Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor Ameliorates Zidovudine-Induced Neutropenia in Patients With Acquired Immunodeficiency Syndrome (AIDS)/AIDS-Related Complex

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To evaluate the effect of recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) on patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) who were intolerant to zidovudine because of neutropenia, we performed a randomized, open-label study in which patients were assigned to one of two groups. Zidovudine was discontinued in group A patients before instituting GM-CSF treatment and was restarted in a graduated fashion over 4 weeks. Group B patients continued on full-dose (1,200 mg/d) zidovudine therapy while beginning GM-CSF therapy. A total of 17 patients were entered, eight in group A and nine in group B. Five of eight patients in group A and seven of nine in group B had a history of Pneumocystis carinii pneumonia (PCP). All were homosexual males, except one female in group A who was the sex partner of a bisexual male with AIDS. All patients had neutropenia (absolute neutrophil count [ANC] <1,000/µL) while taking full-dose zidovudine. The mean CD4 (± SD) lymphocyte level was 37 (± 29)/µL and 39 (± 44)/µL in groups A and B, respectively. After randomization, patients were begun on subcutaneous GM-CSF at a dose of 1.0 µg/kg/d. Patients in group A received 2 weeks of daily GM-CSF, at which time zidovudine was restarted if the ANC was greater than 1,000/µL; if the ANC was less than 1,000/µL, the dose of GM-CSF was increased to 3.0 µg/kg, and at 2-week intervals either zidovudine was restarted or the dose of GM-CSF was increased to 5 µg/kg and then 10 µg/kg, to maintain the ANC greater than 1,000/µL. Group B patients received full-dose zidovudine concurrently with GM-CSF administration. The dose of GM-CSF was increased every 2 weeks if necessary to keep the ANC greater than 1,000/µL while maintaining full-dose zidovudine therapy. Patients in each group showed an increase in total white blood cell (WBC) count. Neutrophils and eosinophils were responsible for the majority of this increase. Patients in group A had a more rapid increase in WBC than those in group B; however, by week 8, the WBC in each group was essentially equal. Viral replication as measured by human immunodeficiency virus (HIV) p24 antigen (Ag) was decreased in four patients in each group, increased in one patient in each group, and remained unchanged in the remainder. The ability to culture virus from peripheral blood mononuclear cells was not changed by the regimen. The major toxicities of the regimen were fever and malaise. We conclude that daily subcutaneous GM-CSF at a relatively low dose is capable of ameliorating neutropenia in patients with AIDS or ARC and can sustain leukocyte counts during concomitant zidovudine therapy.

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ZIDOVUDINE is currently the primary antiretroviral agent that has demonstrated effectiveness in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC). More than half of the patients who take zidovudine eventually discontinue the drug because of toxicity. Bone marrow suppression resulting in neutropenia and anemia is often the dose-limiting toxicity of zidovudine treatment. Severe anemia can be managed with red blood cell (RBC) transfusion, but the neutropenia cannot be managed in a similar fashion. In addition to the quantitative decreases in leukocytes due to human immunodeficiency virus (HIV) infection and/or antiretroviral therapy, HIV-infected patients may have qualitative leukocyte abnormalities. Defects in the neutrophil respiratory burst and defective microbicidal activity in both neutrophils and monocytes have been observed following HIV infection. These quantitative and qualitative defects may be important in the pathophysiology of certain infectious complications.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a glycoprotein produced by T lymphocytes, endothelial cells, and fibroblasts that stimulates production and function of neutrophils, eosinophils, and monocytes. We have previously demonstrated that GM-CSF is safe and effective in raising the leukocyte count when administered to HIV-infected patients with AIDS or ARC who were neutropenic because of their HIV infection. Because primary therapy of HIV infection uses zidovudine, a myelosuppressive agent, we sought to extend this initial observation to study concurrent administration of zidovudine and GM-CSF in a group of AIDS or ARC patients hematologically intolerant of zidovudine alone. We observed that concomitant use of GM-CSF and zidovudine was reasonably well tolerated and GM-CSF was capable of ameliorating zidovudine-induced neutropenia.

