Etretinate Therapy for Refractory Sclerodermatous Chronic Graft-Versus-Host Disease


Chronic graft-versus-host disease (GVHD) is the most common late complication of allogeneic bone marrow transplantation (BMT). The sclerodermatous form of the disease is often refractory to standard treatment modalities. Based on reports of response to etretinate, a synthetic retinoid, among patients with scleroderma, we have added etretinate to the treatment regimen of 32 patients with refractory sclerodermatous chronic GVHD. This case series is comprised mainly of patients who had chronic GVHD of long duration (median of 30 months before the initiation of etretinate). Most had failed to respond to three or more agents before etretinate treatment was started. Clinical response was assessed after 3 months of therapy. Five patients did not complete a 3-month trial. Among the 27 patients evaluable for response, 20 showed improvement including softening of the skin, flattening of cutaneous lesions, increased range of motion, and improved performance status. Four showed no response after 3 months of therapy and 3 had progression of their sclerosis. Overall, etretinate has been fairly well tolerated in our patients, with skin breakdown and/or ulceration leading to its discontinuation in 6 patients. We believe the results in our patients are encouraging and suggest that further evaluation of etretinate in the treatment of sclerodermatous chronic GVHD is warranted.

© 1999 by The American Society of Hematology.

MATERIALS AND METHODS

Between July 1989 and September 1995, we used etretinate to treat 32 patients with refractory sclerodermatous chronic GVHD. Potential patients were identified from among those transplanted at the Johns Hopkins Oncology Center and those referred to our Chronic GVHD Consultation Clinic. The diagnosis of sclerodermatous chronic GVHD was made clinically in patients who had previous histologic documentation of cutaneous GVHD. All patients had received a therapeutic trial of standard therapy for their chronic GVHD, such as steroids and/or CSA for a minimum of 3 months, before the initiation of etretinate therapy. All patients were felt to have either progressive or persistent disease despite treatment with such agents. Patients were maintained on therapeutic doses of immunosuppressive therapy, to which etretinate was then added. All patients received standard supportive measures, including prophylaxis against infections, as well as a thorough evaluation and recommendations by physical therapy.

Patients in this case series were treated over a 6-year period, and the method of administration of etretinate changed as our experience with this agent in this population grew. Initially, the agent was administered in the same dose and dosing schedule used for other dermatologic conditions, with the full desired dose (1.0 mg/kg/d) being administered from the initiation of therapy. Over time, we found that patients tolerated the drug best when it was started at a lower initial dose and gradually increased according to patient tolerance. The initial dose ranged between 0.25 and 1.0 mg/kg/d administered orally in two to four divided doses. Our current approach is to start at 0.25 mg/kg/d on two divided doses and increase over 2 weeks towards the full desired dose of 1 mg/kg/d. Serum cholesterol, triglycerides, and liver enzymes were measured and adjustments in therapy were made based on these results.

All patients were observed by the multidisciplinary team in our Chronic GVHD Clinic. The clinical response to therapy and development of side effects were recorded. Initial response was assessed at a minimum of 3 months of therapy. In addition to the subjective reporting of the patient, improvement was documented when we had evidence of softening of the skin, flattening of cutaneous lesions, objective increases in range of motion, and/or subjective increases in muscle strength as measured by the physical therapist on the team.

RESULTS

These 32 patients, transplanted at a number of different institutions, represent a heterogeneous group, with the common feature being the development of refractory sclerodermatous chronic GVHD. The age of these patients, at the time of BMT, ranged from 5 to 49 years (median, 29 years). Fifteen patients were male. The transplants were performed for a variety of hematologic conditions: chronic myelogenous leukemia (11...
patients), acute myelogenous leukemia (7 patients), acute lymphoblastic leukemia (5 patients), aplastic anemia (3 patients), myelodysplastic syndrome (2 patients), Hodgkin’s disease (1 patient), non-Hodgkin’s lymphoma (1 patient), chronic lymphocytic leukemia (1 patient), and multiple myeloma (1 patient).

Nineteen of the 32 patients underwent an allogeneic BMT from an HLA-identical sibling donor. Three patients received marrow from related donors who were not a complete HLA match: either one-antigen (n = 2) or two-antigen (n = 1) mismatches. Two patients have undergone two transplants. In both cases, the second transplant was performed using marrow from the same matched sibling donor. Eight patients had transplants from unrelated donors. Most transplants (20/34) were performed using total body irradiation as part of the conditioning regimen. With respect to the first or only transplant for the 32 patients, 30 are known to have received CSA as prophylaxis against acute GVHD; 16 received CSA in combination with other agents, including steroids, methotrexate, and azathioprine. Twenty-four of these patients developed acute GVHD requiring therapy; 10 had involvement of the skin alone, 1 is reported to have had acute GVHD limited to the liver, and the remainder were felt to have had multiorgan acute GVHD.

