Long-term Effectiveness and Safety of Recombinant Human Interferon Gamma Therapy for Atopic Dermatitis Despite Unchanged Serum IgE Levels

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Objective: To assess the long-term effects of recombinant human interferon gamma treatment of atopic dermatitis (AD).

Design: Case series. Patients were treated for up to 24 months.

Setting: University dermatology outpatient clinics in Ann Arbor, Mich, and Portland, Ore.

Patients: Twenty-four of 32 eligible patients who participated in a previously reported, 12-week, double-blind, placebo-controlled study of recombinant human interferon gamma treatment for AD were enrolled.

Intervention: Patients self-administered recombinant human interferon gamma, 50 µg/m², by daily subcutaneous injection.

Main Outcome Measures: Overall response; body surface area of involvement; clinical severity scores for pruritus, erythema, edema, excoriation, dryness, scaling, and lichenification; other atopic symptoms; and laboratory parameters, including serum IgE levels, were monitored at quarterly visits. Results at 1 and 2 years were compared with baseline values.

Results: All efficacy parameters improved (P<.05). For example, pruritus was reduced by 50% after both 1 (n = 24, P<.001) and 2 (n = 16, P = .005) years. Allergic conjunctivitis and allergic rhinitis also improved (P<.01). Eosinophil counts decreased significantly (P<.001). IgE levels increased. Clinical improvement more closely correlated with changes in eosinophil counts (r = 0.3-0.5) than with changes in IgE levels (r = 0.0-0.2). Only 1 patient discontinued therapy because of adverse effects (flulike symptoms).

Conclusions: The initial efficacy and adverse effects reported for recombinant human interferon gamma treatment of patients with AD were maintained after 2 years of long-term use. Recombinant human interferon gamma seems to be a well-tolerated and effective agent in the long-term therapy of patients with AD. Therapies that correct cellular immune defects, but not humoral immune defects, may be effective in the treatment of patients with AD.

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Although atopic dermatitis (AD) is a common condition, there are no entirely satisfactory treatments. Conservative treatments are frequently insufficient or impractical. Corticosteroids, although frequently effective, cannot be used continuously because of significant adverse effects. Newer modalities, such as oral cyclosporine, are effective but likewise limited by adverse effects. For example, in the treatment of psoriasis with cyclosporine, approximately 20% of patients discontinued treatment within 2 years because of adverse effects.

Interferon gamma has consistently demonstrated activity in patients with AD. Results of short-term, open-label studies show interferon gamma to be a well-tolerated and potentially effective treatment for patients with AD and the optimal dose to be 50 µg/m². In a 12-week, double-blind, placebo-controlled study, interferon gamma was superior to placebo in the improvement of overall severity, erythema, and excoriations and erosion. However, despite reduction of induration, pruritus, dryness, and lichenification in the treated group compared with those receiving placebo, the differences were not statistically significant. Similarly, whereas all associated atopic symptoms improved with treatment, only conjunctivitis and blepharitis improved significantly; allergic rhinitis and asthma did not.

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PATIENTS AND METHODS

STUDY DESIGN

Patients who completed the 12-week, double-blind trial of recombinant human interferon gamma therapy for AD were offered the opportunity to enroll in the open-label, maintenance-phase therapy and were evaluated at either The Oregon Health Sciences University, Portland, or the University of Michigan Medical Center, Ann Arbor. Protocols were approved by respective institutional review boards, and all patients gave signed informed consent. Pretreatment and subsequent evaluations were as previously detailed and consisted of clinical laboratory evaluations (complete blood cell counts with differential, blood chemistry, serum IgE, and urinalysis) and clinical assessments consisting of total body surface area (TBSA) of involvement and total clinical severity (TCS). Total clinical severity consisted of the combined scores for erythema; edema, papulation, and induration; pruritus; excoriations and erosions; scaling and dryness; and lichenification, each measured on a half-point incremental scale from 0 to 3 (0 indicating absent; 1, mild; 2, moderate; and 3, severe). Assessments of other associated atopic symptoms (allergic rhinitis, conjunctivitis and blepharitis, and asthma on a 0-3 scale), infections, concomitant medications, and adverse events were also made. Overall, global assessments were also made at each visit as 0 (no change relative to baseline), ± 1 (>25% better or worse), ± 2 (>50% better or worse), or + 3 (resolved). Patients self-administered recombinant human interferon gamma, 30 µg/m², by daily subcutaneous injection and were prescribed 0.1% triamcinolone acetonide ointment and 1% hydrocortisone cream in 0.45-kg jars for use as needed.