MATERIALS AND METHODS

Patients who met the Centers for Disease Control (CDC) criteria for AIDS or ARC (ARC = symptomatic HIV-positive with T lymphocyte count <200/µL on zidovudine not meeting CDC criteria for AIDS) were eligible for enrollment in the study after giving informed consent. The study was approved by the Institu-
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Clinical and laboratory monitoring. Before and during the course of the study, patients were monitored by the recording of vital signs, physical examination, and laboratory data. In addition to complete blood cell counts (CBC) with differential, platelet count and reticulocyte count, and liver chemistries, the following immunologic and virologic tests were performed: lymphocyte phenotyping, quantitative immunoglobulin determinations, serum HIV p24 antigen (Ag) (Abbott, North Chicago, IL; enzyme-linked immunosorbent assay [ELISA]), HIV cultures from separated peripheral blood lymphocytes and monocytes, and skin testing to trichophyton, candida, tetaus toxoid, and purified protein derivative.

Recombinant human GM-CSF. Recombinant human GM-CSF was supplied by Schering, Kenilworth, NJ, as a lyophilized powder, which was reconstituted with sterile water. Specific activity of the product expressed in Escherichia coli was 10^7 U/mg.

Study design. This was a randomized, open-label study with two groups. In group A, zidovudine was discontinued and patients were then begun on subcutaneous GM-CSF at a dose of 1 µg/kg/d. The dose of GM-CSF was increased only at the end of weeks 2, 4, 6, 8, 10, 12 and thereafter there were no significant differences in ANC between the groups.

The mean platelet counts (Fig 3) were 1,180,000/µL in group B. Ten patients had HIV p24 antigen levels greater than 10,000 copies/mL and seven of these patients were continued on their regimen. The mean (±SD) CD4 helper lymphocyte level was 37 (±29)/µL in group A and 39 (±44)/µL in group B. Ten patients had HIV p24 antigen levels greater than the limit of detection (50 pg/mL) (five in group A, five in group B) at enrollment in the study.

Hematologic and immunologic effect. The hematologic response to GM-CSF is shown in Fig 1. Within 1 week of commencing once daily subcutaneous GM-CSF, the leukocyte count increased significantly in both groups. Increases in neutrophilic and eosinophilic granulocytes were responsible for the majority of the increase in the white blood cell (WBC) count (Figs 2 and 3). There was no consistent or sustained change in either lymphocyte (including CD4 and CD8 cells) or monocyte cell counts over the course of the study. The increase in neutrophil count was chronologically earlier and of greater magnitude in the patients who discontinued zidovudine on institution of GM-CSF therapy (group A). However, the difference was only significant at week 2 (P = .028) and thereafter there were no significant differences in ANC between the groups.

The mean platelet counts (Fig 4) in patients remaining on the study did not change in either group. However, this may be misleading, as a total of five patients were withdrawn from the study because of significant thrombocytopenia (platelet count <50,000/µL), which was a protocol criteria for removal from study and discontinuation of both GM-CSF and zidovudine. Most of these patients had resolution of their thrombocytopenia after discontinuing patients who tolerated the zidovudine/GM-CSF combination, and elected to, were continued on their regimen.

The CBC was monitored weekly for the first 4 weeks and then at intervals of every other week. Bone marrow aspirates and biopsies were obtained at baseline and at weeks 4 and 12. HIV p24 antigen, CD4 and CD8 lymphocyte quantitation, and HIV viral cultures were obtained at regular intervals during the course of the study. Prophylaxis for Pneumocystis carinii pneumonia (PCP) was allowed, including aerosolized pentamidine.

RESULTS

Patient characteristics for both groups are shown in Table 1. There were 17 patients enrolled, 16 men and one woman. All but five patients had a history of at least one episode of PCP. The mean (±SD) CD4 helper lymphocyte level was 37 (±29)/µL in group A and 39 (±44)/µL in group B. Ten patients had HIV p24 antigen levels greater than the limit of detection (50 pg/mL) (five in group A, five in group B) at enrollment in the study.