Chronic GVHD developed 1 to 24 months post-BMT (median, 7 months) and involved the skin and/or fascia in all patients. Other sites or organs were also involved in all but 4 patients. Before initiating etretinate, all but 1 patient had received systemic steroids for their chronic GVHD. All but 2 patients had received additional agents, including CSA (N = 24), thalidomide (N = 14), psoralen-ultraviolet A irradiation (PUVA) (N = 12), azathioprine (N = 10), FK506 (N = 1), colchicine (N = 1), and photopheresis (N = 1), before starting etretinate. Fourteen of the patients had received three drugs/modalities and 9 patients had received four before etretinate therapy was started. The time from the onset of chronic GVHD to the initiation of etretinate therapy ranged from 3 to 84 months (median, 30 months).

As shown in Table 1, the main indication to start etretinate was progression of sclerodermatous skin changes despite treatment (21/32). Less commonly, etretinate was started for failure to improve (N = 8). Two patients received etretinate for the development of sclerodermatous changes while on full-dose therapy for lichenoid chronic GVHD and 1 patient received etretinate for a flare of previously controlled sclerodermatous GVHD.

The intention was to assess response after 3 months of therapy. Five patients received less than 3 months of therapy and are considered nonevaluable for response. The course was shorter than 3 months in these 5 patients because of skin breakdown (N = 1), patient choice to stop the drug after 1 day (N = 1), and early death not considered directly attributable to etretinate (N = 3). All patients were considered evaluable for toxicity.

Among the 27 patients evaluable for response, 20 have shown improvement while receiving etretinate. Two of these patients have continued to improve after the withdrawal of the drug. In the majority of these patients, response has been evidenced by improved functional status and objective increase in range of motion. Likely as a result of the duration, extent, and severity of disease, most patients have not had complete reversal of their sclerodermatous chronic GVHD. However, 2 patients have had nearly complete resolution of the sclerodermatous GVHD. Of the remaining 7 evaluable patients, 3 had progressive disease and 4 had equivocal or no response but did not progress while on therapy.

The duration of therapy in the evaluable patients has ranged from 3 months to 3 years, with 14 patients continuing to receive etretinate at the time that these data were compiled. The drug was discontinued after 3 months in the remaining evaluable patients for the following reasons: maximal improvement (N = 4), skin breakdown and/or ulceration (N = 5), progressive sclerosis (N = 3), and death due to bacterial pneumonia and liver failure (N = 1).

All 32 patients were evaluable for toxicity, as shown in Table 2. Previously reported side effects with this agent have been observed among our patients.9 All patients have noted cracking of their nails. Many patients have had scaling and/or ulceration of the skin. This required discontinuation of the etretinate in 6 of 32 patients: 1 before a full 3-month trial could be completed, 1 in whom a response to the therapy was observed, and 4 in whom no response was seen despite a 3- to 10-month trial. Xerosis, cheilitis, pruritus, transient hypertiglyceridemia, transient hypercholesterolemia, and eye irritation have occurred but have not necessitated stopping administration of the drug. Some patients have also noted thinning of the hair. No serious organ toxicity attributable to etretinate has been documented. Four patients died during this period. Three patients died of, or with, infections. In one case, the cause of death was unknown.

DISCUSSION

As reported in this case series, the systemic administration of the vitamin A derivative, etretinate, has produced encouraging results among patients with refractory sclerodermatous chronic GVHD. Whereas Gryn and Crilley10 have reported on the use of topical retinoic acid (tretinoin) in 1 patient with cutaneous GVHD, our interest in this class of agents stems from their use in a variety of dermatologic conditions, including scleroderma.1-8 The skin manifestations of the autoimmune disease, systemic sclerosis (scleroderma), are clinically and histologically similar to the cutaneous manifestations of sclerodermatous chronic GVHD. Both conditions are characterized by excess collagen production. Although the exact mechanism of action of etretinate is not clearly understood, it is likely that inhibition of fibroblast growth and decreased collagen production in dermal fibroblasts is of importance.11-15 Patients with sclerodermatous chronic GVHD may fail to improve either because of progressive chronic GVHD or when there is no improvement of their fibrosis, despite stable or improved GVHD.

Because GVHD is felt to be immune mediated, standard approaches to chronic GVHD have, to date, been aimed at immunosuppression. Retinoids have been shown to affect the production of various cytokines in vitro.16-22 It is of interest that immunomodulatory effects of retinoids are being recognized. We do not know if etretinate works predominantly as an immunosuppressant in this setting, because as our patients were failing to respond or, more commonly, progressing despite immunosuppressive therapy when etretinate was added. We do not know how the immune process connects to the resolution of fibrosis, but it seems reasonable to administer a therapy with a
unique mechanism of action to patients who have significant sclerodermatous involvement. The probable effects on fibroblasts make etretinate an attractive consideration in such patients.

Although etretinate has been relatively well-tolerated in our patients, there are important potential toxicities that must be closely monitored. Of particular concern is the fact that etretinate is teratogenic and must not be administered to women who are pregnant or who intend to become pregnant. Although many BMT patients are rendered sterile by the procedure, not all patients will be permanently infertile. The period of time during which pregnancy should be avoided after discontinuation of etretinate therapy has not been established. The drug is stored in adipose tissue and has been detected in the blood of some patients even 2.9 years after therapy was stopped. Acetretin, a less lipophilic formulation of etretinate, has now replaced Tegison and will be used in subsequent studies. Other less common but serious side effects include hepatotoxicity. Although relatively uncommon and usually reversible, there have been at least four reports of hepatitis-related deaths worldwide. Our patient who died of bacterial pneumonia developed liver failure during this septic event and not during the previous 12 months of etretinate therapy. Etretinate and other retinoids have been associated with pseudo-tumor cerebri in less than 1% of patients treated but was not seen in any of our patients.

