Etretinate Augments Interferon Beta-1b Effects on Suppressor Cells in Multiple Sclerosis

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Background: Interferon beta treatment is only partially effective in multiple sclerosis (MS) suggesting a potential role for adjunctive therapies. Retinoids can augment the clinical efficacy of type 1 interferons in patients with cancer. We reasoned that the same might hold in MS. Interferon beta-1b added to peripheral blood mononuclear cells in vitro partially reverses the CD8 suppressor cell defect of patients with MS. All-trans retinoic acid added to peripheral blood mononuclear cells from untreated patients with MS or from controls potentiates this ability of interferon beta-1b to augment CD8 suppressor cell function in vitro.

Objective: To determine whether retinoid administration to patients with MS who are being treated with interferon beta-1b augments their CD8 suppressor cell function.

Setting: A university hospital MS clinic.

Participants: Patients with MS who were being treated with interferon beta-1b, 14 patients with secondary progressive MS and 3 patients with relapsing remitting MS.

Results: Seventeen patients with MS received etretinate treatment for up to 6 months. Planned dosing was 10 mg 3 times daily for the first month, 25 mg twice daily for the second and third months, and 10 mg twice daily thereafter. The 25-mg twice daily dose was not well tolerated and of the 14 patients who remained in the phase 1 clinical trial through month 3 dose reduction to 10 mg thrice daily was required in 1 patient and to 10 mg twice daily in 4 patients. Eleven patients completed the trial. Etretinate treatment significantly augmented suppressor function over baseline values at 1, 3, and 6 months. No meaningful change was noted in disability or quality of life over the course of the phase 1 clinical trial. Neuropsychological testing of completers suggested improvement on selected aspects of verbal memory at 6 months compared with baseline values.

Conclusions: Etretinate treatment at a dose of 10 mg twice or three times daily augments suppressor cell function in patients with MS receiving interferon beta-1b. Higher dose etretinate treatment (25 mg twice daily) is poorly tolerated by patients with MS. Even at 10 mg twice daily adverse experiences involving the mucous membranes and the skin become troublesome for some, but not all, patients. Whether pulse therapy or administration of retinoid restricted to the day of interferon beta dosing will also augment suppressor function, while being better tolerated, remains to be determined.

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INTERFERON BETA preparations are widely employed to treat multiple sclerosis (MS) but they are only partially effective. Retinoids have been found to potentiate the clinical efficacy of interferon alfa and interferon beta preparations (ie, type 1 interferons [INFs]) in patients with cancer.1-3 When type 1 INFs bind to their cell membrane-bound receptor, 2 receptor-associated kinases known as JAK1 and Tyk2 are phosphorylated. These then phosphorylate cytoplasmic proteins known as STAT1 and STAT2 that, once phosphorylated, dimerize, and bind a protein known as p48. The complex translocates to the nucleus and initiates transcription of interferon α (IFN-α) and β (IFN-β) responsive genes. Retinoid treatment increases the levels of STAT1 and STAT2 severalfold.4 Levels of 2 additional IFN-induced transcription factors called “interferon regulatory factor 1” and “interferon regulatory factor 2” are also increased by retinoids.5 For these reasons the response to a given dose of interferon is sometimes increased by retinoid treatment.

Nonspecific CD8 suppressor cell function is subnormal during MS relapses, returning to normal with remission.6 The CD8 suppressor cell function is persistently subnormal in secondary progressive MS.7 Interferon beta-1b treatment augments CD8 suppressor function in patients with MS.8 This restorative effect may contribute to the beneficial effect of the agent in MS. We showed that interferon beta-1b, when added to peripheral blood mononuclear cells from patients with MS or controls in vitro, augments suppressor function and that when all-trans retinoic acid is added as well suppressor function is fur-
PATIENTS AND METHODS

Seventeen patients (9 men and 8 women) from the MS clinic at the University of Chicago, Chicago, Ill, were enrolled in a 6-month phase 1 (safety) clinical trial of etretinate treatment (Tegison; Hoffman-LaRoche Inc, Nutley, NJ). All patients had been receiving interferon beta-1b treatment for at least 6 months and most for several years. The protocol was approved by the University of Chicago Institutional Review Board. All patients gave written informed consent after the nature of the clinical trial had been fully explained.

