Treatment of Chronic Graft-Versus-Host Disease With Clofazimine

By Stephanie J. Lee, Scott A. Wegner, Carol J. Mcgarigal, Barbara B. Bierer, and Joseph H. Antin

Clofazimine (Lamprene) is an antimycobacterial drug that has antiinflammatory activity in a number of chronic autoimmune skin disorders. We report 22 patients treated with clofazimine for chronic graft-versus-host disease (cGVHD). The initial dose was 300 mg orally in a single daily dose for 90 days. After 90 days, the dose was lowered to 100 mg orally each day and the medication continued indefinitely as tolerated. Treatment courses lasted 7 to 835 days and were generally well tolerated. Gastrointestinal side effects occurred in eight of 22 patients (36%) and hyperpigmentation was noted in 12 of 22 patients (55%), which resolved upon decrease or discontinuation of the drug. Over 50% of patients with skin involvement, flexion contractures, or oral manifestations achieved complete or partial responses. Seven of 22 patients (32%) were able to reduce other immunosuppressive medications. Thus, clofazimine is safe and has encouraging efficacy in cGVHD, particularly if sclerodermatous skin, joint contractures, or oral manifestations are present. The mechanism by which clofazimine induces a response is unknown, but might be secondary to suppression of alloreactive T-cell function in cGVHD target organs. Clofazimine deserves further study for the treatment of cGVHD.

C HRONIC graft-versus-host disease (cGVHD) is a frequent late complication of allogeneic bone marrow transplantation. It affects 50% of long-term transplant survivors, and mortality occurs in 20% to 40% of affected patients despite aggressive treatment. Chronic GVHD may involve virtually any organ. Primary therapy for extensive cGVHD typically includes corticosteroids and cyclosporine. However, this combination therapy is often unsuccessful in patients with extensive multiorgan involvement. Azathioprine is sometimes used as a steroid-sparing agent, but is associated with a higher risk of infections. All of these conventional agents are associated with significant therapy-related complications. Because of the toxicity and incomplete response rate of conventional treatment for cGVHD, alternative approaches are needed for patients who cannot tolerate or do not respond to first-line therapy. One such drug is thalidomide, which is beneficial in 20% to 59% of patients, but often causes sedation and neuropathy and is not commercially available. Case reports exist showing response for other agents, such as penicillamine, photopheresis, and psoralen and ultraviolet A (PUVA) therapy, but experience with these modalities is limited.

Closazimine is an antimycobacterial agent that has been used extensively in the treatment of leprosy and Mycobacterium avium complex since the 1960s. Furthermore, it has demonstrated efficacy in the treatment of immune-mediated skin disease such as cutaneous discoid and annular lupus erythematosus. pyoderma gangrenosum, and pustular psoriasis. The mechanism of clofazimine action in these conditions is unknown, but is thought to reflect functional inhibition of pathogenic T lymphocytes. Although the drug is relatively well tolerated, side effects, when they occur, involve the skin, eyes, and gastrointestinal tract, all of which are major sites of cGVHD involvement. Clofazimine is secreted in sweat, sebum, tears, and saliva, and clofazimine crystals are found precipitated in Peyer’s patches, skin, lymph nodes, spleen, and other organs in patients receiving long-term therapy. We hypothesized that clofazimine might have efficacy in cGVHD given its apparent immunomodulatory action and tissue distribution.

MATERIALS AND METHODS

Patients treated before August 1992 received clofazimine (Ciba-Geigy Inc, Summit, NJ) off protocol. Patients treated after that date were enrolled on an open-label, phase II trial of clofazimine. The phase II study was approved by the Human Research Committee of the Brigham and Women’s Hospital, Boston, MA. All patients received clofazimine, 300 mg in a single oral dose with food for 90 days. After 90 days, the dose of clofazimine was reduced to 100 mg daily. Patients enrolled in the phase II study received clofazimine provided by Ciba-Geigy Inc.