### Table 1. Summary of Patients Presented According to Response to Etretinate

<table>
<thead>
<tr>
<th>SID</th>
<th>Onset of Chronic GVHD (day post-BMT)</th>
<th>GVHD Therapy Administered Before Etretinate</th>
<th>Duration of GVHD Before Etretinate (days)</th>
<th>Reason for Starting Etretinate</th>
<th>Response</th>
<th>Duration of Etretinate*</th>
<th>Reason for Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>304</td>
<td>Steroids, azathioprine, thalidomide, colchicine</td>
<td>1,046</td>
<td>Progression</td>
<td>Improvement</td>
<td>36 mo (off and on)</td>
<td>Maximal improvement—continued to improve off etretinate</td>
</tr>
<tr>
<td>6</td>
<td>700</td>
<td>Steroids, CSA</td>
<td>215</td>
<td>Failure to improve</td>
<td>Improvement</td>
<td>8.5 mo</td>
<td>GVHD almost completely resolved</td>
</tr>
<tr>
<td>8</td>
<td>279</td>
<td>Steroids, CSA, PUVA</td>
<td>866</td>
<td>Failure to improve</td>
<td>Improvement</td>
<td>5 mo</td>
<td>Maximal improvement—continued to improve off etretinate</td>
</tr>
<tr>
<td>11</td>
<td>454</td>
<td>Steroids, CSA</td>
<td>91</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>80</td>
<td>Steroids, CSA, thalidomide</td>
<td>1,447</td>
<td>New onset scleroderma</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>397</td>
<td>Steroids, CSA</td>
<td>220</td>
<td>Progression</td>
<td>Improvement</td>
<td>12 mo (until death)</td>
<td>Died (COD bacterial pneumonia/liver failure)</td>
</tr>
<tr>
<td>15</td>
<td>180</td>
<td>Steroids, thalidomide, PUVA</td>
<td>1,245</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>178</td>
<td>Steroids, thalidomide, PUVA, photopheresis</td>
<td>1,019</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>34</td>
<td>Steroids, azathioprine, thalidomide, PUVA</td>
<td>2,058</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>724</td>
<td>Steroids, CSA</td>
<td>407</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>192</td>
<td>Steroids, CSA</td>
<td>1,044</td>
<td>Progression</td>
<td>Improvement</td>
<td>14 mo</td>
<td>GVHD almost completely resolved</td>
</tr>
<tr>
<td>21</td>
<td>151</td>
<td>Steroids, CSA, thalidomide, FK506</td>
<td>534</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>85</td>
<td>Steroids, CSA, PUVA</td>
<td>1,861</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues intermittently</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>225</td>
<td>Steroids, CSA, PUVA</td>
<td>1,367</td>
<td>Failure to improve</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>100</td>
<td>Steroids, CSA, azathioprine</td>
<td>2,556</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>72</td>
<td>Steroids, CSA</td>
<td>1,112</td>
<td>Failure to improve</td>
<td>Improvement</td>
<td>4 mo</td>
<td>Skin breakdown</td>
</tr>
<tr>
<td>29</td>
<td>1,117</td>
<td>Steroids, CSA, PUVA, azathioprine</td>
<td>201</td>
<td>Progression</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>26</td>
<td>CSA, PUVA, azathioprine</td>
<td>624</td>
<td>New onset scleroderma</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>454</td>
<td>Steroids, CSA, thalidomide, PUVA</td>
<td>386</td>
<td>Progress</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>306</td>
<td>Steroids, CSA, thalidomide</td>
<td>1,551</td>
<td>Progress</td>
<td>Improvement</td>
<td>Continues</td>
<td></td>
</tr>
</tbody>
</table>

(Continued on following page)
We believe that the preliminary results in this series of patients are encouraging and suggest that further evaluation of etretinate in the treatment of sclerodermatous chronic GVHD is warranted. Etretinate may offer a new therapeutic option in this setting; however, where it might fit into the treatment schema remains to be determined. The activity of the sclerotic process and, therefore, the determination of response presents unique challenges in this setting. In addition, given the potential toxicities of etretinate, we believe that further study in the form of a clinical trial using a systematic approach to determine duration of therapy, response rate, and toxicity is needed.

**REFERENCES**

18. Ney UM, Ball IJ, Hill RP, Westmacott D, Bloxham DP: Anti-inflammatory effects of synthetic retinoids may be related to their immunomodulatory action. Dermatologica 175:93, 1987 (suppl 1)

From www.bloodjournal.org by guest on June 12, 2017. For personal use only.
Etretinate Therapy for Refractory Sclerodermatous Chronic Graft-Versus-Host Disease