Table 1. Patient Characteristics on Entry to Study

<table>
<thead>
<tr>
<th></th>
<th>Group A (N = 8)</th>
<th>Group B (N = 9)</th>
<th>Totals (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>38 ± 5.7</td>
<td>39.7 ± 6.1</td>
<td></td>
</tr>
<tr>
<td><strong>History of previous OI (PCP)</strong></td>
<td>5/8</td>
<td>7/9</td>
<td>12</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>CD4 cells (per µL)</strong></td>
<td>37 ± 29</td>
<td>39 ± 44</td>
<td>12</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td>ECOG 0</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>ECOG 1</strong></td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OI, opportunistic infection; ECOG, Eastern Cooperative Oncology Group.
Fig 1. Change in total WBC count during the course of subcutaneous GM-CSF administration. The results shown are the means (±SD) of the patients in each group. (■) Group A; (○) group B. Differences between groups are not significant.

Fig 2. Change in the ANC during the course of subcutaneous GM-CSF administration. The results shown are the means (±SD) of the patients in each group. Differences between groups are not significant, except at week 2: \( P = .029 \).

Fig 3. Change in the eosinophil count during the course of subcutaneous GM-CSF administration. The results shown are the means (±SD) of the patients in each group. Differences between groups are not significant.

Fig 4. Platelet counts during course of subcutaneous GM-CSF. Differences between groups are not significant.

Both zidovudine and GM-CSF. The baseline platelet count did not predict the later development of significant thrombocytopenia. Significant thrombocytopenia occurred at weeks 5 and 10 in group A patients and at weeks 4, 7, and 12 in group B patients. Hemorrhagic manifestations did not occur in any of the significantly thrombocytopenic patients. There were adequate numbers of megakaryocytes seen in the bone marrow of the only patient who had a bone marrow examination at the time of development of thrombocytopenia.

Neither the reticulocyte count nor the hematocrit was affected by GM-CSF treatment. A total of 15 patients (seven of eight in group A and eight of nine in group B) required packed RBC transfusion for symptomatic anemia.

Bone marrow aspirates and biopsies did not show any significant changes by light microscopy other than for previously described increases in overall cellularity on GM-CSF. There were adequate numbers of megakaryocytes present in the one patient who had a bone marrow examination performed within 7 days of developing thrombocytopenia. No patient that demonstrated anergy during baseline evaluation regained the ability to respond to skin test antigens when retested.

Subjects in group B were more likely to require an increase in GM-CSF dose to maintain the ANC greater than 1,000/μL (Table 2), although in the majority of patients in both groups a GM-CSF dose of 1 μg/kg was adequate. At week 4, three subjects required dose escalation to 3 μg/kg. Only one patient required dose escalation to 5 μg/kg, and this occurred at week 12 after an initial satisfactory response that lasted 8 weeks. At the same time, this individual developed fever and significant malaise and subsequently discontinued both drugs with gradual resolution of symptoms. However, he was diagnosed with his first episode of PCP a few weeks later.

GM-CSF effects on HIV. All patients had serum HIV p24 Ag levels measured at baseline. The serum HIV p24 Ag levels in group A measured at end of study or at discontinuation from study remained essentially unchanged when
compared with baseline levels in four of eight patients (Fig 5). Levels were increased in two of eight patients and decreased in two of eight patients. In group B patients, HIV p24 Ag levels remained below the detectable limit of 50 pg/mL in four of nine patients, decreased in four of nine patients, and increased in one patient (Fig 5).

During the first 4 weeks of the study, at the time interval when group A patients were not taking zidovudine, one patient in group A demonstrated an increase in HIV P24 Ag after discontinuing zidovudine. The HIV P24 Ag level had decreased to 139 pg/mL, falling further back to baseline of 76 pg/mL at week 5.

Additionally, one patient in group B demonstrated a decrease in HIV P24 Ag after starting GM-CSF. The HIV p24 Ag was 295 pg/mL at baseline (on zidovudine alone). Then, after GM-CSF was started, it decreased to 51 pg/mL at week 1, 88 pg/mL at week 2, and 96 pg/mL at week 4.