STATISTICAL ANALYSIS

Patients were considered as 2 independent groups, those completing 1 year (y-1) and those completing 2 years (y-2) of therapy. Analyses were performed using a spreadsheet (Excel, Microsoft Corp, Seattle, Wash). Two-tailed paired t tests were used to compare changes in y-1 and y-2 relative to the respective baseline values. Because of dropouts between years 1 and 2, baseline values for y-1 and y-2 may differ. Regression analysis with 95% confidence limits was performed to compare changes in TBSA, TCS, and overall severity scores with changes in IgE levels and eosinophil counts. Differences were considered statistically significant at P < .05, P > .05 and P < .1 were considered moderately significant. Variation is expressed as SEM.

RESULTS

Because AD is a chronic disease, it is imperative that any proposed therapy have persistent efficacy and acceptable adverse effects during years of use. For this reason, at the conclusion of the 12-week, placebo-controlled study, patients were offered open-label, maintenance-phase treatment. This report provides data from that longitudinal study of patients with AD followed up for 12 to 24 months while receiving subcutaneous recombinant human interferon gamma. The results show that the efficacy and adverse effects indicated by the 12-week study not only persist for extended periods but the significance of the improvements was strengthened during long-term use of recombinant human interferon gamma. There were no reductions in serum IgE levels and no correlation between clinical improvement and IgE measurements. In contrast, therapy significantly reduced circulating eosinophil and basophil numbers, and the reduction in eosinophil counts correlated moderately with clinical improvement.

PATIENTS

Twenty-four of 32 eligible patients chose to participate in this maintenance-phase study. Mean age was 36.0 ± 2.4 years (range, 11-57 years); 18 were males and 6 were females. Mean duration of AD before study enrollment was 23.1 ± 3.7 years. Mean quantity of topical corticosteroid prescribed during the study was 0.86 ± 0.09 kg each of 0.1% triamcinolone acetonide ointment and 1.0% hydrocortisone cream. Eight patients discontinued therapy between years 1 and 2 because of improvement without therapy (1 patient), inconvenience (2 patients), noncompliance (2 patients), ineffectiveness (1 patient), flu-like symptoms (1 patient), and unknown reasons (1 patient, unavailable for follow-up).

REDUCED DISEASE EXTENT

For y-1, baseline TBSA was 56.4 ± 4.8%, which was reduced to 20.5% ± 3.9% at the end of the first year (n = 24, Figure 1). For y-2, baseline TBSA was 60.4 ± 4.9%, which was reduced to 36.1% ± 7.0% after 2 years of recombinant human interferon gamma therapy (n = 16, Figure 2). Each was highly significant (P < .001). These data reflect the observations that 23 of 24 patients at 1 year and 14 of 16 patients at 2 years exhibited reduced extent of AD signs at follow-up (not shown). The difference between TBSA at 1 and 2 years was not statistically significant (P > .05).

IMPROVED GLOBAL ASSESSMENT

The physician-assessed overall severity, which was defined as 0 at baseline, was reduced at both 1 and 2 years. Mean improvement at 1 year was 1.7 ± 0.1 (of a possible 3.0, n = 24, P < .001, Figure 1) and at 2 years was 1.3 ± 0.2 (n = 16, P < .001, Figure 2). These results reflect a 25% to 50% improvement in 7 of 24 patients and a greater than 50% improvement in 17 of 24 patients after 1 year and a 25% to 50% improvement in 1 of 16 patients and a greater than 50% improvement in 10 of 16 patients after 2 years (not shown).

IMPROVED TCS

The TCS equally weights the 6 individual severity parameters and yields an aggregate score on a 0 to 18 scale. At baseline, patients assessed after y-1 had a TCS of
12.9 ± 0.4, which improved to 7.7 ± 0.7 (n = 24, P < .001, Figure 1) after 1 year of therapy. Similarly, patients assessed after y-2 had a TCS of 13.2 ± 0.5 at baseline, which improved to 7.7 ± 1.2 (n = 16, P < .001, Figure 2) after 2 years of recombinant human interferon gamma therapy.

INDIVIDUAL SEVERITY PARAMETERS

Figure 3 demonstrates the reduced severity of all clinical parameters at 1- and 2-year follow-up visits. In general, each was evaluated as moderate to severe (between 2 and 3 on the assessment scale) at baseline and improved to mild to moderate after both 1 and 2 years. All parameters were highly significantly improved after 1 year (n = 24, P < .001) and maintained significance after 2 years (n = 16, P < .05) of therapy. As noted with TBSA, no parameter was significantly different after 2 years compared with after 1 year of therapy.

ASSOCIATED ATOPIC SYMPTOMS

As was found in the 12-week study, associated atopic symptoms improved after 1 and 2 years of treatment in patients with baseline disease. After 1 year (Figure 4), allergic conjunctivitis was reduced from a mean severity score of 1.5 ± 0.1 to 0.6 ± 0.1 (n = 16, P < .001) and allergic rhinitis was reduced from 1.2 ± 0.1 to 0.5 ± 0.2 (n = 15, P < .005). After 2 years of therapy, the reduction in these symptoms remained significant (Figure 4, P < .01). The reduction from 1.2 to 0.95 for y-1 and from 1.3 to 0.3 for y-2 in asthma symptoms was not significant at either time.