Fourteen patients had secondary progressive MS and 3 patients had relapsing-remitting MS. Mean (±SEM) age was 45.0±2.8 (age range, 29-58 years). There were 5 premenopausal women, all of whom were made aware both verbally and in writing of the need to exercise adequate birth control indefinitely. The planned etretinate dose was 10 mg 3 times daily for the first month, 25 mg twice daily for the second and third months, and 10 mg 3 times daily for the fourth through sixth months. Etretinate treatment was taken with meals. Venous blood was drawn at baseline and at 1, 3, and 6 months for evaluation of suppressor cell function. An electrocardiogram was obtained at baseline and complete blood cell counts, liver profiles, and lipid profiles were obtained at baseline and at 1, 3, and 6 months. Neurologic examinations were conducted at these times and Expanded Disability Status Score,11 Scripps Rating Scale,12 and Quality of Life instrument score recorded.13 A limited neuropsychological battery was administered at baseline and at 6 months.

RESULTS

DOSE TOLERANCE

All 17 patients completed the first month of the phase 1 clinical trial at an etretinate dose of 10 mg 3 times daily. Dose escalation to 25 mg twice daily was well tolerated and of the 14 patients who remained in the clinical trial through month 4 dose reduction to 10 mg 2 or 3 times daily was required in 5 patients.

DROPOUTS

One patient with progressive MS withdrew after 3 months because of skin changes (see “Skin and Mucous Membrane Changes” section below). Two patients with progressive MS stopped treatment after 4 months, one because of skin changes and the second because another neurologist switched the treatment to glatiramer acetate. An additional patient with relapsing-remitting MS stopped treatment after 5 months during an attack of MS from which the patient ultimately recovered completely.

SKIN AND MUCOUS MEMBRANE CHANGES

Retinoids inhibit keratinization and major dermatologic side effects were encountered. Fourteen patients re-
ported 1 or more of the following: (1) dryness of skin, eyes, mouth, or nose; (2) rash and/or scaling, itching, and redness or peeling especially of hands and feet; (3) cracking of toenails and fingernails; (4) hair loss including scalp, eyelashes, and eyebrows; and (5) cheilosis (chapped lips). These skin changes were tolerable to most patients at an etretinate dose of 10 mg 3 times daily but intolerable at a dose of 25 mg twice daily. Two patients dropped out because of skin changes.

OTHER UNTOWARD EVENTS

One progressive patient developed depression 3 months into the clinical trial. The emotional well-being score embedded in the Quality of Life instrument (see “Quality of Life” subsection of “Clinical Results” section below) did pick up the depression. This patient had a history of a prior major depression 2 years earlier. The patient responded promptly to antidepressant medication and completed the clinical trial.

BLOOD CHEMISTRY

In published series 25% of the patients treated with etretinate have shown an elevation in the levels of plasma triglycerides, 15% changes in high-density lipoproteins, 7% an elevation in cholesterol, and 15% an elevation in liver enzymes. In this study 10 patients had normal triglyceride values (≤1.80 mmol/L [≤160 mg/dL]) at baseline, 6 had mild elevations (<2.82 mmol/L [<250 mg/dL]), and 1 was highly elevated (≥2.82 mmol/L [≥250 mg/dL]). Values over the course of the clinical trial remained normal in 4 patients, were mildly elevated on at least 1 occasion in 10 patients, and became highly elevated in 3 patients. There was no change in cholesterol values over the course of the clinical trial. High-density lipoprotein cholesterol values were normal at baseline in 15 patients and low (ie, abnormal) in 1. Four patients with normal baseline values showed low values on 1 or more occasions over the course of the clinical trial and the patient with a low value at baseline remained low. No meaningful changes were noted in the liver profile over the course of the clinical trial. White blood cell, red blood cell, and platelet counts were also unchanged.

CLINICAL RESULTS

Expanded Disability Status Score

No meaningful changes in mean score were noted over the course of this intention-to-treat clinical trial (Table 1). Of the 16 patients evaluable at 6 months the Expanded Disability Status Score was improved in 1, unchanged in 12, and worse in 3 including 1 relapsing-remitting patient who was in the midst of an attack, as the clinical trial ended. The patient subsequently recovered to the clinical trial enrollment baseline value.

Scripps Rating Scale

No meaningful change was noted over the course of the clinical trial (Table 1).

Quality of Life

A Quality of Life instrument13 was administered at baseline and at 3 and 6 months. The Quality of Life instrument evaluates mobility, symptoms, emotional well-being, general contentment, thinking, fatigue, and family and social well-being. There was no meaningful change in any of these measures over the course of the clinical trial or in the composite score (Table 1). Emotional well-being, general contentment, and family and social well-being scales were lower at baseline in dropouts than in completers and the difference for the 3 scores combined was statistically significantly different for completers than for dropouts (61.18±4.3 vs 44.33±5.19, P<.03) suggesting a potential role for quality of life screening in patient selection for clinical trials.