The frequency of recovery of HIV from cultures of patients' peripheral blood monocytes did not change over the course of the study. Thus, the combination of GM-CSF and zidovudine did not appear to consistently increase HIV P24 Ag or other measures of HIV activity in these study patients and may have resulted in a decrease in viral activity.

Infections on-study. Patients in both groups either had recurrent or persistent viral and/or fungal infections. Documented bacterial infections occurred in four patients, two in each group (Table 3). The ANC in the 2 group A patients was greater than 1,500/μL in each at the time of diagnosis of infection. The ANC in the group B patient with the rectal abscess was 4,480/μL when he went to surgery for drainage. The patient who developed Pseudomonas pneumonia and bacteremia had an ANC of 2,937/μL the week before his diagnosis, which decreased to 220/μL at diagnosis, resulting in a dose increase of GM-CSF to 3 μg/kg. In addition to these culture-documented bacterial infections, three infections clinically diagnosed as bacterial in origin occurred.

![Graph](https://example.com/graph.png)

**Table 2. Dose of GM-CSF and Reasons for Discontinuing Study**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Discontinuing Study</th>
<th>GM-CSF Dose (μg/kg)</th>
<th>Time of GM-CSF Escalation (wk)</th>
<th>Weeks on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Patient request</td>
<td>1.0</td>
<td>—</td>
<td>44</td>
</tr>
<tr>
<td>04</td>
<td>Fatigue/weakness</td>
<td>1.0</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>06</td>
<td>Fatigue/weakness</td>
<td>1.0</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>07</td>
<td>CNS lymphoma</td>
<td>1.0</td>
<td>—</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>Thrombocytopenia</td>
<td>3.0</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Intercurrent illness</td>
<td>1.0</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>Thrombocytopenia</td>
<td>1.0</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>Patient request</td>
<td>1.0</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>Fever/intercurrent illness</td>
<td>5.0</td>
<td>8, 12</td>
<td>15</td>
</tr>
<tr>
<td>03</td>
<td>Thrombocytopenia</td>
<td>3.0</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>05</td>
<td>Disease progression/CNS lymphoma</td>
<td>3.0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>08</td>
<td>CMV retinitis</td>
<td>1.0</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>09</td>
<td>CMV colitis</td>
<td>1.0</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>Thrombocytopenia</td>
<td>1.0</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>Thrombocytopenia</td>
<td>3.0</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>Disease progression</td>
<td>3.0</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CMV, cytomegalovirus.

**Table 3. Infections on-Study**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Oral thrush</td>
<td>Clotrimazole troche</td>
</tr>
<tr>
<td>04</td>
<td>Oral thrush</td>
<td>Clotrimazole troche</td>
</tr>
<tr>
<td>06</td>
<td>Herpes simplex virus</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>07</td>
<td>Herpes zoster</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>09</td>
<td>Herpes simplex virus</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>13</td>
<td>Herpes simplex virus</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>15</td>
<td>Pneumonia/bacteremia</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>17</td>
<td>Perirectal abscess</td>
<td>Surgery, penicillin, flagyl, ciprofloxacin</td>
</tr>
</tbody>
</table>

| Group B     |           |           |
| 01          | Cellulitis (face) | Bristopen |
| 03          | Oral thrush | Clotrimazole troche |
| 05          | Herpes simplex virus (hand) | Acyclovir |

*Positive culture.
†ANC > 2,400/μL.
‡ANC = 1,500/μL.
§ANC = 2,937/μL week before diagnosis, ANC = 220/μL at diagnosis.
||ANC = 4,480/μL.
Table 4. Side Effects of Combination GM-CSF and Zidovudine

<table>
<thead>
<tr>
<th></th>
<th>Group A (N = 8)</th>
<th>Group B (N = 9)</th>
<th>Total (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Malaise</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Local erythema at injection site</td>
<td>8</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50,000/μL)</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

These infections included two episodes of cellulitis and one episode of sinusitis. All of the bacterial infections responded to antibiotic therapy.