Patients treated on protocol received baseline evaluations including a history and physical examination, complete blood count with differential, complete chemistry panel, and lymphocyte phenotyping panel. When indicated, patients were evaluated by an oral surgeon and ophthalmologist, and flexion contractures, when present, were measured by a physical therapist. Skin, liver, lung, or mucus membrane biopsies were performed as clinically indicated. Physical assessment was repeated every 2 weeks and laboratory studies were repeated every 4 weeks during the study. Lymphocyte phenotyping for T, B, and natural killer cell antigens was performed by direct immuno fluorescence using monoclonal antibodies directed against CD3, CD5, CD4, CD8, CD56, CD57, CD16, and CD19. Studies were performed on enrollment in the study, at 3 months, and every several months thereafter, as long as patients remained on study. Patients received pneumocystis and pneumococcal prophylaxis, as well as Ig replacement if sinopulmonary infections occurred in the setting of Ig deficiency. All patients received their primary follow-up care and evaluation for response to clofazimine at the Brigham and Women’s Hospital. Therapy was discontinued if patients experienced progressive cGVHD despite clofazimine, intolerable side effects, or reached a plateau without further improvement. Therapy could be reinitiated if cGVHD recurred; however, only an aggregate best response for all courses is reported. Two patients received their initial bone marrow transplants at other hospitals; these patients were treated with adoptive immunotherapy and for their subsequent cGVHD at the Brigham and Women’s Hospital.

Response rates were determined by review of medical records.
Complete organ responses were defined as resolution of skin, joint, oral, pulmonary, or ocular manifestations. Partial responses were defined as a greater than 50% response in organ involvement, but less than complete response. Stable disease was defined as stable organ involvement despite the tapering of other immunosuppressive agents by at least 50% of the dosage. No response referred to progressive worsening of cGVHD or stability of cGVHD, but inability to taper other medications. When judging overall response, patients experiencing complete resolution of all cGVHD manifestations were considered complete responders, patients with partial response of any organ were classified as partial responders, and those without any organ response or stable manifestations were nonresponders.

RESULTS

Twenty-two patients were studied between November 1990 and December 1995. Nine of the 22 patients (41%) were treated off protocol and 13 of 22 (59%) received clofazimine on protocol. The two treatment groups did not differ with regards to demographics, dose, and schedule of drug administered, or response rate, and results were pooled. Patient characteristics are shown in Table 1. The average age of patients was 36 years (range, 24 to 54 years) and 77% of patients were transplanted for hematologic malignancies. Nineteen of 22 patients (86%) received cyclophosphamide and total body irradiation (1,400 rads) as preparation for transplantation as previously described.22 Sixteen patients (73%) underwent related donor transplantation of whom 3 (14%) developed cGVHD following adoptive immunotherapy; 6 patients (27%) were transplanted from unrelated donors.

Prognostic factors and onset of cGVHD are shown in Table 2. Diagnosis of cGVHD was based either on pathologic documentation of organ involvement or clinical features. Twelve patients (56%) had documented acute grade II to IV GVHD; 16 of 22 patients (73%) had quiescent onset cGVHD and 3 of 22 (14%) had a progressive presentation. Three patients (14%) presented with de novo cGVHD. At initiation of clofazimine therapy, 77% of patients were receiving cyclosporine and steroids, 9% steroids alone, 5% cyclosporine alone, and 9% no other therapy. At the time of clofazimine discontinuation, 55% of patients were receiving cyclosporine and steroids, 18% steroids alone, 5% cyclosporine alone, and 23% no immunosuppression. Follow-up information was collected through June 1, 1996; a total of 6,895 patient-days on treatment had elapsed with an average 231 days per patient.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male/female</th>
<th>Median age (range)</th>
<th>Conditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>8/14</td>
<td>36 (24-54 yr)</td>
<td>Cytosine arabinoside/cyclophosphamide/TBI</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td></td>
<td></td>
<td>Cyclophosphamide/TBI</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td></td>
<td></td>
<td>Busulfan/cyclophosphamide</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>12 (55%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 (32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