Neuropsychological Testing

The group as a whole had an average of 15 years of education and was of average (±SEM) estimated intelligence (National Adult Reading Test Full Scale IQ [NART FSIQ] = 104.2±9.0). All subjects were right-handed. At 6 months, 14 subjects returned for retesting. 10 were still taking etretinate and 4 were no longer taking etretinate. All subjects were administered a short battery of neuropsychological measures assessing memory (Selective Reminding Test, Visual Reproduction), concentration/mental speed (Paced Auditory Serial Addition Test, Trailmaking Test), upper extremity motor speed/dexterity (Grooved Pegboard), speeded word generation (Verbal Fluency), and depression screening (Beck Depression Inventory). Using repeated measures analysis of variance, significant differences suggesting improved performance after 6 months were noted on selected aspects of verbal memory (Selective Reminding Test). Specific indexes included the following: Consistent Long-term Retrieval [CLTR Trial 1] F1,25=11.5, P=.002; and CLTR2, F1,25=8.2, P=.008; CLTR3, F1,25=4.5, P=.04; Long-term Storage Trial 1, F1,25=11.8, P=.002; and Long-term Storage Trial 2, F1,25=4.7, P=.04. All other measures of memory, concentration, upper extremity motor speed/dexterity, speeded word generation, and depression screening did not differ across the 2 assessments.

Table 1. Neurologic Rating Scores in Patients With Multiple Sclerosis Receiving Etretinate Treatment

<table>
<thead>
<tr>
<th>Time of Clinical Trial, mo</th>
<th>Type of Neurologic Test*</th>
<th>EDSS</th>
<th>Scripps Rating Scale Score</th>
<th>Quality of Life Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>5.59 ± 0.36 (17)</td>
<td>65.9 ± 3.1 (16)</td>
<td>107.5 ± 6.1 (17)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>5.56 ± 0.38 (17)</td>
<td>67.4 ± 3.2 (17)</td>
<td>108.3 ± 6.6 (11)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>5.71 ± 0.41 (14)</td>
<td>69.1 ± 2.4 (14)</td>
<td>110.8 ± 6.6 (11)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>5.82 ± 0.37 (16)</td>
<td>67.4 ± 3.2 (16)</td>
<td>113.2 ± 6.3 (12)</td>
</tr>
</tbody>
</table>

*All values are expressed as the mean ± SEM. The parenthetical number represents the number of patients studied. EDSS indicates Expanded Disability Status Score; ellipses, not applicable.

Suppressor Cell Function

Suppressor cell function was improved above baseline values during etretinate treatment (Table 2). Data are pre-
sent both for all patients evaluated at baseline, 1, 3, and 6 months and as paired data comparing baseline 1-, 3-, and 6-month values for individual patients. Etretinate is eliminated slowly so that at least some residual drug effect is likely for weeks to months after stopping treatment. In this intention-to-treat study, dropouts were included in the suppressor cell function evaluations at all time points, whenever possible. All values are statistically significant.

Etretinate treatment of patients with MS receiving interferon beta-1b augments suppressor cell function indicating that retinoid therapy can potentiate at least 1 of the immunomodulating effects of interferon beta-1b in vivo, as it had earlier been shown to do in vitro.10 Retinoids also inhibit interferon gamma production,10,14 and interferon gamma administration to patients with MS has been reported to provoke MS attacks.15 Retinoid therapy lessens the severity of experimental autoimmune encephalomyelitis, a widely studied model disease for MS.16-18 Together these findings suggest a possible adjunctive role for retinoids in the treatment of MS. However, adjunctive therapy with etretinate is far from hazard free. Only 11 of 17 patients completed the 6 months of the clinical trial and 14 patients reported troublesome cutaneous and mucous membrane side effects, sufficient in 2 patients to cause them to drop out of the clinical trial. Hallucinations, probably not drug related, occurred in one dropout and a myocardial infarction, possibly drug related, in a second. One of 3 relapsing-remitting patients experienced a relapse during the clinical trial.

No meaningful changes in Expanded Disability Status Score or Sclerite Rating Scale scores were observed over the course of the clinical trial. Neuropsychological testing at 6 months suggested improved performance in selected aspects of verbal memory as compared with baseline. This finding should be viewed cautiously given the small sample size and bearing in mind that interferon beta treatment alone can improve cognitive performance.19 There was no meaningful change in the quality of life overall, but dropouts scored lower (ie, worse) at enrollment on measures of emotional well-being, contentment, and family and social well-being than completers. Whether such measures can serve as predictors of propensity to drop out will need to be tested in a larger clinical trial. Following completion of this trial etretinate was withdrawn and replaced with acitretin (Soriatane; Hoffman-LaRoche Inc), the active metabolite of etretinate. Acitretin has a much shorter elimination half-life than etretinate (49 hours vs 120 days).

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