Side effects. The majority of patients tolerated treatment with GM-CSF and zidovudine well. Side effects, such as fever and malaise, appeared to increase with increasing GM-CSF dose. Table 4 illustrates the major side effects we observed. Most patients experienced mild to moderate malaise. This appeared to resolve as the study progressed and patients' complaints decreased over time unless progression of disease became an issue. Bone pain occurred in five patients, but was not sufficiently severe to warrant withdrawal from study. Fever, malaise, and bone pain usually were alleviated with ibuprofen. Local inflammation at the injection site was common in all patients at initiation of GM-CSF therapy, but rapidly decreased in severity within a few weeks. No episodes of phlebitis were observed.

Table 2 lists the reasons patients were discontinued from the study. After thrombocytopenia, the major reason was either progression of their underlying HIV-related disease or the need for additional drugs that could be marrow suppressive (such as gancyclovir for CMV infections). Four patients, two in each group, remained on study after the initial 12 weeks. Three of these four were on a GM-CSF dose of 1.0 μg/kg/d. The fourth patient had his dose escalated to 5 μg/kg/d at week 12 and was discontinued at week 15 because of fever and fatigue. He was diagnosed as having his first episode of PCP pneumonia shortly after dropping the protocol.

DISCUSSION

We have studied the safety and efficacy of self-administered subcutaneous recombinant human GM-CSF in AIDS and ARC patients who were neutropenic because of their disease and/or zidovudine therapy. As opposed to patients with neoplasia receiving GM-CSF to alleviate chemotherapy-induced marrow suppression, our patients required relatively low doses of GM-CSF to maintain a neutrophil count greater than 1,000/μL. Patients receiving chemotherapy often require five to 10 times the 1 μg/kg dose necessary in the majority of our HIV-infected patients to overcome myelosuppressive therapy. The explanation for this observation may simply be that zidovudine and HIV are not as marrow toxic as the chemotherapy regimens given to patients with cancer.

Discontinuation of zidovudine before the administration of GM-CSF (group A) resulted in a more rapid increase in WBC count than in patients who continued zidovudine (group B). However, by 6 weeks (2 weeks after group A patients were on full-dose zidovudine [1,200 mg/d]), there was no difference in either the total WBC count or the ANC in either group. This demonstrates both the significant myelotoxicity of zidovudine and the ability of relatively low doses of GM-CSF to overcome this toxicity without first discontinuing zidovudine.

The subcutaneous route for administration of GM-CSF allows for self-administration and was tolerated well in our study. Almost all of our subjects developed local erythema at the injection site, but this was not a significant problem at the doses given and, in most patients, erythema resolved as the subjects became more facile with self-injection. The constitutional symptoms that led to discontinuation of GM-CSF may result from several factors. Our cohort of patients was in a poor prognostic group with a high incidence of opportunistic infection. They had advanced HIV infection and significant immune suppression as indicated by past medical history, and low numbers of CD4 lymphocytes and neutrophils. Many of these patients had persistent low-grade fever and impaired performance status before entry into the study, and it was often difficult to differentiate progression of AIDS from drug toxicity. A larger group of patients will be required to determine this.

One possible explanation for fever, bone pain, and malaise may be GM-CSF's stimulation of monocytes to release cytokines such as tumor necrosis factor (TNF) and interleukin-1, which are capable of inducing these symptoms. Increases in serum TNF have been demonstrated in cancer patients receiving continuous infusion GM-CSF, although it remains to be demonstrated that the low doses of GM-CSF given in this study are also capable of increasing the secretory activity of monocytes in AIDS patients.