Table 2. Chronic GVHD: Onset and Manifestations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Onset cGVHD</th>
<th>Response to clofazimine</th>
<th>Type of transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiescent</td>
<td>16 (73%)</td>
<td>3 (14%)</td>
<td>Allogeneic related donor</td>
</tr>
<tr>
<td>Progressive</td>
<td>3 (14%)</td>
<td></td>
<td>Unrelated donor</td>
</tr>
<tr>
<td>De novo</td>
<td>3 (14%)</td>
<td></td>
<td>Allogeneic related donor + adoptive immunotherapy</td>
</tr>
</tbody>
</table>

**Table 2. Chronic GVHD: Onset and Manifestations**

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Male/female</th>
<th>Median age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic related donor</td>
<td>13 (59%)</td>
<td></td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>6 (27%)</td>
<td></td>
</tr>
<tr>
<td>Allogeneic related donor + adoptive immunotherapy</td>
<td>3 (14%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Evaluable Responses to Clofazimine

<table>
<thead>
<tr>
<th>Organ Involvement</th>
<th>No.</th>
<th>NR (%)</th>
<th>Stable (%)</th>
<th>PR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin*</td>
<td>16</td>
<td>4/16 (25)</td>
<td>3/16 (19)</td>
<td>9/16 (56)</td>
<td>—</td>
</tr>
<tr>
<td>Joints (flexion contractures)</td>
<td>11</td>
<td>3/11 (27)</td>
<td>1/11 (9)</td>
<td>3/11 (27)</td>
<td>4/11 (36)</td>
</tr>
<tr>
<td>Mouth (sores, pain)</td>
<td>6</td>
<td>2/6 (33)</td>
<td>1/6 (17)</td>
<td>3/6 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Lungs (bronchiolitis obliterans)</td>
<td>4</td>
<td>2/4 (50)</td>
<td>1/4 (25)</td>
<td>1/4 (25)</td>
<td>—</td>
</tr>
<tr>
<td>Keratoconjunctivitis</td>
<td>1</td>
<td>1/1 (100)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: NR, no response; PR, partial response; CR, complete response.

* Six sclerodermatous (3 PR, 2 stable, 1 NR), 6 lichenoid (3 PR, 1 stable, 2 NR), 4 mixed features (3 PR, 1 NR).

between clinically sclerodermatous and lichenoid involvement. Three of six (50%) patients treated for oral involvement also partially responded. Seven of 11 (63%) patients had improvement in joint mobility; 4 of these patients (36%) attained complete remissions with release of contractures. Only one partial response was seen in patients treated for pulmonary or ocular symptoms, although the evaluable patient population was small (n = 5).

Overall, 12 of 22 (55%) patients achieved a partial response. Patients with both limited disease (4 of 6 [66%]) and with extensive disease (8 of 16 [50%]) responded. No overall complete responses were observed. Five patients (23%) decreased the dosages of other immunosuppressive medications by at least 50%, in addition to achieving partial organ responses. Two additional patients (9%) also decreased other immunosuppressive medications by 50%, although their symptoms did not improve; these two patients were classified as overall nonresponders.

Sequential lymphocyte phenotyping studies did not show any significant trends during or after treatment with clofazimine (data not shown). White blood cell count, platelet count, hematocrit, and serum bilirubin also did not change significantly (data not shown). Infections were neither quantitatively nor qualitatively increased above baseline during or after treatment with clofazimine (data not shown).

Side effects were generally mild. Eight patients (36%) had abdominal symptoms, consisting of nausea, vomiting, cramps, constipation, or diarrhea. These symptoms were considered intolerable in 4 of 22 (18%) patients and resulted in discontinuation of clofazimine. Twelve patients (55%) developed red-brown hyperpigmentation of the skin and conjunctiva, but none requested withdrawal from the study. No ophthalmologic complications were observed. All side effects were reversible upon stopping clofazimine treatment.

Six patients (27%) died between 7 to 482 days after starting clofazimine: 2 from infection (1 on therapy at 252 days; 1 off therapy for 402 days after 20 days of clofazimine), 1 from bronchiolitis obliterans (on therapy at 7 days), 1 from leukemic relapse (off therapy for 277 days after receiving 233 days of clofazimine), 1 from an ill-defined neuromuscular process (off therapy for 239 days after receiving 104 days of clofazimine), and 1 after electing to discontinue dialysis (87 days after starting clofazimine, but off therapy). Clofazimine was not believed to be contributory to these deaths.