LABORATORY PARAMETERS

After 1 year of treatment, the total white blood cell count was reduced from 0.75 ± 0.04 × 10^9/L to 0.34 ± 0.05 × 10^9/L, the neutrophil count was reduced from 0.46 ± 0.03 × 10^9/L to 0.31 ± 0.03 × 10^9/L, the basophil count was reduced from 0.96 ± 0.1 × 10^9/L to 0.56 ± 0.06 × 10^9/L, and the eosinophil count was reduced from 0.62 ± 0.13 × 10^9/L to 0.21 ± 0.04 × 10^9/L (P < .001 for each, Figure 5). Lymphocyte and monocyte counts were not significantly reduced. After 2 years, total white blood cell, basophil, and eosinophil counts continued to be significantly reduced (Figure 5). Although values reached abnormally low counts (<1.5 neutrophils × 10^9/L) in only 2 patients, 1
patient experienced recurrent grade II neutropenia (<1.0 × 10^9/L) while taking daily recombinant human interferon injections and, therefore, received every-other-day dosing, which reversed the neutropenia.

Results of laboratory testing also revealed a statistically significant increase in mean aspartate aminotransferase level (normal range, 9-34 U/L) from 28.2 ± 1.4 U/L to 40.4 ± 3.8 U/L at 1 year (P = .0015), which was lowered to 32.4 ± 2.8 U/L at 2 years (P = .26 relative to baseline). Alanine aminotransferase level (normal range, 6-34 U/L) went from 25.3 ± 2.2 U/L at baseline to 37.2 ± 4.1 U/L after 1 year and to 32.4 ± 2.8 U/L after 2 years (P = .006 for both). Although these numbers are statistically significant, the clinical relevance is uncertain because the maximum aspartate aminotransferase level was 73 U/L (2 times baseline for that patient) and the maximum alanine aminotransferase level was 88 U/L (4 times baseline). Similarly, serum creatinine level (normal range, 35-97 µmol/L) was also mildly elevated from 81 ± 3 µmol/L (1.07 ± 0.04 mg/dL) at baseline to 91 ± 4 µmol/L (1.19 ± 0.05 mg/dL) after 2 years (P = .03), but the maximum value was only 100 µmol/L (1.31 mg/dL).

**SERUM IgE LEVELS**

Serum IgE levels (normal range, 12-240 µg/L) were not reduced by treatment with recombinant human interferon gamma but actually showed trends toward increased levels, as was seen in the 12-week study.  For y-1, the mean baseline IgE level was 9516 ± 1949 µg/L (9.52 ± 1.95 mg/L), whereas the level at 1 year was 21962 ± 7704 µg/L (21.96 ± 7.70 mg/L) (P = .13); for y-2, the baseline IgE level was 13030 ± 1872 µg/L (13.03 ± 1.87 mg/L), and the level at 2 years was 19524 ± 4498 µg/L (19.52 ± 4.50 mg/L) (P = .27).

**ADVERSE EVENTS**

In general, recombinant human interferon gamma was a well-tolerated treatment. Adverse events are presented in Table 1. Adverse events that were considered drug related were identified as potential adverse events in previous reports of the use of interferon gamma in the treatment of patients with AD: neutropenia; hepatic transaminitis; and the flulike symptoms of myalgia, fever, chills, malaise, and headache. There was 1 newly reported adverse event that may or may not be related to recombinant human interferon gamma use: splenomegaly was detected by physical examination and confirmed by ultrasound examination in 1 patient in whom the sign abated spontaneously. This patient had no other abnormalities relating to hypersplenism. The occurrence of cutaneous viral infections and their sequelae are common in patients with AD and are considered to be related to the disease and not to the therapy. Only 1 patient discontinued therapy because of an adverse event (flulike symptoms that did not remit).

**CLINICAL IMPROVEMENT CORRELATES WITH EOSINOPHIL REDUCTION MORE STRONGLY THAN WITH IgE**

The results of linear regression analysis comparing percent reduction of absolute eosinophil counts and serum IgE levels with percent reduction of TBSA, TCS, and overall improvement are presented in Table 2. Changes in IgE levels correlated marginally at best (r = 0 to ± 0.2) with changes in clinical parameters, with no statistical significance (eg, for TCS for y-1, P = .46; TCS for y-2, P = .77). In contrast, changes in eosinophil counts correlated moderately well (r = ± 0.3 to ± 0.5), with the exception of TBSA at 1 year. The correlation of changes in eosinophil counts to changes in TCS were the strongest and were of moderate statistical significance (for y-1, P = .07; for y-2, P = .10).
and symptoms is maintained considerably beyond the 12 weeks previously studied in a double-blind, placebo-controlled study. All AD clinical efficacy parameters that were measured (TBSA, TCS, overall severity, erythema, edema, pruritus, excoriations, dryness, and lichenification) were significantly improved relative to baseline values at both 1 and 2 years of therapy, including those that, although improved, had not achieved statistical significance. One obvious caveat in the interpretation of these data is the open-label design. However, our results are consistent with those observed in the initial, placebo-controlled phase. In that study, the improvement seen in the placebo group peaked at 7 weeks and had already begun to return to baseline values at the 12-week visit. This observation is in accordance with a review of the literature on placebo effects, which concludes that the duration of placebo effects reported is 3 weeks to, at most, 1 year for some patients with pain.

The benefit of long-term recombinant human interferon gamma therapy for associated atopic symptoms was also predicted by the short-term, double-blind, placebo-controlled trial. Improvement was noted in allergic conjunctivitis and blepharitis and in allergic rhinitis, as was found in the 12-week study. There was inconsistent improvement of asthma, which failed to achieve statistical significance perhaps because baseline severity and the number of affected patients were low.

Results of laboratory studies revealed statistically significant changes after treatment. As previously reported,

Table 1. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>1</td>
</tr>
<tr>
<td>Malaise</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Gastric and esophageal ulcers</td>
<td>1</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>1</td>
</tr>
<tr>
<td>Transaminis</td>
<td>4</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
</tr>
<tr>
<td>Acne vulgaris</td>
<td>2</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Arthralgias</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Congestion</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
</tr>
<tr>
<td>Theophylline toxic reaction</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>1</td>
</tr>
</tbody>
</table>

and symptoms, we also noted minimally decreased hepatic transaminase levels. Prudence suggests monitoring liver function periodically in patients treated with recombinant human interferon gamma to detect possible hepatotoxic effects.

Results of the present study confirm the paradox that even after 2 years of therapy with recombinant human interferon gamma, patients with AD do not have lower IgE levels and, in fact, tend to have increased serum IgE levels. Various reasons have been posited by these authors, to which the reader is referred. Such a dissociation with improved clinical manifestations and persistently elevated IgE levels also occurs in the treatment of patients with AD with cyclosporine. The dramatic reduction in circulating eosinophil counts that we observed during treatment with recombinant human interferon gamma provides evidence of a change in the immunologic milieu from TH2 to TH1 dominated. Because clinical improvement in general, and TCS in particular, correlated better with reduced circulating eosinophil counts than with reduced serum IgE levels, our data highlight the importance of cellular immune defects and apparently reduce the importance of humoral defects (ie, elevated IgE levels) in the maintenance of AD. However, we did not measure Fcɛ receptor expression on antigen-presenting cells; thus, we cannot entirely exclude the possibility that the antigen-focusing effects of IgE via its receptor on Langerhans cells are disrupted by recombinant human interferon gamma treatment. The relationship of this observation to the apparent switch from a TH2 milieu in acute lesions to a TH1 milieu in chronic lesions may be that recombinant human interferon gamma therapy halts the initiation of new lesions, although we did not directly address this issue in this cohort.

The results of this long-term study demonstrate that the adverse effects of recombinant human interferon gamma therapy are acceptable, with no serious adverse events occurring in any of the patients. Although many patients complained of flulike symptoms such as headache, myalgia, arthralgia, fever, and malaise early during treatment, most hardened to these symptoms and seldom reported such symptoms during long-term treatment. Only 1 patient discontinued therapy because of adverse effects, and this was because of previously documented malaise. Our updated information demonstrates that the safety and efficacy of recombinant human interferon gamma therapy observed in the 12-week trial

Table 2. Correlation of Eosinophil Count Reduction With Clinical Improvement

<table>
<thead>
<tr>
<th>Clinical Parameter (Year-2)</th>
<th>Correlation With Percent Eosinophil Change (Pearson r)</th>
<th>Correlation With Percent IgE Change (Pearson r)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year-1</td>
<td>Year-2</td>
</tr>
<tr>
<td>Total body surface area involvement</td>
<td>0.2*</td>
<td>0.3†</td>
</tr>
<tr>
<td>Total clinical severity</td>
<td>0.4*</td>
<td>0.5‡</td>
</tr>
<tr>
<td>Overall improvement</td>
<td>0.3§</td>
<td>0.3‡</td>
</tr>
</tbody>
</table>

* n = 19.
† n = 14.
‡ n = 15.
§ n = 20.
is maintained during long-term use. Furthermore, this clinical improvement occurs in the context of increased serum IgE levels but reduced circulating eosinophil counts.

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