In the absence of concomitant zidovudine, thrombocytopenia has not been observed in our previous intravenous and subcutaneous studies of GM-CSF treatment of AIDS and ARC patients. In light of the observed improvement in thrombocytopenia in many HIV-infected patients with zidovudine therapy, the development of significant thrombocytopenia (<50,000/μL) in our patients was an unexpected occurrence. There are several possible explanations for this observation. One is simply that platelet counts in HIV-infected patients may wax and wane due to idiopathic thrombocytopenic purpura (ITP). Because of intense hematologic scrutiny of patients in this study, declining platelet counts may have been more frequently detected and resulted in withdrawal from the study as per protocol requirement. Another possible explanation is that thrombocytopenia resulted from zidovudine-induced marrow toxicity that was not observed in previous zidovudine studies because neutropenia would precede thrombocytopenia in patients not receiving GM-CSF, and zidovudine treatment would be discontinued before significant thrombocytopenia could develop. A third and more intriguing hypothesis is that the administration of GM-CSF stimulated macrophage phagocytosis so that clinically significant ITP was either induced or accelerated and zidovudine-induced marrow suppres-
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was not designed to demonstrate efficacy of the combina-
both been implicated in the pathogenesis of thrombocytope-
macrophages by GM-CSF could result in accelerated clear-
ance of immunoglobulin coated platelets. In support of this
possibility is the report of relapse of ITP in a patient
receiving GM-CSF for advanced malignancy.15

As has been observed in other reports on the clinical use
of GM-CSF, eosinophils make up a significant part of the
WBC response. We could not discern any toxicity resulting
from this eosinophilia, although the duration of the study
may not have been sufficient to result in clinically evident
side effects.

Bacterial infections occurred in these patients despite
maintaining the ANC greater than 1,000/muL. The study was
not designed to demonstrate efficacy in preventing infec-
tions, as we did not compare the rate of infection to a
control group that was neutropenic and not given GM-CSF.
The use of GM-CSF did not appear to prevent migration of
neutrophils, as demonstrated by abscess and cellulitis
formation.

The observation that infections, particularly opportunistic
bacterial infections, occurred in these patients despite
normal neutrophil counts is not surprising and is further
evidence that the deficit in the ability to defend against
microbial infection in HIV-infected patients involves other
factors such as specific defects in antibody production or
qualitative neutrophil abnormalities and not simply neutro-
phil numbers.

Recombinant GM-CSF elevated the ANC in neutropenic
patients and allowed continued use of full-dose zidovudine
in patients who otherwise would have possibly had to
discontinue or alter their antiretroviral therapy. Our study
was not designed to demonstrate efficacy of the combina-
tion of zidovudine plus GM-CSF in changing the natural
history of AIDS or ARC. We did not observe a consistent
change in serum HIV p24 Ag levels or increased recovery of
HIV from monocytes cultured in vitro during the study. In
vitro data suggest that GM-CSF may increase replication
within macrophages of certain isolates of HIV particularly
tropic for these cells, making the addition of GM-CSF to
the regimen of patients with HIV infection somewhat
problematic and controversial.16,17 However, both this study
and our previous studies of GM-CSF in AIDS patients6,11
have failed to demonstrate consistent stimulation of viral
production that could be attributed to GM-CSF alone and
not to the discontinuation of an antiviral agent. In addition,
Pluda et al18 have shown increases in HIV P24 Ag levels in
patients on GM-CSF, but only when zidovudine had been
discontinued. We observed a similar effect in one patient in
whom an increase in serum HIV p24 Ag was noted when
zidovudine was discontinued. This was followed by a
decrease to pre-GM-CSF levels within 2 weeks of restart-
ing zidovudine. There is also in vitro evidence that GM-
CSF enhances the antiviral effect of zidovudine, probably
by increasing drug entry into the monoocyte and thereby
increasing intracytoplasmic levels of zidovudine.18 We did
not measure intracellular zidovudine levels; this phenome-
non could possibly explain the decrease in HIV p24 Ag
levels in patients on the combination. Studies should be
performed to test whether this in vitro phenomenon is
important clinically and whether increasing the ANC to
normal in neutropenic AIDS/ARC patients changes infec-
tious events, especially bacterial infections. In addition, the
future use of the combination will also be determined by
the efficacy of other less myelosuppressive antiretroviral
agents now being studied.

We have demonstrated overall tolerance of the combina-
tion, as well as certain potentially limiting toxicities, particu-
larly thrombocytopenia. The optimal use of GM-CSF in
HIV-infected patients receiving zidovudine will require
further clinical trials, especially now that the recommended
close of zidovudine has been decreased, apparently without
loss of efficacy.

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