated skin disease.

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