**DISCUSSION**

Clofazimine has been used extensively for the treatment of leprosy and Mycobacterium avium complex and reported to be useful in several immunologically mediated skin disorders. In an open trial, 10 patients with pyoderma gangrenosum were treated with clofazimine with achievement of complete remission in 7 and partial responses in 2.18 Multiple open label trials have shown clofazimine to be effective in the treatment of cutaneous lupus lesions14,28 of pyoderma gangrenosum and its variants16-19 and of psoriasis.20

The mechanism of action of clofazimine is unclear, although several studies have suggested that it has immunomodulatory effects.29 Documented effects of clofazimine, in vitro, include an inhibition of lymphocyte responsiveness to mitogen stimulation,30 possibly due to increased release of lysophospholipids,31 decreased neutrophil motility,30 increased spontaneous production of reactive oxidants by mononuclear leukocytes,32 increased synthesis of prostaglandin E2,32 and increased clearance and degradation of circulating immune complexes by macrophages in vitro.33

A number of reports have demonstrated effects of clofazimine that might predict increased immune activity. In vitro studies of peripheral blood monocytes from healthy volunteers have demonstrated increased major histocompatibility complex (MHC) class II expression following incubation with clofazimine,34 increased oxygen uptake during phagocytosis in neutrophils derived from patients with pyoderma gangrenosum during clofazimine therapy,37 and decreased suppressor T-cell activity in mycobacteria-infected mice during clofazimine treatment.35 In our study, we observed no consistent changes in the percentages or absolute numbers of CD4+ helper T cells, CD8+ cytotoxic/suppressor cells, or CD16+ natural killer cells. Serial lymphocyte functional studies were not performed.

The majority of in vitro studies used concentrations of clofazimine, which are achievable in vivo, as a 300 mg daily dose results in predicted serum levels of 1.0 µg/mL.36 The half-life of clofazimine in man is approximately 70 days due to its highly lipophilic nature.13,23,37 However, in vivo efficacy of clofazimine may be related to high local tissue levels of the drug. Crystals of clofazimine have been shown by electron microscopy to be present in skin, Peyer’s patches, and the reticuloendothelial system for a prolonged time following therapy. Because these sites are target organs for cGVHD, increases in local concentration may accentuate the immunosuppressive effects of clofazimine at these sites.

Long-term complications from prolonged use of clofazimine in humans have not been demonstrated38 and eight of our patients have been treated for more than a year. In other settings, commonly reported side effects include skin discoloration, gastrointestinal symptoms (nausea, cramping, diarrhea, constipation), and ocular symptoms, which are reversible upon discontinuation of the drug.13,23,22,29,40 We observed both gastrointestinal and cutaneous side effects. We did not observe any ocular complications of clofazimine therapy.

In summary, clofazimine is safe and has encouraging efficacy in the treatment of cGVHD. The results in patients
with scleroderma, joint, or oral involvement were particularly encouraging. The lack of observed infectious complications differentiates clofazimine from first-line treatments for cGVHD and is an attractive feature of the drug, given the already markedly impaired immune function in patients with this disease. Furthermore, if clofazimine allows reduction in cyclosporine and corticosteroid requirements, it may reduce the risk of complications due to iatrogenic immunosuppression. Given its relative lack of toxicity, we suggest that clofazimine deserves further study in the treatment of cGVHD.

ACKNOWLEDGMENT

We thank the nurses, housestaff, fellows, and our colleagues at the Brigham and Women’s Hospital for the care of these patients.

REFERENCES

Treatment of Chronic Graft-Versus-Host Disease With Clofazimine

Stephanie J. Lee, Scott A. Wegner, Carol J. McGarigle, Barbara E. Bierer and Joseph H. Antin

Updated information and services can be found at:
http://www.bloodjournal.org/content/89/7/2298.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml